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Human radiation protection is a field that calls on complementary and multidisciplinary skills. Recent radiological incidents and accidents have demonstrated the essential role of IRSN’s advanced technical platform in conducting assessments. Feedback from these events shows that a high-quality assessment can only be achieved quickly and efficiently in a cutting-edge technological environment based on dynamic research programs.

Throughout the years IRSN has gained national and international renown for its work in managing the medical aspects of irradiation accidents. In several real-world situations, multidisciplinary teams have conducted assessments to establish the causes of accidents and their impact on human health. The first article in this chapter recalls the latest accidents occurring in radiotherapy and radiosurgery, and presents the Institute’s research on the biological mechanisms of complications encountered in radiotherapy treatments. Lessons learned from these assessments have stressed the importance of supporting active research in this area. In the coming years, radiopathology research is expected to reinforce knowledge on the risks inherent to radiotherapy and the use of cell therapy in treating radiological burns.

Estimating the dose absorbed by the body or a targeted organ still remains a difficult task today in situations involving internal contamination. It is therefore essential to have an exact idea of the location and residence time of radionuclides in the body. For several years now, the Institute has been conducting research on how to employ innovative techniques to improve risk assessment in this type of exposure situation. The article on analytical ion microscopy highlights research work that has determined the most common sites of uranium accumulation in tissue and cells. In experimental models set up in the Human Health and Environmental areas of the ENVIRHOM program, high-precision maps indicating uranium micro-locations in various sensitive organs were obtained for the first time using analytical ion microscopy. This type of study should lead to a better understanding of the biological mechanisms involved, as well as the physiological, or even pathological, consequences of radionuclide bioaccumulation phenomena.

The impact of nuclear facilities on human health and the environment inevitably leads to the recurrent question on the effects of low-dose exposure. While all categories of the population are concerned, special focus has been placed on children. A German study published in late 2007 put forward that there was a greater risk of leukemia in children (aged from 0 to 4) living within 5 kilometers of nuclear facilities. At the request of the ASN, the French nuclear safety authority, IRSN conducted a critical review of studies published on the subject. The results report that numerous studies have sought to explain the exceptionally high incidence of leukemia observed around certain nuclear sites by focusing on multiple potential risk factors. In most of the studies, quite varied in their approach, researchers come up against methodological limitations that make it difficult to demonstrate the chain of causality. Although the most widely supported hypothesis points
to an infectious cause linked to the mixing of populations around nuclear sites, it is still difficult to determine why the incidence of leukemia observed is higher there than elsewhere, due to insufficient knowledge on the risk factors contributing to childhood leukemia. Large-scale national or international epidemiological studies should therefore be initiated on this subject.

- Monitoring worker exposure is one of the Institute’s major concerns. Through its various activities, IRSN continuously seeks to improve its skills in absorbed-dose assessment. Recent implementation of new risk assessment tools is the result of this policy. The last article in this chapter describes the methods used to improve assessment of the potential cancerous effects of internal contamination in workers from the nuclear industry (Areva) in France. New investigations were conducted to retrospectively assess exposure to uranium and the related chemical products at various workstations. A database on exposure according to the jobs performed was created to reconstruct individual exposure cases. In a context where no data is available on individual internal exposure, this database provides an alternative for assessing exposure retrospectively. It can easily be applied to other facilities in the nuclear industry. This approach can serve as a basis for further epidemiological studies aiming to improve quantification of the risks associated with worker exposure to ionizing radiation.
LESONS LEARNED FROM ASSESSMENTS ON RADIOThERAPY ACCIDENTS and research on radiotherapy complications

Marc BENDERITTER, Fabien MILLIAT, Agnès FRANÇOIS
Radiopathology and Experimental Therapy Laboratory

In the last few years the Institute has been asked to apply its expertise to studying the causes of radiotherapy overdoses and their medical consequences. Having had the foresight to unite multidisciplinary skills in this field several years ago, it was well prepared for this task.

Lessons learned from this experience emphasize the need to develop new research programs to study the medical complications of radiotherapy, in preparation for risk assessments entailed by changes in this discipline.

Radiotherapy and radiation protection applied to patients: benefits and risks

Several hundreds of thousands of patients suffer from cancer every year and more than half of these patients are treated, or have been treated, by radiotherapy applied alone or combined with other treatments such as surgery or chemotherapy. In France, the number of people treated each year by radiotherapy is estimated at 200,000, while in Europe this figure reaches 1.5 million, and 1 million in the United States. Eradication of tumors through radiotherapy is increasingly effective, but the medical world is still confronted with toxic side effects that affect healthy tissue in 5 to 10% of these patients.

Radiotherapy regulations in France are based on the European Council directive 97/43/Euratom of June 30, 1997, which is specific to the radiation protection of patients and has been transposed to the public health code. The two basic principles stipulate that the therapeutic act must be justified, and protection must be "optimized".

Justification consists of providing support to confirm the technical choice made. Optimization aims to reduce the dose received by healthy tissue "as much as possible", while ensuring treatment efficacy.

Accidental overexposure in radiotherapy

In France, since 2005, any event occurring in a radiotherapy facility that could impact human health must be declared to the nuclear safety authority, the ASN. After investigation, the event may be qualified as an incident, or even a severe accident. Since that date, about twenty radiotherapy incidents or accidents have been declared. These overdose accidents in radiotherapy vary in their degree of severity, and are often associated with new radiotherapy procedures, such as conformational radiotherapy (as in the accidents at the university medical center in Grenoble and the hospital in Épinal) or stereotactic radiotherapy (as was the case at the university medical centers in Lyon and Toulouse) (Figure 1).
Between May 2004 and May 2005, at the Jean Monnet Hospital in Épinal, 24 patients were significantly overexposed during prostate cancer treatments based on conformational radiotherapy. On October 12, 2006, the Minister for Health referred the case to the Institute, who was to apply its knowledge in radiopathology “to determine the recommended treatment for each victim of the Épinal radiotherapy accident, providing each person with the best possible health care”. The Minister called on IRSN again in March 2007 regarding the potential overexposure of 423 patients at the Jean Monnet Hospital between 2001 and 2006.

More recently, a third case was referred to the Institute involving patients treated by radiotherapy between 1987 and 2001 in the same hospital. The conclusions of these various assessments revealed deviations from procedure in setting up treatments and providing patient follow-up, as well as certain cases of systematic overexposure. The knowledge and competence acquired by IRSN on the toxic effects of cancer radiotherapy on healthy tissues in the abdominal and pelvic area contributed significantly to assessing the patients’ state of health, classifying the cases according to the severity of complications, and proposing therapeutic lines of action to the ad hoc medical committee in charge of handling the medical treatment of these patients.

The stereotactic radiosurgery accident at the Toulouse university hospital center involved a cohort of 145 patients, treated for benign tumors of the central nervous system (neuromas, meningiomas, pituitary adenomas), malignant tumors (metastatic tumors of the brain, gliomas), and vascular lesions (artery and vein malformations). The ASN called on IRSN to analyze the health risk resulting from patients’ overexposure to radiation, subsequent to inadequate calibration of the accelerator. The circumstances were analyzed in the first assessment report submitted by the Institute on October 16, 2007. Although it involved a large number of patients treated over a period of several months, the radiosurgery accident at the Toulouse medical center was quite different from the radiotherapy accidents that occurred in Épinal. The Toulouse accident was caused by an initial error in accelerator calibration. This error induced deviations in the doses delivered to patients, variable from one patient to another, depending on the targeted volume to be treated and the pathology in question. It was therefore particularly complicated to ascertain the health impact of this accident in terms of radiation-induced secondary neurological complications. Assessment of these consequences required a special scientific approach, conducted in several phases, some at the Toulouse hospital, which at times mobilized twenty to thirty people from IRSN over certain periods. This assessment determined the state of health as well as the psychological state of the patients, and classified them according to the severity of their complications. Individual dosimetry data was reconstructed for each of the 145 patients. The recommendations issued by IRSN were for the most part followed by the ASN in implementing the measures required to manage this accident.

The collective assessments provided by IRSN called on the skills of the Institute’s hospital physicists, dosimetry specialists, and radiopathologists. They contributed to creating a greater awareness of the risks inherent to these medical practices. A certain number of lessons were learned through these different assessments, many of which were inspired by experience acquired in the field of nuclear safety.

Reinforcing equipment inspections before setting into operation

The latest radiotherapy devices can deliver doses more accurately calculated according to the volume of the tumor to be irradiated, sparing the healthy tissue surrounding the tumor. In this way, higher doses can, in theory, be used safely for improved therapeu-
tic effect. These increasingly complex devices feature very sophis-
ticated systems providing automatic adjustment of the radiation
beam, driven by embedded software that also ensures safety func-
tions. However, most of these devices do not allow the radiothera-
pist to directly check the dose actually delivered and its spatial
geometry during treatment sessions. Consequently, the human-
machine interface and, more generally, designed-in operating
safety features on this equipment are critical parameters that
determine the quality and safety of treatments.

IRSN observed that regulations relative to operation of this equip-
ment are based on a European directive that primarily aims to achieve
"free circulation" of medical devices on the European market, based
on compliance with harmonized standards. Yet the conditions for
implementation of this directive do not allow for in-depth examina-
tion of safety design on equipment as complex and innovative as,
for example, the Cyberknife, which features a linear particle accel-
erator mounted on a robot arm, a technology that has the advantage
of performing stereotactic irradiation while avoiding sensitive organs.
The same applies to the process of setting the equipment into
operation, which does not always provide all the necessary safeguards,
especially with regards to calibration. IRSN considers that inspection
of these devices, which intrinsically constitute a significant radio-
logical hazard for patients, should be reinforced, so that applicable
methods approach those practiced in nuclear facilities.

Developing a nuclear safety culture in
radiotherapy clinics

Implementation of the Cancer Plan led to an acceleration in the
acquisition of sophisticated equipment in radiotherapy clinics.
Applying these devices implied more widespread use of high-per-
formance treatments to the benefit of patients, as shown by nation-
wide statistics. However, in spite of the quality assurance techniques
implemented systematically to ensure compliance with operating
procedures, IRSN considers that in several clinics the insufficient
number of radiophysicists, added to the lack of an adequate safety
culture in the radiotherapy teams, leaves too much room open for
undetected malfunctions, especially with regards to equipment
adjustments, which could entail serious consequences for
patients.

The gradual introduction of systematic in vivo dosimetry, the rein-
forcement and recognition of the radiophysicist as a profession, in
terms of both numbers and academic education, and their place in
the organization of radiotherapy departments, are all factors of
progress.

A better understanding of clinical data on
radiotherapy side effects

Several studies conducted in various countries have been published
on the frequency of radiotherapy-related complications for different
types of pathology, and an international classification system exists
to "grade" the severity of these side effects. Certain radiotherapy
clinics provide in-depth, long-term clinical follow-up for their
patients. On the national scale, however, the assessments that IRSN
has conducted at the request of public authorities following radio-
therapy incidents or accidents have brought to light differences in
clinical follow-up protocols, which vary depending on the clinic or
hospital in question.

