Nuclear power plant and childhood leukaemia

Report by the pluralist working group

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Commissioned by:

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INTRODUCTION

The potential carcinogenicity of many environmental agents (be they physical, chemical or infectious), the discovery of paediatric cancer clusters and the theory that there is a causal link between these clusters and the environment, have given rise to considerable concern among both parents and professionals. As a result, the latter are increasingly exerting their right, as citizens, to demand clear and understandable information on research and scientific findings.

The only way to raise public confidence in the skills and credibility of the different people involved in these issues is to improve the educational methods employed; information must be based on the findings of multidisciplinary and pluralist expert committees, tasked with defining the research required with the help of civil society representatives. Hence, setting up an independent dialogue between different disciplines prior to studying a real or potential problem is essential to effectively informing the general public and, if necessary, explaining any uncertainties or subtleties. This approach removes any doubts as to the validity of the information provided.

Excessive precaution could generate concern without providing enough information, and could therefore perpetuate public distrust and the feeling that public understanding of research is treated with disregard.

Given the uncertainty regarding the health repercussions – and notably the risk of cancer potentially associated with ionising radiations, high-voltage power lines, electromagnetic fields, pollution, infections, etc. - it is essential that we carry out multidisciplinary and pluralist studies and that we supply objective information. This information should not attempt to conceal any contradictions, and should be updated regularly. Research into gene-environment interactions should provide a clearer understanding of the role of environmental factors, and of predisposed genetic vulnerability to such factors.

Is there a link between nuclear power plant and the risk of leukaemia in children? There is no official answer to this question, barring that exposure to high doses or to high dose rates increases the risk. Many other genetic and environmental causes must also be taken into consideration, in order to prevent any misunderstanding. The molecular heterogeneity of leukaemia must also be taken into account when interpreting the data.

Despite this complexity, the general public needs objective, comprehensible information. Scientists are under the obligation to meet the legitimate expectations of a society that is not only fully aware of its "right to know", but is also eager for greater humanity and trust.

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I. PRESENTATION OF THE WORKING GROUP ENTITLED "NUCLEAR POWER PLANT AND CHILDHOOD LEUKAEMIA"

1

1.1. Background

Acute forms of leukaemia account for 30% of childhood cancers. In France, their annual incidence rate in children aged from 0 to 14 years old is 470. This rate has been stable since the National Registry of Childhood Blood Malignancies was set up in 1990; around 80 new cases are observed every year in young people aged 15 to 19 years old. Acute lymphoblastic leukaemia (ALL) accounts for 85% of cases, with a peak in the incidence rate between the ages of 2 and 4. Acute myeloblastic leukaemia (AML) accounts for 15%, with no age peak.

Considerable therapeutic progress has been made over the last 30 years, resulting in a cure rate of 80% for ALL and 60% for AML. This has been made possible by the gradual adaptation of therapeutic protocols to the clinical, biological and molecular prognostic classification of the disease. In addition, it should be pointed out that the organisation of paediatric oncology, which took place from the late 70s onwards in industrial countries, greatly facilitated the development of clinical research and access to high-quality care.

The risk factors for leukaemia are still far from being fully understood, despite the fact that a great deal of research has been conducted into the role of genetic factors (5% of cases) and environmental factors, including ionising radiations in various situations of actual and potential exposure.

The risk of developing cancer following exposure to ionising radiations depends on a number of factors: dose, dose rate, type of radiation, acute or chronic exposure, organ/tissue/cell sensitivity, the type of damage done (genomic damage in particular), the modalities of DNA repair and of cell clone elimination, and the possibly cumulated effects of genetic, physical and chemical factors.
In the radiation protection field, radiation doses are generally classed as follows: high doses (> 1 Sievert[1] (Sv)), low doses (<100 millisieverts (mSv)) and very low doses (< 1 mSv). The doses attributable to discharge from nuclear installation are very low (from just a few microSv to a few dozen microSv). The general public often finds it hard to understand the concept of doses.

Following acute exposure to doses above 50 mSv (in children) and above 100 mSv (in adults), the risk of developing cancer or leukaemia increases. This was demonstrated in the survivors of the Hiroshima and Nagasaki atomic bombings. Leukaemia occurred essen-

1 The sievert (Sv) expresses the effective dose received by an individual, taking into account the type of radiation and its biological effect. The gray (Gy) is the dose absorbed. In traditional imaging and radiotherapy, 1 Gy can be regarded as being equivalent to 1 Sv.

tially in children below the age of 5, 2 to 5 years after exposure, and the risk persisted for several decades.
Taking possible bias into account, contamination due to the Chernobyl accident increased the risk of leukaemia for eleven years after the explosion, in children between the ages of 0 and 5 years living close to Chernobyl at the time of the accident and exposed to a bone marrow dose of more than 10 mGy (equivalent to about 10 mSv). These children primarily developed Acute Myeloblastic Leukaemia (Noshchenko et al. 2010). However, it is worth pointing out once again that information relating to the Chernobyl accident is fragmented.

Patients who have received localised radiation therapy for cancer, at authorised doses of more than 20 Gy (12 Gy over 3 days in the case of total body radiation prior to a bone marrow transplant), are known to be at risk of secondary leukaemia. However, the existing illness (generally cancer), the irradiated volume and the chemotherapy usually associated with such treatment must be taken into consideration.

The Oxford Study of Childhood Cancer, published in 1975, concluded that the relative risk of childhood cancer associated with radiation exposure in utero (ranging from a few mSv to a few dozen mSv) was 1.47; these conclusions have been contested in subsequent studies. Research is still ongoing into the possible harmful effects of childhood X-ray treatment; the findings of the "enfant scanner" cohort study, which was recently set up in France by the IRSN, will be analysed and incorporated into the discussions, taking into account the guidelines on X-ray treatment and the changes in X-ray technology.

The development of the nuclear industry has, since the 1980s, raised questions regarding the consequences of an accident and the development of childhood leukaemia clusters in the vicinity of some nuclear installations. However, the theory that there is a direct link between leukaemia and nuclear power plants has not been proven. This can be explained not only by the complexity and diversity of nuclear sites and of the methods employed in epidemiological studies, but also by the weakness of the doses delivered to the neighbouring population.

It should be noted that the average effective dose received by the French population is approximately 3.3 mSv/year. This includes radon (1.4 mSv), medical radiation (0.8 mSv), telluric radiation (0.5 mSv), cosmic radiation (0.3 mSv) and discharge from nuclear power plants (< 0.1 mSv). For information purposes, it should also be pointed out that the maximum authorised dose is 20 mSv/year for occupationally-exposed individuals and 1 mSv/year for the general public.

The existence of a "safe" threshold and the nature of the "dose-effects" relationship at very low doses are still subject to debate. We should add that ionising radiations (natural and/or from nuclear sites) may, in the future, be proven to have an impact on the hematopoietic stem cell of the human foetus (due to a greater level of sensitivity) and on the appearance of preleukaemia clones (a possible source of post-natal transformation).

We understand the concerns of the general public and especially of the parents of sick children, who are sometimes convinced or at least suspect that the information given to them is not entirely true. Indeed, this information is often regarded as inadequate, biased, uncertain, difficult to understand and deceptive.
The concerns of both parents and the general public are not only voiced collectively, but also individually through GPs, hospital practitioners and doctors in maternal and child welfare organisations and schools. The latter lack the basic information needed to answer

such concerns, and are not adequately trained to discuss the possible interactions between human health and the environment.

The extremely rapid broadcasting of information by the media can cause public concern and fear. The coverage by the British and French media of the La Hague nuclear fuel reprocessing plant (1990-1998) is a good example of this: it was suggested that children and young people below the age of 25, living within 10 km of the plant, were at greater risk of developing leukaemia. However, as the numbers were low, the risk was insignificant (although close). A cancer registry has now been set up for the *Manche* region of northern France, and research is continuing.