In the case of the accident in Épinal, the fact that there was practi-
cally no patient follow-up was the main reason that explained why
malfunctions remained undetected, which, in the long run, was
seriously detrimental to the health of several patients. IRSN consid-
ers that there is still room for progress: professional organizations
should initiate action to set up a standard and systematic approach
to clinical follow-up of patients that would facilitate comparison
of professional practices, and research should be conducted to move
forward in radiotherapy protocols. Standard practices in clinical
follow-up would provide an additional safeguard in treatment
safety, since it would also allow alert signals to be passed on to the
radiotherapist.

Amplify research efforts on irradiation
side effects

In France, every year 60% of cancer patients receive external radio-
therapy treatments, for 3.8 million sessions. This technique shows by
far the best cost-efficiency ratio, since 50% of the curative treat-
ments represent only 12% of the costs of cancerology. But the
drawback to this efficiency is the side effects that appear, which
are variable depending on the organ treated. Some of them disap-
pear spontaneously, while others occur inevitably. Unfortunately,
5 to 10% of patients develop more or less serious complications
late in their radiotherapy program. In France, there is no record
of the percentage of cases showing complications late in radio-
therapy treatment, making it extremely difficult to conduct epi-
demiological studies in this area.

IRSN therefore considers that there is a knowledge deficit in risk
assessment and quantification with regards to this type of compli-
cation. Creating a national register to record radiotherapy complica-
tions, and launching epidemiological studies conducted by both
radiotherapists and physicians from the various medical specializations involved (gastroenterologists, pulmonologists, dermatologists, neurologists, etc.) should contribute to better risk assessment of radiotherapy complications.

While funds allocated to cancer research are significant and have led to considerable progress, no specific financing has been dedicated to research on radiotherapy side effects. The Institut Gustave Roussy, one of the most renowned clinics for cancer treatment in Europe, and IRSN have been forerunners in this area for several years. Research conducted through this partnership has started to reveal the biological mechanisms involved in the development of radiotherapy complications. Results have also led to the identification of biomarkers and proposals for new treatments. The first transfers of research results to clinical studies are now under way.

IRSN considers that if patients are to reap the full benefits of this work, translational research programs must be developed to transfer scientific knowledge on radiotherapy complications to the clinical sphere, a major challenge for today and the future. Multi-institutional research programs should unite complementary skills in radiobiology, radiopathology, radiotherapy, and dosimetry to create operational synergy around risk assessment for optimal use of radiation treatments in the medical field.

Even today, the most severe cases of radiotherapy complications cannot be treated through conventional therapeutic programs. IRSN considers that the development of translational research programs aiming to validate the use of new therapeutic approaches, such as cell therapy, in treating severe radiotherapy complications, and securing their transfer to the clinical environment is necessary to ensure the best possible health care for patients in these critical situations.

The Institute’s position concerning R&D on radiotherapy side effects

Research on the biological mechanisms involved in radiotherapy complications

Special focus has been given to intestinal complications, which are part of a change process classically defined in terms of early and late effects. Early effects, or acute radiation-induced enteritis, affect 80% of patients receiving radiotherapy in the abdominal and pelvic area, and may evolve gradually into radiation-induced fibrosis, or chronic radiation-induced enteritis (in 5 to 10% of patients). These complications can have a significant clinical impact due to the chronic nature of the lesions, and the associated morbidity and mortality rates. IRSN developed its research programs based on the assumption that ionizing radiation has a toxic effect resulting from a pathological scarring process in irradiated tissue. The early effects are due to the impact of ionizing radiation on highly proliferating tissue compartments, such as the epithelium, and on micro-vasculization. Early effects participating in the development of late effects are referred to as “consequential fibrosis”. Late effects resulting from consequences on the vascular and mesenchymal compartments are referred to as “primary fibrosis”. Different types of local irradiation are now available for animal experimentation, capable of producing lesions comparable to those observed on different human organs (intestine, skin, lungs).

In this context, IRSN research has set out to achieve the following goals:
- understand the mechanisms involved in the cell and tissue response of healthy tissue located in the irradiated field;
- propose new tools for diagnosis and prognosis of radiotherapy side effects during the clinically silent phase;
- propose new radiation protection treatments for healthy tissue that do not have a protective effect on the tumor.

Research programs that have been conducted approach these questions at different phases, ranging from studies on new therapeutic targets to implementation of second-phase clinical development studies.

Developing experimental models to study radiotherapy complications in the abdominal and pelvic area

The analysis of intestinal radiological complications in humans requires working on a large number of surgical resections, which are relatively difficult to obtain. By working in cooperation with a hospital structure, IRSN can obtain these surgical specimens (such as a resection of irradiated small intestine) and gain access to the “tissue library” of the pathology department. This valuable biological material is used to study the pathological physiology of radiation enteritis in the patient.

An accurate description of the cascade of events occurring in tissue after irradiation requires kinetic studies that cannot be conducted on humans. Experimental models of radiation fibrosis were therefore set up for the rat and mouse to describe morphological changes in the intestine after irradiation. In spite of their limits, these animal models contribute useful information on the processes involved in lesions and scarring of digestive tissue. One of the models calls on surgery to permanently attach a loop of small intestine in the scrotum after castration. In this way, fractionated radiation can be applied to the loop to model primary fibrosis. Another model
developed at IRSN consists of applying single-dose irradiation to a loop of small intestine externalized for radiation purposes only. This model is used to develop consequential fibrosis (Figure 2).

Models using cell cultures to characterize pathological scarring in the intestine have also been developed. Mesenchyme cells, namely sub-epithelial myofibroblasts, smooth muscle cells, and endothelial cells, are the most frequently used in IRSN’s radiopathology laboratory, since they contribute to the toxic effects of radiotherapy in tissue. Based on samples taken from patients, primary cultures are obtained and are used to specifically study the response of a certain type of cell, or the interaction between two cell partners through co-culture techniques.

The purpose is to use these various models to acquire knowledge on the mechanisms associated with the initiation and progression of radiotherapy complications and their treatment. This new knowledge can then be correlated with clinical observations on patients, and new therapeutic targets can be validated in clinical studies carried out with hospital partners.

Characterizing initiation and progression mechanisms of radiotherapy side effects

Part of the general development mechanisms of fibrosis in a radiation-induced intestinal fibrosis model were recently characterized in the IRSN radiopathology laboratory. Two biological factors involved in the initiation and progression of radiation enteritis were studied: the Transforming Growth Factor β (TGFβ) and the Connective Tissue Growth Factor (CTGF).

TGFβ is a ubiquitously secreted cytokine. It plays a role in regulating differentiation and proliferation mechanisms in several types of cells. The three isoforms (β1, 2 and 3) bind to the same receptor, but have different cellular expressions. CTGF is a growth factor involved in fibrosis processes. It is produced in large quantities by special cells (fibroblasts) after activation by TGFβ.

Vascular lesions are considered to be a determining event in the initiation and progression of radiation-induced tissue damage, since they generate ischemia and tissue hypoxia phenomena, which contribute to the noxious effects observed in radiation fibroses. Researchers have sought out the physiological, pathological, and molecular mechanisms involved in the pathogenesis of radiation-induced vascular damage to define therapeutic strategies capable of protecting healthy tissue after irradiation.

To begin, vascular lesions were characterized on the basis of rectum samples from 38 patients subjected to pre-operative radiotherapy to treat adenocarcinoma of the rectum. This work was conducted in cooperation with Dr. E. Deutsch (radiotherapist at the Institut Gustave Roussy in Villejuif) and Pr. J.-C. Sabourin (pathologist at the university medical center in Rouen). The vascular lesions observed were characterized by their focal nature and the absence of systemization. Immuno-histochemical markers revealed vascular fibrosis in these patients, characterized by significant proliferation and migration of the vascular smooth muscle cells and a fibrogenic phenotype (Figure 3). In a later phase, researchers set out to discover some of the physiological and pathological mechanisms that cause radiation-induced vascular fibroses.

The possibility of an integrated response of the entire vessel after irradiation has not yet been explored. Radiation-induced disturbances in vascular matrix remodeling could therefore be the result of dysfunctioning between endothelial cells (EC) and smooth muscle cells (SMC).

Co-culture models were developed for in vitro study of communication between these two types of cell. Results showed that proliferation of SMCs was stimulated in the presence of irradiated ECs. They also revealed that SMCs had a greater tendency to migrate within a lesion area in the presence of irradiated ECs. As concerns the fibrogenic phenotype, it was shown that several proteins (CTGF, PAI-1, COL1A2 and COL3A1) involved in the cellular mechanisms stimulated after irradiation increase in SMCs in the presence of irradiated ECs. To characterize the soluble factors that may be involved in the induction of this fibrogenic differentiation, secretion of the growth factor TGFβ1 was measured after EC irradiation. This secretion was stimulated in the irradiated ECs. Results suggest that the TGFβ1 from the ECs could activate signaling pathway in SMCs through paracrine effects. The molecular cascade of TGF signaling was characterized. Various techniques from molecular biology (transfection, antisense Smad3 siRNA, gene reporter), pharmacology (anti-TGFβ-RII neutralizing antibody), and immunocytochem-
This work developed new knowledge on the molecular mechanisms at work in vascular lesions after irradiation. It demonstrates the importance of relationships between the different types of vessels cells, and the role of the TGFβ biological factor.

Another example from the study on the role of CTGF also illustrates the Institute’s approach in research on the biological mechanisms involved in radiotherapy complications. The IRSN radiopathology laboratory recently characterized part of the general radiation-induced fibrogenesis mechanisms in a model of radiation-induced intestinal fibrosis, radiation enteritis. In genomics experiments (using a DNA chip) conducted on human fibrosis biopsies, researchers revealed the role of a molecular cascade that depends on small GTPases from the Rho family and their effectors, ROCK proteins. These intracellular signaling proteins intervene in the organization of the cytoskeleton of myofibroblasts by controlling actin polymerization. In vitro research specified that the Rho/ROCK cascade is involved in regulating the expression of pro-fibrosis genes such as CTGF and extracellular matrix molecules (collagen, fibronectin, MMP, etc.) (Figure 4).

In other work carried out by the radiopathology laboratory, results showed that inhibition of the Rho pathway makes it possible to regulate the radiation-induced thrombogenic and pro-inflammatory phenotype in endothelial cells. This cellular and molecular characterization work led to an in vivo assessment on the efficacy of Pravastatine, a pharmacological inhibitor of the Rho/ROCK pathway. This molecule was chosen because it has been used clinically in treating cardiovascular pathologies for over ten years, simplifying transfer to a clinical environment.

Proposing new therapeutic alternatives for treating radiotherapy side effects

Studies began by evaluating the preventive effect of Pravastatine on the development of late radiation-induced intestinal fibroses in the rat. Histopathological analysis of the tissue showed that this treatment controlled radiation-induced intestinal toxicity in the medium term (15 weeks) by restoring the structure of the external muscle tunic, while at the same time reducing the extent of fibrosis areas. The most significant result was observed 26 weeks after irradiation. The tissue was almost completely restored in the treated group. In other experiments conducted in cooperation with the group led by Pr. J. Bourhis from the Institut Gustave Roussy, Pravastatine did not result in protection of the tumor in vivo and even increased the tumor’s sensitivity to radiation in vitro. The difference in the effect observed on healthy tissue and on the tumor in pre-clinical experiments encouraged researchers to investigate the protective effect of Pravastatine on patients treated for cervi-
3.1

cal cancer by pelvic radiotherapy. The effect was compared to that obtained through placebo treatment of digestive tract, bladder, and vagina symptomatology observed 18 months after radiotherapy.

In a later phase, the effect of Pravastatine on acute radiation-induced toxicity, its impact on patient comfort, and its effectiveness against fibrosis will be tested. This protocol was assessed by the ethics committee of the Institut Gustave Roussy and received a favorable opinion. An application has been submitted for authorization to begin clinical research.

Radiopathology research perspectives

Lessons learned from assessment of radiotherapy accidents emphasize the importance of supporting active research in radiopathology. Research and assessment activities concerning high-dose irradiation in the coming years will be built around two major programs at the Institute: an experimental research program on the risks involved in using ionizing radiation to treat cancer (ROSIRIS), conducted in association with Inserm, and a cell-therapy program that aims to promote innovative treatment of irradiated tissue by transferring cell therapy to the clinical environment, performed in cooperation with the Armed Forces health service.

References

NEW BIOINDICATORS SET TO WORK
in studying the Dakar accident

On June 3, 2006, after taking a gamma-ray image on a worksite in Dakar, Senegal, an iridium-192 source came loose from its guide tube and remained trapped in the ejection duct. The duct and guide tube were then stored in an office for several weeks until July 31, 2006, when the equipment was packaged and sent by express delivery to Abidjan in the Ivory Coast. The first time the gamma ray projector was used at Abidjan, the technician realized that an object was jammed in the ejection tube, keeping the source from moving, and discovered that the iridium source had been removed from its holder.

IRSN was called on to conduct a dosimetric and biological assessment on the 65 people potentially irradiated (either during the storage period, in preparation and handling of the package at Dakar, in air transport, or while attempting to shoot images at Abidjan) and to issue an opinion on the severity of radiation-induced damage on the most affected victims. Four of these people presented localized radiation-induced lesions and were taken to the Percy Military Hospital in Clamart, France beginning on August 30, 2006.

In a large-scale accident, the main problem is sorting the victims, based on the absorbed dose of radiation or the severity of radiation-induced damage. In the Dakar accident, it was difficult to sort the victims because of the time that had elapsed between the date of irradiation and the moment that people became aware of the accident, resulting in a period that could have reached several weeks in certain cases.

Assessment of the absorbed dose was conducted on all victims using biological dosimetry. Dicentric chromosomal aberrations in blood lymphocytes were counted in two phases: a quick classification phase based on 50 cells observed per person, followed by a much longer, but more accurate phase based on the study of 250 to 500 cells per person.

New methods tested
Other methods for assessing radiation-induced damage were also used to analyze this accident. The purpose was to determine whether it was possible to classify a large population into three or four categories based on simple criteria.

For the first time, dicentric aberrations were systematically detected through an automated process based on analyzing microcopy images of irradiated lymphocyte cultures.

Of the 46 individuals tested in this manner, automatic detection proved to be more efficient than the manual observation of 50 cells adopted in the sorting phase.

It was less efficient, however, than the conventional assessment method applied to 500 cells.

Development of this approach should nonetheless be pursued, especially since it could also be used to assess irradiation heterogeneity.

Another technique explored, based on oligonucleotide chips (Figure 1), consists of
Figure 1  Principle of competitive hybridization on an oligonucleotide chip.

analyzing the levels of expression of certain genes after irradiation. For example, the level of expression of 25,000 genes was measured on victims of the Dakar accident using blood lymphocytes from 20 individuals subjected to varying degrees of exposure. After analyzing the results, 22 candidate genes were selected, whose levels of expression seemed to indicate a level of exposure. Unfortunately, technical problems related to sample transport made it impossible to completely validate these results.

An initial assessment of irradiation after an accident is classically obtained by a full blood count, which provides information on the state of the blood (red blood cells, white blood cells, platelets), thereby reflecting the state of the bone marrow, which may be destroyed by irradiation, affecting the person’s vital prognosis. Dosing the plasma concentration of a specific growth factor, Flt3-ligand, also provides an indication that bone marrow activity has resumed. These two measurements were taken simultaneously on all potentially irradiated individuals. Combined analysis of the complete blood count and Flt3-ligand values resulted in a unique severity score, which showed good agreement with the irradiation dose esti-
mated using dicentric chromosomal aberration analysis (Figure 2).

This correlation also made it possible to quickly identify those victims who were at the greatest risk. Nonetheless, for the Dakar accident, the significant interval between exposure and analysis limited the validity of the approach. It will require confirmation through retrospective studies on other irradiation accidents.

In conclusion, the Dakar accident provided the opportunity to implement and demonstrate the validity of a certain number of innovative experimental approaches resulting from research conducted by IRSN throughout the years on radiation accidents.

Figure 2: Linear regression analysis between the complete blood count/Flt3-ligand score and the irradiation dose defined by cytogenetic biological dosimetry. Results show that the score can be used to identify patients who have received an irradiation dose greater than 0.5 Gy.
To understand how radionuclides are transferred and transported into ecosystems and humans through chronic exposure, maps must be established showing the distribution of contaminants in the biological structures targeted by bioaccumulation phenomena. Among the various techniques used for analysis and imaging, ion microscopy, or the SIMS technique, based on coupling secondary ion emission with a mass spectrometer, represents a powerful tool capable of recognizing the locations of radionuclide accumulation in tissue and cells.

The fate of uranium

Initiated in 2001 at IRSN, the ENVIRHOM research program seeks to broaden knowledge on the risks that prevail when humans and ecosystems are chronically exposed to low-dose ionizing radiation. One of the main subjects of study in the program is the biokinetics of radionuclides in organisms and their biological impact under exposure conditions of this type. The program has therefore placed particular focus on cell and tissue structures capable of accumulating the incorporated radionuclide(s), thereby contributing new knowledge towards a better understanding of the mechanisms at work and the biological and clinical consequences of these bioaccumulation phenomena.

To study radionuclide accumulation processes in living organisms, various experiments were conducted on rodents contaminated by adding uranyl nitrate to their drinking water [Paquet et al, 2006; Donnadieu-Claraz et al, 2007], and on the fresh-water bivalve Corbicula fluminea, invertebrate mollusks exposed to uranium through gill respiration and food capture [Simon et al, 2004 and 2005; Fournier et al, 2005].

This discussion focuses on the study of the uranium distribution profiles in the targeted organs after internal contamination through chronic exposure to this radionuclide. The biological matrices analyzed were the renal cortex in the rat, and the gills of Corbicula fluminea. Various analysis techniques were used, including SIMS (Secondary Ion Mass Spectrometry) and EFTEM (Energy Filtered Transmission Electron Microscopy), along with spectroscopic methods such as EELS (Electron Energy Loss Spectroscopy) and ESI (Electron Spectroscopic Imaging).

This research set out to examine the hypothesis postulating that uranium incorporated through chronic contamination modifies iron metabolism [Donnadieu-Claraz et al, 2007], since uranium uses the same transporters as iron. A comparative study of the retention sites of these two elements was therefore conducted using the above-mentioned analytical methods.
A primary ion source generates the incident beam, which is then steered, focused and rastered over the surface to be analyzed using a system based on electrostatic lenses and raster steering deflectors. The sputtered secondary ions are accelerated and focused in the secondary ion column, and directed towards the entrance slit to the mass spectrometer. The latter consists of an electrostatic sector, which sorts the ions according to a given energy, and a magnetic sector, which selects the ions according to their mass-to-charge ratio. At the spectrometer exit, the resulting secondary ion beam is directed towards an electron multiplier connected to an electronic system. The result provides the mass spectra, isotopic ratio measurements, and concentration profiles as a function of the profile depth.

The lenses located in the secondary ion transfer column before the mass spectrometer are used to form an image of the location from which the particles were sputtered from the solid surface. Ion imaging is used to represent the spatial distribution of the various elements under study in the selected matrix.

Complementary analysis techniques

The SIMS technique
The purpose of SIMS (secondary ion mass spectrometry), or analytical ion microscopy, is to obtain an elemental and isotopic analysis of a solid surface using an ion beam coupled with a mass spectrometer. The principle consists of bombarding the sample using a charged particle beam set to an accelerating voltage of roughly 10 KeV. The primary ion beam impacts the target particles, ejecting those located on the free surface, a portion of which is ionized spontaneously. These “secondary ions” are then accelerated and analyzed using a mass spectrometer to reconstruct the chemical and isotopic composition of the sample surface.

The SIMS instrument used in this study (the Caméca IMS 4F-E7), conceived by Castaing and Slodzian [Castaing et al, 1962; Slodzian, 1964], is represented schematically in Figure 1. A primary ion source generates the incident beam, which is then steered, focused and rastered over the surface to be analyzed using a system based on electrostatic lenses and raster steering deflectors. The sputtered secondary ions are accelerated and focused in the secondary ion column, and directed towards the entrance slit to the mass spectrometer. The latter consists of an electrostatic sector, which sorts the ions according to a given energy, and a magnetic sector, which selects the ions according to their mass-to-charge ratio. At the spectrometer exit, the resulting secondary ion beam is directed towards an electron multiplier connected to an electronic system. The result provides the mass spectra, isotopic ratio measurements, and concentration profiles as a function of the profile depth.

The lenses located in the secondary ion transfer column before the mass spectrometer are used to form an image of the location from which the particles were sputtered from the solid surface. Ion imaging is used to represent the spatial distribution of the various elements under study in the selected matrix.

Figure 1 Schematic representation of the Caméca SIMS 4F-E7 instrument.
All the sources, the beam transfer components and the sample chamber are placed under a “secondary vacuum” of approximately $10^{-13}$ bar.

Two primary ion sources may be used, the choice depending on the type of element to be analyzed. To detect positive secondary ions, a negative primary ion beam is selected ($O_2^+$, $O^-$ ions from an oxygen source). Conversely, sputtering negative secondary ions requires a positive primary ion beam ($Cs^+$ ions from a cesium source).