It should be added that in these two countries (France and Great Britain), studies conducted in the vicinity of several nuclear sites (multi-site studies) do not show any evidence of a significant rise in the incidence of acute leukaemia; this does not prove that there is no risk at all, but has led to the development of more robust research methods. Indeed, telling the public that there is no proof naturally leads to doubts about the value of the research conducted and raises the following questions:

- what are the other possible causes of leukaemia (possibly associated with ionising radiations from nuclear sites or with the indirect effects of nuclear power plant construction)?
- can ionising radiations have other health repercussions, even at very low doses?

In Germany, the problem resurfaced on 10th December 2007, following a press release from the Federal Office for Radiation Protection (Bundesanstalt für Strahlenschutz, BfS), presenting the results of a study performed by the Childhood Cancer Registry (Kinderkrebsregister) at the University of Mainz. The press release stated that there was an excessively high incidence of acute leukaemia in children between 0 and 4 years old, living within 5 km of German nuclear power plants. The study was purely descriptive and did not establish a causal link. The press release was issued further to several studies of the Kruemmel nuclear power plant, which began between 1992 and 1997 and were followed by a number of multi-site studies, including a case-control study in children below the age of 5 (KiKK study). Besides an increased incidence of leukaemia in the areas studied, the authors observed that the risk lessened as the distance from the nuclear sites increased.
Further studies were commissioned but, for methodological reasons, have not provided any information on the potential causes underlying these observations (neither exposure to ionising radiations, nor other factors).

The data collected and published in Germany, and the ensuing media backlash, led the Nuclear Safety Authority (ASN) to consult the IRSN[2] and the InVS[3]. It also contacted the group of experts established under article 31 of the Euratom treaty, to get its opinion on the German findings. The IRSN and the InVS sent a joint memorandum to the ASN, the DGS[4] and the DPPR[5], recommending a critical review of the knowledge of childhood leukaemia causes and, in particular, of the impact of exposure to ionising radiations near to nuclear installations. The IRSN and the InVS also suggested setting up an independent, pluralist working group on this subject.

The review, which analysed epidemiological studies on the frequency of leukaemia in children and young adults below the age of 25 living close to nuclear installations, was

2 IRSN: Institute for Radiation protection and Nuclear Safety
3 InVS: Institute for Public Health Surveillance
4 DGS: General Directorate of Health
5 DGPR: General Directorate of Risk Prevention

presented in March 2008 (IRSN 2008): it covered 198 nuclear facilities in ten countries, for which descriptive results were available. The review proposed using 4 grades to describe the excess of cases of childhood leukaemia in the vicinity of nuclear sites: no excess, unconfirmed excess, possible excess, confirmed excess. Three excesses were considered **possible** (including La Hague) and three excesses were considered to be **confirmed clusters** (Sellafield, Dounreay and Kruemmel).

An analysis of the 25 multi-site studies published does not show any evidence of an increased risk of childhood leukaemia, with the exception of the German study which focused on children below the age of 5.

The review, which focused on 10 of the 35 countries with a nuclear power industry, showed a wide diversity in the approaches taken and the methods used. It also stressed the need to conduct critical (rather than just descriptive) studies on both a national and international scale in order, if possible, to explain the local excesses observed and improve the knowledge of other genetic and environmental causes of childhood leukaemia. Further to these recommendations, the ASN suggested setting up a pluralist working group tasked with improving the knowledge of this subject, defining which areas of research to pursue and/or develop, and helping to deliver clear, comprehensible information to the general public.

1.2.Creation of the pluralist working group

Two meetings, involving all the government departments interested in organising discussions on the situation in France, were held at the ASN on 12th March and 10th July 2008. The following proposals emerged from these meetings:

- Set up **an independent, pluralist, technical working group** with the following mandate:

– Issue an opinion on the available epidemiological knowledge of the effects of nuclear power plant (NPP), focusing in particular on the risk of childhood leukaemia;
– Define the research needed to improve the existing data;
– Help to deliver clear, transparent and regular information to the general public.