<table>
<thead>
<tr>
<th>Performance and limitations of the SIMS technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>- SIMS can detect and measure almost all elements in the periodic table, including their isotopes.</td>
</tr>
<tr>
<td>- Sensitivity is approximately 1 atomic ppm for most elements, but may reach up to 1 atomic ppb for some. This technique can be used to detect trace elements, and even ultra-trace elements.</td>
</tr>
<tr>
<td>- Elemental distributions for a given surface can be determined using a lateral resolution of approximately 1 µm, with concentration profiles that depend on the profiling depth in the matrix, at a resolution of approximately 1 nm.</td>
</tr>
<tr>
<td>- The instrument has high mass resolution (up to approx. 10^6), mass resolution is defined by the expression $R = M/\Delta M$, where M is the molecular mass of the detected ion. It can discriminate the molecular mass of two very close elements, separated by a distance of $\Delta M = 10^{-4}$ M.</td>
</tr>
<tr>
<td>- SIMS is a destructive analysis method: the sample is eroded during the experiment.</td>
</tr>
<tr>
<td>- It is difficult to determine the absolute concentration of an element, which is one of the major drawbacks of this technique. The secondary ion emission process is too complex to establish a global model of the analysis process, not to mention analytical quantification [Wittmaack, 1980; Benninghoven, 1987]. Obtaining an absolute concentration can only be achieved by taking measurements on standard samples from the same matrix as the sample to be analyzed, at known concentrations of the element, distributed homogeneously throughout the matrix. In the case of this study, it would have been very difficult to prepare standard biological samples.</td>
</tr>
<tr>
<td><strong>The EFTEM technique</strong></td>
</tr>
</tbody>
</table>

This instrument offers the possibility of using electron energy loss spectroscopy (EELS) and electron spectroscopic imaging (ESI) to characterize and map the chemical elements in the sample at very high sensitivity and high lateral resolution, i.e. approximately 10 nanometers [Bordat et al, 2000; Lechaire et al, 2008].

The technique is based on analyzing the energy distribution of fast incident electrons, initially almost monochromatic, once they have crossed through the sample. Multiple physical processes can cause electrons to lose energy as they penetrate through a solid. High electron energy loss analysis focuses on the excitation states of electrons produced by the target particles, based on atomic orbitals as they approach the Bloch state and ionization. The ionization thresholds are set to the core electron binding energy of the sample and are superimposed on a permanent decreasing field. When coupled with energy-filtered imaging, this technique can be used to map the various elements to be found in the structure. This examination, conducted in cooperation with the Inra Nurelice Laboratory in Jouy-en-Josas, was performed on a EFTEM Zeiss EM 902.

**Experiment protocols and preparation of biological samples**

Animal experiments involving contamination of *Corbicula fluminea* bivalves were carried out in the IRSN radioecology laboratory [Simon et al, 2004 and 2005]. Collected in the Gironde region, from Lac Sanguinet, the mollusks were contaminated with a uranyl nitrate solution introduced in the aquarium, at a uranium content of 500 µg/l and 20 µg/l. Exposure time was 10 days for the higher concentration, and 10, 40, and 90 days for the lower concentration. The bivalve gills were then sampled, prepared for observation under an optical microscope and analyzed with SIMS and EFTEM techniques.

Preparation of a biological sample for study under a charged particle beam must meet several requirements:
- for SIMS, the surface of the sample must be perfectly flat and polished. Otherwise, the ion beam produced from the sample surface is not isotropic and the resulting image is always out of focus, regardless of how finely the instrument has been tuned;
- biological samples are not good conductors, and may even be isolating.

Bombarding the sample with ions or electrons may produce charge effects, a phenomenon that results in charge accumulation on the sample surface.

To correct this problem, the slices are placed on a conducting plate (gold plate finished to a mirror surface) for SIMS analyses, or a gold grid is laid on the sample for transmission electron microscopy.

Gills of control bivalves not exposed to uranium were also prepared for examination using these various analysis techniques. Animal experiments involving contamination of rats were carried out by IRSN at the radiotoxicology laboratory [Paquet et al., 2006]. Adult Sprague-Dawley rats were subjected to chronic contamination for periods of nine and 18 months through uranium ingestion by drinking mineral water containing enriched and spent uranyl nitrate.
The incident electron beam energy was 120 KeV.

### Uranium distribution in gills of *Corbicula fluminea*

The gill is an organ located on both sides of the mollusk’s body, in the form of inner and outer demibranches. Each demibranch consists of an ascending limb and descending limb, connected to the gill axis (Figure 2).

The basic element of the gill is the filament (Figure 3). All filaments are arranged in series, parallel to each other. They are responsible for respiration and capturing food particles through cilia surrounding the filaments. Lateral cilia circulate water through the gill tissue, lateralfrontal cilia collect food particles, and frontal cilia carry food to the body of the bivalve.

Results obtained using SIMS

The mass spectra obtained on control samples and contaminated samples (Figure 4) reveal the presence of uranium in the tissue in ten days exposure period. The fact that there is no peak at mass 238 in the control sample mass spectrum (< 1 count per second) indicates that the uranium detected in the contaminated sample comes only from the contaminant and confirms that the SIMS technique is appropriate for detecting trace amounts of uranium in the *Corbicula fluminea* samples. Ion images of 40Ca+ show gill morphology (Figure 5). Ion images of 238U+, representing contamination ingested at 20 µg/l for 90 days, reveal uranium distribution within the gills.

Distribution is heterogeneous (forming clusters greater than 1 µm) and is located mainly in the filaments and on the periphery of the interlamellar junctions. This result holds for all types of contamination studied.

Table 2 gives all the results obtained. A greater accumulation of uranium appeared in the gills when contamination was ingested at 500 µg/l, but uptake in this case occurred soon after exposure began. The exposure time did not seem to significantly increase the level of uranium retained in the gill structure.

### Comparative study of retention areas between uranium and iron using SIMS

The analysis results on iron detected in the contaminated mollusk gills were comparable to those obtained from the control samples (Figure 6), where iron was retained in large aggregates (a few micrometers in diameter) in the gill matrix.

For bivalves exposed to uranium, ion images of 56Fe+ and 238U+ respectively. The uranium content in the mineral water was 40 mg/l, corresponding to a daily ingestion of approximately 1 mg of uranium per animal. The renal cortex samples were prepared for SIMS analyses. Rat kidneys that had not been contaminated by uranium were also examined.

### Stringent experimental conditions for SIMS and EFTEM analyses

SIMS analysis experimental conditions (choice of primary ion beam, primary ion beam intensity, primary and secondary ion beam accelerating voltage, raster pattern, etc.) are shown in Table 1. A preliminary study was carried out to determine the optimum experimental conditions, since a compromise must be found between sputtering speed, which must not be too high, and detection sensitivity, which must be as high as possible.

Analysis were conducted in several steps. For uranium detection, the mass spectra were obtained around the mass of isotope 258 of uranium, then, in the same analysed area, elemental ion images were captured at a calcium mass of 40, to visualize the tissue morphology, and 238 for uranium. These analyses were carried out at low mass resolution (M/ΔM = 300). To detect the main iron isotope at mass 56, it was necessary to operate at high mass resolution (M/ΔM = 3,000) to separate detection of the very close 40Ca16O+ group, also present in biological tissue. For each range studied, mass spectra and ion images were recorded for 40Ca+, 56Fe+, and 238U+.

In studies carried out using EFTEM, iron and uranium were identified using characteristic rays Fe-L2,3 (708 eV) and U-O4,5 (96 eV). The filtered image showing the tissue structure was obtained at an energy loss of 250 eV. The incident electron beam energy was 120 KeV.

<table>
<thead>
<tr>
<th>Experimental conditions</th>
<th>238U+ detection</th>
<th>56Fe+ detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary ion beam</td>
<td>O2+</td>
<td>O2+</td>
</tr>
<tr>
<td>Primary ion beam accelerating voltage</td>
<td>12.5 KeV</td>
<td>12.5 KeV</td>
</tr>
<tr>
<td>Primary ion beam intensity</td>
<td>7.10^-9A</td>
<td>2.10^-9A</td>
</tr>
<tr>
<td>Secondary ion beam accelerating voltage</td>
<td>4.5 KeV</td>
<td>4.5 KeV</td>
</tr>
<tr>
<td>Primary ion beam raster pattern</td>
<td>200 x 200 µm^2</td>
<td>100 x 100 µm^2</td>
</tr>
<tr>
<td>Mass resolution</td>
<td>M/ΔM = 300</td>
<td>M/ΔM = 3,000</td>
</tr>
</tbody>
</table>

Table 1 Experimental conditions for analyses based on the SIMS technique (Caméca 4F-E7).
Comparison of results obtained using other analysis and imaging techniques

The results obtained in this study were compared with those achieved using other analysis techniques, namely the NanoSIMS 50 (Laboratoire Léon Latarjet/Institut Curie-Orsay) and energy-filtered transmission electron microscopy (Laboratoire Nurélice/Inra, Jouy-en-Josas).

The Cameca NanoSIMS 50 is a new-generation instrument. It features a smaller primary ion beam (which can reach roughly 20–30 nanometers) than the SIMS instrument in our laboratory (measuring about one micrometer), providing ion images with better lateral resolution.

were compared. Superimposing the SIMS images (Figure 7) shows that uptake of these two elements does not occur at the same locations.

<table>
<thead>
<tr>
<th>Condition</th>
<th>20 µg/l 10 days</th>
<th>20 µg/l 40 days</th>
<th>20 µg/l 90 days</th>
<th>500 µg/l 10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>238U⁺ (counts/s)</td>
<td>&lt; 1</td>
<td>70 - 90</td>
<td>50 - 80</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 2. 238U⁺ results according to bivalve exposure conditions.
### 3.3 Uranium distribution in the renal cortex of the rat

#### Results obtained using ion microscopy

The renal cortex consists of glomeruli, proximal kidney tubules (PKT), Henlé’s loop, distal kidney tubules (DKT), and collecting ducts (Figure 10).

Results obtained using EFTEM (Figure 9) show distributions for uranium (red) and iron (blue) on the image of the contaminated gill structure (gray). These chemical images, taken at a lateral resolution of roughly 20-30 nanometers, demonstrated that, aside from uranium accumulation in vessels located inside gill filaments (confirming SIMS results), uranium was also present inside the frontal and lateral cilia located around the outside of the filaments, with cilia thickness measured at about 200 nm. It is also interesting to note that iron accumulates in different locations than the contaminant.

Analysis of the EELS spectrum produced by the primary electron beam, carried out on cross-sections through control gill samples, did not detect any uranium, thereby demonstrating that any naturally-occurring trace of this radionuclide present in the samples did not influence the measurement results.

These various areas can be distinguished on both cross-sectional views observed under an optical microscope and on the SIMS images shown in Figure 11. Ion images of $^{40}$Ca$^+$ are representative of the tissue structure that can be observed through an optical microscope. These points of interest were studied for two contamination periods, one lasting nine months, and the other 18 months.

The comparison of mass spectra (Figure 12) performed on a control sample and a contaminated sample for 18 months revealed uranium in the tissues subsequent to contamination. After a contamination period of nine months, spectral analyses only showed uranium retention in the proximal kidney tubules. Overlaid ion images of $^{40}$Ca$^+$ and $^{238}$U$^+$ (represented in gray and red, respectively) obtained from this structure reveal a heterogeneous distribution of uranium in the form of clusters from one to two...
### Figure 6
Control sample of Corbicula gill. a) Mass spectrum. b) Ion images of $^{40}$Ca$^+$ and $^{56}$Fe$^+$ (100 x 100 µm$^2$).

### Figure 7
Overlaid images of Corbicula fluminea gills contaminated with uranium (500 µg/l, 10 days); $^{40}$Ca$^+$ (blue), $^{238}$U$^+$ (pink), $^{56}$Fe$^+$ (green).

### Figure 8
Overlaid ion images of $^{40}$Ca$^+$ (red), $^{238}$U$^+$ (green), $^{56}$Fe$^+$ (blue) obtained using a NanoSIMS 50 on a gill contaminated at a rate of 500 µg/l over a period of 10 days.
3.3

3.3 causing a functional deficiency of the kidney. To confirm this hypothesis, it would be prudent to envisage conducting animal experimentation where the rat is contaminated over at least nine months, then not exposed to uranium for a few months before being sacrificed to observe whether the uranium is eliminated after uptake in the proximal kidney tubules.

Comparative study of retention areas between uranium and iron using SIMS technique

SIMS data (mass spectra and ion images) obtained from the renal cortex of the control rats indicate that iron was distributed in a large number of sizeable clusters throughout all structures (Figure 15). Analysis results on the contaminated rats are comparable to those obtained on the unexposed animals. Overlaid ion images

micrometers in diameter (Figure 13). However, the results shown in the mass spectra and elemental images obtained from exposed rodents over an 18-month period indicate that the radionuclide accumulated in all the cortex structures: glomeruli, proximal kidney tubules, Henlé’s loop, distal kidney tubules, and the collector ducts (Figure 14). Uranium was not distributed homogeneously throughout the various structures, and the amount retained appears greater for the concentration ingested over 18 months than for the 9-month contamination period.

These significant results suggest that the uranium uptake kinetics depend on the period of exposure of the rat. Accumulation in all the renal cortex structures of the animals exposed for 18 months may perhaps be related simply to the long lifetime of the rats,
3.3

Figure 12 Mass spectra. a) Control kidney. b) Contaminated kidney.

Figure 13 Overlaid ion images of rat kidneys, $^{238}$U$^+$ (red) and $^{40}$Ca$^+$ (gray). Contamination at 9 months.

Figure 14 Overlaid ion images of rat kidneys, $^{238}$U$^+$ (red) and $^{40}$Ca$^+$ (gray). Contamination at 18 months.
ated with a mass spectrometer revealed, for the first time, heterogeneous distributions of this radionuclide in two biological matrices. In the gills of the *Corbicula fluminea* bivalve, the experiment results (mass spectra and ion images) showed that uranium accumulated in clusters in the gill structure, just 10 days after exposure to a very low concentration of this element in water (20 µg/l).

In rats contaminated over periods of nine and 18 months through ingestion of 40 mg/l of uranium in their drinking water, SIMS data suggested uranium retention kinetics in the renal cortex that depend on the contamination period. In animals exposed for nine months, only the proximal kidney tubes showed any accumulation of uranium, whereas in rodents of *56Fe*⁺ et *238U*⁺ suggest that, as in the case of the bivalves, there is no interaction between iron and uranium (*Figure 16*).

### Conclusions and outlook

Conducted within IRSN’s ENVIRHOM research program, this study showed that analytical ion microscopy, or SIMS, in the laboratory is completely adequate to study distribution profiles of radionuclides present in low concentrations in biological matrices after internal contamination.

In the case of uranium contamination resulting from chronic exposure, the ion beam analysis and imaging technique associated with a mass spectrometer revealed, for the first time, heterogeneous distributions of this radionuclide in two biological matrices. In the gills of the *Corbicula fluminea* bivalve, the experiment results (mass spectra and ion images) showed that uranium accumulated in clusters in the gill structure, just 10 days after exposure to a very low concentration of this element in water (20 µg/l).

In rats contaminated over periods of nine and 18 months through ingestion of 40 mg/l of uranium in their drinking water, SIMS data suggested uranium retention kinetics in the renal cortex that depend on the contamination period. In animals exposed for nine months, only the proximal kidney tubes showed any accumulation of uranium, whereas in rodents
exposed for 18 months, all the structures in the renal cortex contained clusters of the contaminant.

The study also showed that, for both biological matrices, there was no correlation between iron and uranium uptake points.

All these results were confirmed and validated with results achieved using other analysis techniques: ion microscopy with the Cameca NanoSIMS 50, and the EFTEM technique, combining electron energy loss spectroscopy (EELS) with electron spectroscopic imaging (ESI).

This research also demonstrated that these techniques are capable of providing complementary information. In the context of studies conducted on ecosystems, this experimental contribution will be pursued on another biological matrix: the Danio fish, focusing on the reproductive system and larvae.

With regards to studies on the rat, SIMS analyses will continue, but will focus on another radionuclide, $^{137}$Cs. Rat organs such as the liver, kidney, thyroid gland, skeletal muscle, and the heart will be examined.

Study of uranium distribution on the scale of the cell is also envisaged. Preliminary analyses carried out on cell cultures appear promising.

References


3.4

EPIDEMIOLOGICAL STUDIES OF LEUKEMIA INCIDENCE in children and young adults living around nuclear facilities: a critical review

Dominique LAURIER, Marie-Odile BERNIER, Sophie JACOB, Klervi LEURAUD, Camille METZ, Éric SAMSON
Epidemiology Laboratory

Patrick LALOI
Radiobiology and Epidemiology Department

An epidemiological study published at the beginning of 2008, concerning the entire fleet of nuclear power plants in Germany, showed that there was an increased risk of developing leukemia in children under five years of age living less than five kilometers from a nuclear power plant [Kaatsch et al, 2008]. A great deal of research has been carried out on this subject since the early 1980s [Laurier, 1999; Laurier, 2002]. To situate the results of the German study in the context of available epidemiological knowledge, the epidemiology laboratory at IRSN compiled data on this subject and conducted a critical analysis of results relative to the risk of leukemia in children and young adults below the age of 25 living in the vicinity of nuclear facilities. The conclusions of this study were published in a report in April 2008 [Bernier et al, 2008]. It is based on the most exhaustive as possible review of epidemiological studies published in the international literature describing the frequency of leukemia in areas close to nuclear facilities located in different countries around the world. The published results were then submitted to critical review. Discussions on the results also took into consideration conclusions from studies that did not focus on nuclear facilities, within the methodological limits associated with descriptive epidemiological studies. The potential causes of childhood leukemia and the main hypotheses explored to explain the localized incidence clusters observed in the vicinity of certain nuclear facilities were also discussed.

Background information and methods

Leukemia is not a frequent pathology in children: every year in France there are about 470 new cases and 75 deaths from childhood leukemia for a population of about 12 million children (aged 0 to 14) [Clavel et al, 2004]. Acute lymphoblastic leukemia accounts for nearly 80% of leukemia incidence in children. A peak appears in the frequency of this type of leukemia between the ages of 1 and 6. The few recognized risk factors of childhood leukemia include trisomy 21, Fanconi anemia, external exposure to high-dose ionizing radiation, and administration of the alkylating drugs used in chemotherapy. Other factors that are suspected but whose role has not yet been confirmed include low-dose exposure to ionizing radiation, electromagnetic fields, pesticides, benzene, infectious agents, and others. According to estimations by some authors, for example, natural radiation could be responsible for nearly 20% of cases of childhood leukemia in Great Britain [Wakeford, 2004].

Although several potential risk factors have been put forward, today there is little information available to explain the causes of leukemia, and 90% of leukemia cases remains unexplained.
The method used for this review is based on bibliographical research compiled from the Scopus and PubMed databases. Other documents were obtained from IRSN archives and through direct contact with researchers in France and abroad. In total, several hundreds documents (reports, articles in scientific journals) on the risk of leukemia in young people aged under 25 living around nuclear sites were collected. Several types of study of varying quality have been conducted, such as local and multi-site cluster studies, control and cohort case studies, radioecological studies, and dosimetry work, to name a few. The review made a distinction between two types of research:

- descriptive studies, which aim to estimate the frequency of leukemia incidence and detect any excess risk within a given population;
- analytical studies, that seek to determine the factors that could explain any excess risk of leukemia incidence within a population.

**Review of descriptive studies**

Descriptive studies try to answer the question: "Is the frequency of leukemia in the vicinity of a particular site higher than elsewhere?". It is important to emphasize that these studies are not designed to search for the factors that explain cases clusters. The methods employed are generally quite simple and are based on counting the number of cases in the surrounding areas, most often defined by concentric circles (*Figure 1*).

In total, results from descriptive studies are available for 198 nuclear sites, located in ten different countries: Great Britain, Germany, France, Sweden, Spain, the USA, Canada, Japan, Switzerland, and Israel. The results of all these studies were reviewed, making a distinction between local studies focused on a specific site, and multi-site studies simultaneously covering a group of sites within a given country, thereby covering a larger population. Evaluation criteria were applied in order to assess the reliability of collected results.

Criteria were defined according to the type of data in question (morbidity/mortality), the geographical area studied (relevance of the size and boundaries of the areas considered), the power of the study (ability to reveal a low excess risk) and the statistical significance of any observed excess, the validity of the statistical methodology, the reproducibility of results (excess revealed by different methods), and lastly, the persistence of excess over time (*Figure 2*).

Among the 198 sites reported, three excesses met the stated evaluation criteria and were considered as confirmed clusters. These sites were Seascale (near the Sellafield plant in England) [Black, 1984; COMARE, 1996], Thurso (near the Dounreay plant in Scotland) [Heasman et al, 1986; COMARE, 2005] and Elbmarsch (near the Kruemel plant in Germany) [Grosche, 1992; Wichmann, 2004; Hoffmann, 2007]. Other clusters were well documented, especially in Great Britain, near the Aldermaston and Burghfield sites [COMARE, 2005; Roman et al, 1987] and in France, near the reprocessing plant at La Hague [Viel, 1995; Guizard et al, 1997], but the data currently available is not sufficient to confirm excess risk (*Figure 3*).