- Set up a **planning and monitoring committee** composed of institutional bodies (ASN, DGS, DGPR, AFSSET[6], INCa[7]), centres of expertise (IRSN, InVS, INSERM[8]) and associations (ANCCLI[9], SFCE[10], associations of parents of children with leukaemia, environment protection associations, etc.).

A mission statement signed by the ASN, the DGS and the DGPR, reporting the creation of this pluralist working group, was sent to the prospective chairperson, D. SOMMELET, Senior Professor of Paediatrics at Nancy University Hospital and independent of all the above-mentioned organisations (18th August 2008).

6 AFSSET: French agency for environmental and occupational health safety
7 INCa: National Cancer Institute
8 INSERM: National Institute of Health and Medical Research
9 ANCCLI: National Association of Local Information Commissions and Committees
10 SFCE: French Society of Paediatric Oncology

1.2.1. Mission statement

The working group (WG) is entitled "Technical, pluralist working group on the risk of cancer and leukaemia in the vicinity of nuclear power plants".

The mission statement defines the following roles and responsibilities (see appendix 1):

- Put together a working group composed of French and foreign experts with complementary skills and interests;
- Draw up guidelines for improving the existing knowledge on the link between childhood leukaemia and nuclear power plant (especially the impact of very low doses of ionising radiations). These guidelines will be made public.
- Present the progress of this work to the national committee tasked with planning and monitoring the measures needed to improve the available knowledge of the effects of discharge from the nuclear industry on the health of people living nearby.

The creation of these two bodies (including the WG on the risk of leukaemia in the vicinity of nuclear power plants) was reported in a **press release on 9th October 2008** (APM[13]). **Rules of Procedure** were drawn up and approved in March 2009, and included provisions on the appointment of experts, confidentiality and deontology.

1.3. The working methods of the WG

1.3.1. Introduction

The strength of the WG lies in its independence, its multidisciplinary nature and its plurality. It provides an arena for discussion and analysis, and for defining the areas of research to pursue. Each topic is discussed from several angles, thanks to the mixed composition of the WG: epidemiologists, nuclear power and radiation protection specialists, paediatric oncologists (who specialise in particular on the treatment and study of haematological malignancies) and representatives of the civil society (selected for their skills in the above-mentioned areas and/or the experience they have gained in the past from investigations into events that caused public concern, such as exposure to ionising radiations and/or other environmental agents).

The diversity of the WG members and of their knowledge requires an approach based on complementarity, a common language, and a sharing of topics and tasks in areas that not all the members are fully familiar with.

The individualisation of the working group is warranted by the development of descriptive and analytical epidemiology in paediatric oncology (especially in the field of haematological malignancy), the need to reply as clearly as possible to questions from parents whose children are (or may be) suffering from leukaemia, and the knowledge and actions needed to protect the public. Nevertheless, it is important not to underestimate the difficulties and constraints arising from the complexity of the knowledge required and of the methods that will allow us to confirm, reject or merely suggest that there may be a causal link between leukaemia and low-dose ionising radiations.

13 APM: French medical news agency

1.2.2. Composition of the working group

Danièle Sommelet	Chairperson Senior Professor of Paediatrics
Pierre Barbey	Scientific advisor at ACRO[11] University of Caen-Basse Normandie
André Baruchel	Paediatric onco-haematologist Assistance Publique - Hôpitaux de Paris
Pierre Bey	Senior Professor of Radiation Therapy - Institut Curie
Olivier Catelinois	Project Manager - InVS
Michel Chartier	Deputy Head of the Radiation Protection Research and Expertise Department - IRSN
Christian Chenal	ANCCLI
Jacqueline Clavel	Epidemiologist, Research Director at INSERM, Head of the environmental epidemiology of cancer team, CESP, Inserm, UMRS-1018, University of Paris-Sud, Head of the National Registry of Childhood Blood Malignancies
Florent De Vathaire ***	Epidemiologist - INSERM
Bertrand Gagnière	Medical doctor and epidemiologist
Bernd Grosche	Epidemiologist - Federal Office for Radiation Protection Germany
Claire Faure	INSERM, UMRS-1018 – University of Paris-Sud, IFR69
Sophie Jacob	Epidemiologist - IRSN
Dominique Laurier	Head of the epidemiology laboratory - IRSN
Yves Marignac	Director of WISE Paris[12]
Yves Perel **	Paediatric onco-haematologist - Bordeaux
Philippe Unwin	General delegate - Source Vive association
Blandine Vacquier	Epidemiologist - InVS
David Vernez *	AFSSET