Among the multi-site studies surveyed (25 studies in eight different countries), those that best met the assessment criteria were the recent studies conducted in Great Britain [COMARE, 2005], in Germany [Kaatsch, 2008] and in France [White-Koning et al, 2004] (*Figure 4*). These studies do not indicate, across all the sites examined, an increased risk of leukemia in children aged 0 to 14 or young adults (aged 0 to 24) near nuclear facilities. Few studies provide results specific to the age group ranging from 0 to 4 years. Given the current state of knowledge, however, the results of the German study are not supported by studies conducted in other countries. In particular, recent geographic studies conducted in Great Britain [Bithell, 2008] and France [Laurier et al, 2008] do not reveal any increase in the risk of leukemia incidence in children aged 0 to 4 in the vicinity of nuclear power plants. Other studies have shown local excess of childhood leukemia in areas where there are no nuclear facilities. Furthermore, several studies...
3.4 People and ionizing radiation

Studies on the risks of leukemia around nuclear sites are numerous and diverse, making it necessary to examine each new result in the light of available scientific knowledge. Lastly, it is important to point out the significant limitations inherent to descriptive studies, which make it difficult to interpret results. Studies on the risks of leukemia around nuclear sites are numerous and diverse, making it necessary to examine each new result in the light of available scientific knowledge.

Figure 2 Analytical approach.

Figure 3 Results per site: 198 sites, 10 countries.

show spatial and temporal clusters of leukemia incidence in children that are not related to the presence of any potential sources of risk [Bernier et al, 2008].
Review of analytic studies on the potential causes of observed local excess

Subsequent to descriptive studies in which leukemia clusters were observed close to certain nuclear facilities, several investigations were launched to identify factors that might explain these excesses, in particular close to the sites at Sellafield, Dounreay, Aldermaston, and Burghfield in the United Kingdom, La Hague in France and Kruemmel in Germany. These works were based on various approaches and protocols, including epidemiological studies (type of geography, control groups, cohorts), measurement of doses received by the population, and radioecological assessments. Three main hypotheses were put forward to try to explain why the observed risk was higher in the vicinity of certain nuclear facilities:

- a link with environmental exposure due to radioactive or chemical discharges from nuclear facilities;
- a link with fathers' exposure to ionizing radiation before children were conceived;
- an infectious cause related to the population mixing with large-scale construction sites, such as that of a nuclear power plant.

Some research focused on a possible connection to environmental exposure caused by radioactive or chemical discharges from nuclear facilities, as in Great Britain [COMARE, 1988; COMARE, 1989; COMARE, 1996] or in France, in work by the Nord-Cotentin Radioecology Group [GRNC, 1999; GRNC, 2002]. Results indicate that doses received due to discharges from nuclear facilities are low and cannot explain the excess risk observed at specific locations.

The hypothesis based on a relationship with the father's occupational exposure to external ionizing radiation before child conception was proposed for the Sellafield site [Gardner et al., 1990], but was not confirmed later, and today seems to have been rejected [Doll et al., 1994].

The hypothesis on an infectious cause related to population mixing around nuclear sites was put forward by Kinlen [Kinlen, 1988] and
German nuclear power plants. To date, no similar observations have been made in other countries, including France. The published German study cannot explain the observed excess.

Furthermore, several studies have attempted to explain the local excess of leukemia around certain nuclear sites by focusing on multiple potential risk factors. Among the different areas explored, the hypothesis based on an infectious cause related to population mixing around the nuclear sites seems to be the most well-founded. However, to date, the infectious agent(s) involved have not been found.

Determining the causes of the local excess of leukemia observed close to certain nuclear sites is limited by lack of knowledge on the risk factors of childhood leukemia. Development of broader analytical studies, reaching a national or international scale is necessary to clarify leukemia aetiology.

Even today, although several suggestions have been proposed, the origin of the clusters observed close to certain nuclear sites has not been established. However, it should be noted that most of these studies present methodological limitations (geographical case studies or studies of small populations), making it difficult to detect any causal link. In addition to this problem, there is no available knowledge on the risk factors associated with childhood leukemia. Large-scale analytical studies such as those under way in France, based on the national register of malignant hemopathy in children, could provide a better understanding of the causes behind clusters of childhood leukemia.

**Conclusion**

Since the 1980s, many descriptive studies have estimated the frequency of leukemia in young people living close to nuclear facilities. These studies were conducted in answer to a demand for information on the part of local populations, and also contribute to the discussion on the effects of low environmental doses. The bibliographical review showed great diversity in the approaches taken and methods used.

Local excess of childhood leukemia exist in the United Kingdom close to the reprocessing plants at Sellafield and Dounreay, and in Germany close to the Kruemmel nuclear power plant. Nevertheless none of the multi-site studies currently available, including in France, show an overall increase in the frequency of leukemia in children and young people aged 0 to 14 or 0 to 24 in the vicinity of nuclear sites. A recent epidemiological study described an excess of leukemia in children aged 0 to 4 around German nuclear power plants. To date, no similar observations have been made in other countries, including France. The published German study cannot explain the observed excess.
References

NEW APPROACH TO EPIDEMIOLOGICAL FOLLOW-UP OF WORKERS EXPOSED TO INTERNAL CONTAMINATION RISKS: applying the Job Exposure Matrix

Irina GUSEVA CANU, Éric SAMSON
Epidemiology Laboratory

Workers in the nuclear industry may be exposed to ionizing radiation through external radiation, internal radiation, or a combination of both. For over ten years, the IRSN epidemiology laboratory (Lepid) has conducted studies on workers in the nuclear field (at CEA, Areva NC, and EDF), to assess the cancer mortality risk associated with external radiation exposure [Guseva Canu et al, 2008; Rogel et al, 2005; Telle-Lamberton et al, 2004; Telle-Lamberton et al, 2007]. In the last three years, Lepid has initiated other studies that also take into account internal radiation risks, through the European ALPHA-RISK Program and a common-interest program carried out with Areva. These studies have led to two doctoral theses in epidemiology.

Internal radiation occurs when radioactive particles are inhaled or ingested, or taken up through a wound. While the effects of external radiation (from X-rays and gamma rays) have been extensively explored in large-scale epidemiological studies [Cardis et al, 2005], the effects due to incorporation of uranium particles and other alpha-emitting elements remain relatively unknown [Cardis et al, 2007].

Calculating the organ dose caused by internal radiation requires reconstructing the particle exposure situation. Doses assessed in this way can present significant uncertainty due to incomplete data on the history of worker exposure, heterogeneity in the methods and indicators used to measure exposure, difficulty in interpreting individual biological data (worker monitoring in radiotoxicology), and the numerous hypotheses used to assess internal exposure [Guseva Canu et al, 2008; Boice et al, 2006].

Moreover, exposure to certain substances (chemical products, asbestos, tobacco, alcohol), which could contribute to cancer risk, quite often are not systematically taken into account [Guseva Canu et al, 2008]. It is therefore difficult to draw conclusions on the relationship between cancer mortality and internal exposure to uranium based on available epidemiological studies. This highlights the need to develop alternative approaches to internal dosimetry that are capable of reconstructing exposure to multiple risk factors.

The Job Exposure Matrix, which establishes a correspondence between a list of jobs and exposure indicators [Goldberg et al, 1993], is one of the possible alternatives.

The purpose of this article is to demonstrate how the job exposure matrix approach can be used to characterize exposure in the French nuclear industry, based on the pilot study conducted by IRSN at the Areva NC plant in Pierrelatte.
Method used to build the job exposure matrix

The Areva NC plant (former Cogema) in Pierrelatte is involved in several phases of the nuclear fuel cycle. From 1960 to 1990 the main activities in the plant focused on uranium enrichment, and the chemical conversion of uranium since the 1980’s. Workers may therefore have been exposed to uranium particles and aerosols, as well as the chemical products used in the process. Most workers have held steady jobs in the plant, and consequently have received regular medical follow-up throughout their career. That is why Lepid, in agreement with Areva physicians, chose the Pierrelatte plant for its first epidemiological study on workers that risk uranium contamination.

The structure of the job exposure matrix [Guseva Canu et al, 2008] covered three dimensions – job description, exposure, and time period – to take into account changes over time in the processing and exposure conditions in the plant.

The list of jobs and workstations for the different periods and the list of exposure agents (uranium-containing products and other carcinogenic, mutagenic, or toxic chemical products) to which workers may have been exposed were defined by an expert committee composed of 23 members familiar with the history of the processes and products used in the plant and their chemical and radiotoxic effects, as well as safety engineers, radiation protection specialists, chemical engineers, occupational physicians, toxicologists, dosimetry specialists, and epidemiologists.

The frequency of exposure and the amount of product that workers were potentially exposed to in the course of their career were defined as exposure indices. A committee of assessors estimated these indices on a relative scale from 0 to 3. The assessors were selected from three populations: “A” for workers active in the plant with considerable seniority and thorough knowledge of their working environment; “R” for retired workers; and “AR” for plant retirees belonging to ARGCEA (an association of CEA-Cogema retirees).

For the latter worker population, a computer file of updated addresses was available, making it easy to contact the relevant persons. Nonetheless, since this population could have had a life style significantly different from the other retirees due to its participation in an association, the survey also included the other retiree population, classified in the “R” group. Assessment work was standardized using an assessment guide, common to all three populations, that explained the purpose of the study, the conditions for participating (on an anonymous, volunteer basis), assessment instructions, and the assessment grid to be completed.

The grids filled in by the active workers were collected at the plant by the safety engineers, and those completed by retired workers were sent in by mail. Nonetheless, since this population could have had a life style significantly different from the other retirees due to its participation in an association, the survey also included the other retiree population, classified in the “R” group. Assessment work was standardized using an assessment guide, common to all three populations, that explained the purpose of the study, the conditions for participating (on an anonymous, volunteer basis), assessment instructions, and the assessment grid to be completed.

The grids filled in by the active workers were collected at the plant by the safety engineers, and those completed by retired workers were sent in by mail. All the assessor responses were centralized, input, and processed statistically using the technique derived from the Delphi method [Dalkey and Helmer, 1963]. This technique was used to statistically examine the distributions resulting from the assessors’ answers, in order to obtain a Frequency score and a Quantity score representative of each job/period combination for each exposure agent. The final matrix was validated by experts after examining the internal coherence of the matrix, as well as its

<table>
<thead>
<tr>
<th>Exposure agents</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - F1 natural U compounds</td>
<td>UF₆, UF₄, UF₂(NO₃)₆, (UO₂₄, nH₂O)</td>
</tr>
<tr>
<td>2 - M1 natural U compounds</td>
<td>(U₂O₃)(NH₄)₂, U₁O₆, UO₂F₂, UO₃</td>
</tr>
<tr>
<td>3 - S1 natural U compounds</td>
<td>UO₂</td>
</tr>
<tr>
<td>4 - F1 U compounds from reprocessing</td>
<td>UF₆, UF₄, UO₂(NO₃)₂, (UO₂₄, nH₂O)</td>
</tr>
<tr>
<td>5 - M1 U compounds from reprocessing</td>
<td>(U₂O₃)(NH₄)₂, U₁O₆, UO₂F₂, UO₃</td>
</tr>
<tr>
<td>6 - S1 U compounds from reprocessing</td>
<td>UO₂</td>
</tr>
<tr>
<td>7 - Chlorinated substances</td>
<td>Perchloroethylene, tetrachloroethylene, trichloroethylene, dichloromethane, polychlorinated biphenyls (PCBs)</td>
</tr>
<tr>
<td>8 - Fluorinated substances</td>
<td>Hydrofluoric acid, tungsten hexafluoride, fluoroite, potassium fluoride</td>
</tr>
<tr>
<td>9 - Nitrogenous substances</td>
<td>Ammonia, ammonia anhydride, nitric acid, nitrous vapors</td>
</tr>
<tr>
<td>10 - Solvents containing aromatic hydrocarbons</td>
<td>Benzene, toluene, xylene, styrene</td>
</tr>
</tbody>
</table>


Uranium-bearing compounds have been classified in three categories (F, M, and S) according to their solubility in biological tissues (fast, moderate, and slow) [ICRP, 1994].
Results

Internal radiation exposure was represented by several exposure agents, according to two criteria: uranium purity, used to distinguish naturally-occurring uranium components from those coming from reprocessed uranium, containing traces of activation and/or fission products; and transferability (high, medium, low) of uranium par-

---

### Table 2
Composition of assessment committee and participation rate according to type of assessor.

<table>
<thead>
<tr>
<th>Assessor population</th>
<th>Number of surveys distributed</th>
<th>Number of surveys completed</th>
<th>Participation rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (active workers)</td>
<td>182</td>
<td>182</td>
<td>100</td>
</tr>
<tr>
<td>R (retired workers)</td>
<td>197</td>
<td>85</td>
<td>43</td>
</tr>
<tr>
<td>AR (retired workers belonging to the association)</td>
<td>353</td>
<td>86</td>
<td>25</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>732</strong></td>
<td><strong>353</strong></td>
<td><strong>56</strong></td>
</tr>
</tbody>
</table>

### Table 3
Final job exposure matrix (excerpt from the exposure index table)

<table>
<thead>
<tr>
<th>Generic workstation</th>
<th>Period</th>
<th>Unat_1_Freq</th>
<th>Unat_1_Quant</th>
<th>Unat_2_Freq</th>
<th>Unat_2_Quant</th>
<th>Unat_3_Freq</th>
<th>Unat_3_Quant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1_CME2</td>
<td>1966 - 1976</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1_CME2</td>
<td>1976 - 1986</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1_CME2</td>
<td>1986 - 1996</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1_CME3</td>
<td>1966 - 1976</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1_CME3</td>
<td>1976 - 1986</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1_CME3</td>
<td>1986 - 1996</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1_CME4</td>
<td>1966 - 1976</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1_CME4</td>
<td>1976 - 1986</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1_CME4</td>
<td>1986 - 1996</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1_CME4</td>
<td>1996 - 2006</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1_CME5</td>
<td>1966 - 1976</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1_CME5</td>
<td>1976 - 1986</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>1_CME5</td>
<td>1986 - 1996</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>1_CME5</td>
<td>1996 - 2006</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1_CME6</td>
<td>1966 - 1976</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

---

external coherence with respect to exposure in other comparable nuclear facilities. In addition, for a representative sample of workers (1% of the study population), the exposure results provided by the matrix were compared with those in medical files, which served as the reference source for exposure data. Consistency, sensitivity, and specificity of the assessment were evaluated [Bouyer and Hénon, 1994].
particles to biological tissues after incorporation. The exposure agents for which exposure was assessed are given in Table 1. Exposure to each of the 22 exposure agents was assessed for 73 generic workstations. In addition, the generic workstations were divided into several periods (1960-1975, 1976-1983, 1984-1995, 1996-2006), with exposure considered as stable within each one, but variable from one period to another.

In total 353 workers were included in the assessment committee and submitted acceptable assessment grids. Distribution of the assessors according to their source population is shown in Table 2.

At the end of the first statistical review, 84% of the scores attributed by the assessors during the assessment procedure were accepted. The second review and the score arbitration session with the experts gave way to a satisfactory Quantity score and Frequency score for each generic workstation/period pair. These scores were then recorded in the exposure index table presented in Table 3.

In-house specialists at Areva NC Pierrelatte (safety engineers, supervisor in charge of chemical product and asbestos surveillance, and radiation protection specialists) examined the internal coherence of the final matrix, judged satisfactory, to establish internal validation. The exposure data produced by the matrix was compared with data from the workers’ medical files (the data reference), to establish external validation. The results of this validation process are shown in Table 4. In comparing the two data sources, the degree of agreement was estimated based on observed agreement and the Kappa coefficient (used to estimate agreement among the qualitative judgements on exposure provided from medical files, taking into account random factors). According to the interpretation criteria for the Kappa values proposed by Landis and Koch [Landis and Koch, 1977], as regards uranium-containing products, the matrix data showed very good agreement with the medical file data.

Agreement was not as good for chemical products, and was even poor for asbestos exposure. Sensitivity and specificity demonstrated the matrix’s ability to detect exposure to an exposure agent when it was present, or to exclude it when it was not [Last, 1995]. The overall sensitivity and specificity values, close to one, showed that the matrix performed well.

<table>
<thead>
<tr>
<th>Exposure agent</th>
<th>Observed agreement (%)</th>
<th>Kappa (%)</th>
<th>Degree of agreement</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uranium-bearing substances from natural uranium</td>
<td>85</td>
<td>66</td>
<td>Good</td>
<td>0.81</td>
<td>0.96</td>
</tr>
<tr>
<td>Uranium-bearing substances from reprocessed uranium</td>
<td>92</td>
<td>83</td>
<td>Excellent</td>
<td>0.82</td>
<td>0.98</td>
</tr>
<tr>
<td>Asbestos</td>
<td>61</td>
<td>9</td>
<td>Poor</td>
<td>1.00</td>
<td>0.60</td>
</tr>
<tr>
<td>Fiberglass and rock wool</td>
<td>74</td>
<td>27</td>
<td>Mediocre</td>
<td>0.50</td>
<td>0.80</td>
</tr>
<tr>
<td>Chlorinated substances</td>
<td>71</td>
<td>42</td>
<td>Moderate</td>
<td>0.77</td>
<td>0.67</td>
</tr>
<tr>
<td>Fluorinated substances</td>
<td>58</td>
<td>15</td>
<td>Mediocre</td>
<td>0.57</td>
<td>0.60</td>
</tr>
<tr>
<td>Nitrogenous substances</td>
<td>68</td>
<td>36</td>
<td>Mediocre</td>
<td>0.59</td>
<td>0.79</td>
</tr>
<tr>
<td>Total</td>
<td>78</td>
<td>56</td>
<td>Moderate</td>
<td>0.72</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Table 4: Results from comparison between exposure data taken from the matrix and exposure data from worker medical files, used as reference data.
Furthermore, in this study, the aspects listed below actually improved the method:

- a large number of assessors (n = 353) and experts participated in preparation, giving a solid estimation of the chronological changes in exposure conditions and minimizing memory bias;
- information collection was standardized, limiting bias related to the interviewee and improving reproducibility;
- applying the Delphi method reduced the influence of assessor subjectivity in the answers, resulting in a statistical response representative of the group;
- discrimination covered a large number of jobs (74 generic workstations), improving accuracy of the job exposure matrix;
- exposure was assessed before conducting the epidemiological studies, avoiding bias related to the assessor as concerns the vital status and cause of death of the subjects under study.

Nonetheless, the absence of useable data obtained through instrument measurements to characterize exposure represented a significant limitation for the resulting job exposure matrix. Only the relative levels of exposure frequency and quantity were established, which was not sufficient to infer any precise physical significance. These levels represented the “mean exposure levels for the period in question”. By multiplying the exposure frequency and quantity by the period of exposure at a given workstation, it was nonetheless possible to obtain a cumulative exposure score, a known quantitative variable, reflecting exposure to each of the 22 exposure agents in “dose years” for the entire career of each worker. This method has been used in other studies [Rice and Heineman, 2003; Ritz et al., 2006; Seidler et al., 1998] and has proven reliable in demonstrating the relationship between exposure and the pathology under study. The worker cohort from the Areva NC plant in Pierrelatte is currently being studied [Guseva Canu et al., in press].

Agreement between the job exposure matrix data and the medical file data was satisfactory. Agreement was particularly good for uranium-containing products, which are subject to stringent medical surveillance regulations. As regards asbestos, fiberglass, and certain chemical products, however, since their noxious effects were unknown at the time, exposure to these substances was not monitored regularly by occupational medicine in the past. Agreement observed for chemical products was therefore mediocre, and for asbestos was practically null (Kappa = 9%).

This validated the initial hypothesis postulating that the medical files did not provide enough data to reliably assess exposure to chemical products. The job exposure matrix provides a more accurate reflection of chronic low-dose exposure to substances, especially when it is specific to the facility under study. According to the observed sensitivity and specificity values, the established job exposure matrix is a useful tool with a satisfactory performance.

The Job Exposure Matrix: a useful tool with a satisfactory performance

The job exposure matrix presented in this study was established to retrospectively assess exposure of fuel cycle workers to uranium and the associated chemical products. The matrix was validated and today constitutes a source of data on specific exposure at the Areva NC plant in Pierrelatte.

It is used to study the relationship between internal exposure to uranium and cancer mortality in the plant workers. Designed in a relatively simply format (Microsoft® Access database), it can serve to establish epidemiological surveillance of exposure over time, both retrospectively and for predictive purposes. The job exposure matrix is also a tool that the plant can use for risk management: exposure agents listed in the plant’s regulatory occupational risk assessment document [Areva Report, 2005] and also featured in the job exposure matrix are notified in real time by occupational health and safety specialists and safety engineers. The flexibility of the matrix makes it easy to update exposure levels for products that are already listed, and to add new exposure agents. New exposure indices can be incorporated any time, and even better, current exposure data can be replaced by actual measured values. This will become more common as instrumented measurement of the various contaminants used in the plant becomes more widespread.

The method developed to build the job exposure matrix can be used as a prototype for other fuel cycle plants. In the European ALPHA-RISK program, coordinated by IRSN’s epidemiology laboratory, a cohort study was set up, including workers from Comurhex and Areva NC (uranium chemical processing), Eurodif (uranium enrichment), FBFC (fuel manufacture), Socatri (uranium treatment and recovery), and CEA (research). The study aims to quantify the mortality risk related to internal radiation of workers, as a function of exposure. It therefore requires reconstruction of individual exposure to radiation (both internal and external), chemical substances, and other individual risk factors such as smoking, based on different sources of information (medical files, etc.). The job exposure matrix approach can be used to supplement available data and assess exposure for past periods where data is often lacking or unusable.
References

DEVELOPMENT OF AN INSTRUMENTED PHANTOM to measure effective dose at workstations

Carmen VILLAGRASA, Julien DARRÉON, Isabelle CLAIRAND, Ionizing Radiation Dosimetry Laboratory
François QUÉINNEC
External Dosimetry Department

Radiological risk is assessed based on the effective dose, $E$, a value used in radiation protection to define the maximum limits of individual exposure. To determine this value, the dose absorbed by organs must be known, which implies that in theory it is not possible to measure effective dose directly at workstations. Measurable quantities, such as the individual dose equivalent $H_{p}(10)$, were therefore defined in Report 51 by the International Commission on Radiation Units and Measurements (ICRU), to obtain accurate estimates of effective dose.

This is the magnitude that is measured at workstations using dosimeters worn on the chest. The individual dose equivalent, however, was defined for "standard", usually simplified, exposure conditions. Given the characteristics in dosimeter response, it may, in certain situations, significantly under- or overestimate effective dose, and thereby the radiological risk to the worker. A measuring instrument capable of directly assessing the effective dose, $E$, would make it possible to evaluate these deviations.

The solution adopted by IRSN’s Ionizing Radiation Dosimetry Laboratory consisted of designing a human-like dummy equipped with detectors to measure the dose absorbed by organs. The purpose was to build an instrument that would directly measure effective dose, and in the final outcome ensure that personal dosimeters were adequate for the exposure conditions encountered by exposed workers.

A numerical feasibility study to determine photon irradiation fields\(^{(1)}\) demonstrated the advantage of this type of instrument, based on calculations of effective dose and individual dose equivalent $H_{p}(10)$ for the various types of radiation (that are standard and realistic for a given workstation). 24 detection positions were defined inside the phantom to assess effective dose within a 30% tolerance for energy incident photons between 40 KeV and 4 MeV.

Construction of the human-like phantom was part of new thesis work begun in November 2006. The first phase involved developing the detectors to be fitted inside the dummy. These detectors had to meet specific requirements: compact in size (a few cubic centimeters), a very low dose rate detection threshold (on the order of 1 $\mu$Sv/h), a linear energy response (from 40 KeV to 4 MeV), and immediate readout. Fiber optical sensors were selected for their ability to provide practically instant remote readouts. A detector prototype was developed (Figure 1) in cooperation with the particle physics laboratory in Caen (CNRS – IN2P3).

The detector consists of a 6 cm$^3$ plastic scintillator that emits a visible light proportional to the received dose. These photons are sent through a strand of optical fibers to a photomultiplier tube, which converts them into an electrical signal. A program was developed using LabWindows-CVI to manage the detection system, and record and analyze data.

The prototype was characterized. The detector was capable of measuring a dose rate of approximately 1 µSv·h⁻¹. Its response was stable, showing about 5% reproducibility, with background noise measured systematically before each measurement. Since a sub-response was observed for low-energy photons (less than 100 KeV), characterization under metrological conditions has been planned in order to define correction factors that are a function of the incident photon energy, so that the scintillator can be tuned to a degree of response equivalent to that of human tissue.

The second phase of this project, involving complete construction of the dosimeter-equipped dummy, and running tests under real-life conditions, is expected to be completed at the end of 2009.
French regulations require dosimetric monitoring of workers exposed to ionizing radiation. External dosimetry involves assessing the individual dose received by people who have been exposed to a field of radiation (X-rays, gamma, beta, neutrons) produced by an external radioactive source. This can be accomplished by wearing a personal dosimeter, which indicates the dose absorbed by the entire body or part of the body, either in real time, using electronic instruments (referred to as active or operational dosimetry), or at a later time, by reading the dosimeter in a specially equipped laboratory. Regardless of the system used, the dosimeter must be chosen according to the type of radiation to which personnel will be exposed.

IRSN provides dosimetric follow-up for nearly 151,000 workers in France, located at roughly 17,000 sites, covering all sectors of activity: hospitals, clinics, research laboratories, industrial plants, etc. The IRSN dosimetric monitoring laboratory provides and operates nearly 1,500,000 dosimeters every year to fulfill this mission.

A new RPL dosimeter

After using radiographic film dosimetry for several years, and in response to new technical and regulatory requirements, in 2006 IRSN initiated a project to replace the film-based instrument by a more powerful dosimeter. Radiophotoluminescent (RPL) dosimeter technology was chosen, based on a technical study conducted by IRSN in preparing its technical specifications, and proposals submitted by the world’s leading dosimeter suppliers. The main criteria guiding the Institute’s choice included the extremely high-precision measurements achieved by RPL technology, as well as the wide range of dosimetry functions proposed: readout capability, dose imaging, and precise information provided on the type of radiation.

Comparative tests were conducted on the various available dosimetry techniques. Dosimetry based on the RPL technique (Figure 1) achieved greater performance for all criteria defined in the standards, i.e. measurement accuracy, result reproducibility, angular response, energy and dose response (Table 1).

The RPL dosimeter demonstrated certain metrological advantages. It can measure very low doses of just a few microsieverts (µSv), or very high doses (10 Sv or more), which makes this dosimeter appropriate for both individual dosimetric follow-up and radiation monitoring in a work area or in the environment, under both normal and accident exposure conditions. RPL technology also offers high-precision measurements regardless of the radiation incident angle, a characteristic that is essential to cover all the different geometric situations in which dosimeter wearers may find themselves. The possibility of creating an actual digital image of the dose can provide information on worker exposure conditions, for example whether exposure occurred just once or repeatedly, or whether external contamination occurred via radioactive elements or objects (such as a pen) that may have been placed in front of the dosimeter, thereby interfering with measurement.
Information on the type of radiation and its energy level can also be obtained through a special analysis performed on the detector, in the event of confirmed exposure. All this information can be read as many times as necessary.

A new laboratory was created to manufacture and operate the new dosimeter system. Located in Le Vésinet, it employs over 50 people and features a production line with a high degree of automation. With millions of the new RPL dosimeter already operating in Japan, this instrument is obviously an ideal choice for any organization concerned by radiation protection.

**Neutron dosimetry**

Every year in Europe, tens of thousands of workers are exposed to neutron radiation, often combined with gamma radiation. They operate in the nuclear industry (power plants, fuel manufacturing, transport and recycling), in military nuclear applications, research, radiotherapy and industrial use of certain radioactive sources.

Monitoring exposure to neutrons is technically difficult due to their specific nature. These particles are neutral with a very wide energy range, and the biological effects they produce are a function of their energy.

Improving metrology and dosimetry techniques used to ensure radiation protection in the workplace is therefore a major challenge, both in France and around the world. Moreover, regulatory changes lowering detection thresholds have made it necessary to implement a new generation of neutron dosimeters.

<table>
<thead>
<tr>
<th>Film</th>
<th>TLD (thermo-luminescent detection)</th>
<th>OSL (optically stimulated luminescence)</th>
<th>RPL (radiophoto-luminescence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected energy range</td>
<td>• • • •</td>
<td>• • • •</td>
<td>• • • •</td>
</tr>
<tr>
<td>Detection limit</td>
<td>• • •</td>
<td>• • • •</td>
<td>• • • •</td>
</tr>
<tr>
<td>Angular response</td>
<td>• • • •</td>
<td>• • • •</td>
<td>• • • •</td>
</tr>
<tr>
<td>Repeat readings</td>
<td>• • • •</td>
<td>• • • •</td>
<td>• • • •</td>
</tr>
<tr>
<td>Dose imaging</td>
<td>• • • •</td>
<td>• • • •</td>
<td>• • • •</td>
</tr>
<tr>
<td>Data on low-energy X- and gamma radiation</td>
<td>• • • •</td>
<td>• • • •</td>
<td>• • • •</td>
</tr>
<tr>
<td>Data on β energy</td>
<td>• • • •</td>
<td>• • • •</td>
<td>• • • •</td>
</tr>
</tbody>
</table>

* Test results on passive dosimeters available in France.

**Table 1** Comparison of different dosimeters*.
IRSN’s passive neutron dosimeter is based on a PN3-type trace detector. Work conducted by the Institute to improve performance on this type of dosimeter was completed in 2008. The outcome was a new design, the “PN3+”, capable of detecting thermal, intermediate, and fast neutrons, achieved by adding lithium-6 converting filters and cadmium screens (Figure 2).

The proposed result is a more sensitive dosimeter featuring expertise capability, designed for the neutron spectra commonly found in the nuclear industry or medical sector. Like the RPL, traces observed on the surface of the detector can be represented by images. They can also provide information on the spectrum of the incident neutron radiation and, in certain cases, on the angle of incidence.

The new PN3+ neutron dosimeter proposed by IRSN incorporates innovative functions that significantly enhance the conventional performance levels achieved using this detection technique. The PN3+ has measuring capabilities that meet regulatory requirements and offers features that can assess worker exposure conditions. This new dosimeter was set into operation in January 2009.
3.8

KEY EVENTS
and dates

Dissertations Defended

March 27, 2008
- Odile Carvahlo submitted a thesis on "Using concepts from physical optics and image processing techniques to study acute radiation syndrome of the skin: correlation with results from biological and biophysical analyses" at the University of Paris XII.

May 16, 2008
- Moubarak Mouisedine submitted a thesis entitled "Use of human mesenchymal stem cells to treat radiation-induced tissue damage" in Paris.

June 16, 2008

September 29, 2008
- Irina Canu submitted a thesis entitled "Epidemiological study on workers exposed to the risk of absorbing uranium" at the University of Paris VI.

October 13, 2008

October 15, 2008
- Blandine Vacquier submitted a thesis on the "Analysis of mortality in a cohort of French uranium miners" at the Paul Brousse Hospital (Paris region).
OTHER
KEY EVENTS

January 2008
■ Organization of the AM2008 EURADOS Annual Meeting in Paris including the Winter School on “Retrospective dosimetry” and the workshop on “Dosimetric issues in the medical use of ionizing radiation”.

February 2008
■ Publication of the second assessment report on the stereotactic radiosurgery accident at the university medical center in Toulouse: “Dosimetric and clinical assessment, risk analysis”. This report was submitted to the French nuclear safety authority, the ASN.

April 2008
■ Publication of a critical review of epidemiological studies on leukemia incidence in children and young adults living in the vicinity of nuclear facilities.

June 2008
■ The 2008 Laurent EXMELIN scientific award was attributed on June 20, 2008 to an IRSN thesis submitted by Noëlle Pierrat for research work conducted at the IRSN Internal Dose Assessment Laboratory (LEDI), entitled “Voxelized digital phantoms associated with the MCNP Monte Carlo code applied to realistic in vivo measurement of actinides in lungs and contaminated wounds”. This award is attributed every year in recognition of a significant scientific contribution to radiotoxicology.

October 2008
■ A five-year research project was initiated between SDI and FMBC in Moscow (the former IBPh), which aims to improve methods for treating wounds after plutonium or americium contamination, and to assess the associated dose. The main topics of study will include measuring contaminated wounds, the biokinetics involved, and treatment using DTPA.

December 2008
■ Patent application filed for use of a calixarene-based nano-emulsion to decontaminate skin (healthy skin and wounds) contaminated by actinides.