- *AFSSET participated in the WG until 1st September 2009*
- *** Yves Perel participated in the WG until December 2009*
- **** F. Devathaire withdrew from the WG in September 2009*

11 ACRO: Association for the control of radioactivity in the west
12 WISE: World Information Service on Energy

1.3.2. WG meetings

The meeting timetable and the agenda for each meeting are shown in table I.

Table 1: Meeting timetable

Date	Type of meeting	Agenda
Friday 12th December, 2008	WG	Establishment of the WG /mission statement / definition of working method and programme **Presentations:** • Epidemiology of childhood leukaemia – Description and risk factors - **J. Clavel** • Review of epidemiological studies conducted in the vicinity of nuclear facilities - **D. Laurier** • An overview of the French research programme on childhood leukaemia - **J. Clavel** • The Geocap project - section on nuclear sites - **J. Clavel** and **C. Faure** • The expectations of people living close to nuclear installations – **O. Catelinois**
Monday 2nd February, 2009	WG	**Presentations:** • Presentation of the German study, recent publications and the report published by SSK: **B. Grosche** • The different types of nuclear power plant in Germany and the discharge they produce: **A. Heckel - BfS** • French nuclear power plants and the discharge they produce: **F. Féron – ASN** – Nuclear power plant department • Discharge control and environmental monitoring: **JJ. Diana – ASN** – Environment and emergencies department • Calculation of the radiological impact of discharge: **M. Chartier**
Monday 9th March, 2009	Telephone conference	**Reminder of the WG's remit**: firstly, investigate the potential link between nuclear installations and acute leukaemia; secondly, monitor proposals to support and/or launch new studies involving the exploration of other, potentially-related, aetiological factors. • International dimension? The establishment of the "Childhood Leukaemia International Consortium" (CLIC) (J.Clavel). The purpose of CLIC is to promote cooperation between national studies and to set up international studies in order to increase the number of cases and hence take into consideration the heterogeneity of leukaemia. CLIC does not restrict itself to studying ionising radiations.
Thursday 9th April, 2009	WG	**Organisation of the WG**: rules of procedure, communication (relations with monitoring committee, stakeholders and the public), funding of studies, timetable of WG actions. **Presentations:** • The risk factors for childhood cancer: the aetiology of childhood leukaemia - **J. Clavel and C. Faure** • Critical analysis of ongoing epidemiological studies on childhood leukaemia and nuclear power plants - **C. Faure, J. Clavel and D. Laurier** • Evaluation of exposure to radiation around nuclear power plant: critical analysis - **M. Chartier**

Date	Type of meeting	Agenda
Friday 29th May, 2009	WG	**Organisation of the WG**: short-term future of the WG / definition of the themes to address /establishment of sub-groups. Preparation of the scientific seminar on **"Childhood leukaemia, mechanisms and causes", due to be held on 3rd November 2009** in Luxembourg, and hosted by the Article 31 Group of Experts. **Presentations:** • Developing further research strategies in Germany: plans and processes - **B. Grosche** • Bibliographic review - **S. Jacob**
Monday 8th June, 2009	"Sites" sub-group	Objectives and methodology of the proposed approach, definition of the resources needed.
Tuesday 1st September, 2009	WG	Review of the work of the "Sites" sub-group - **Y. Marignac** **Presentations:** • Development of leukaemia, malignant stem cells and multi-step tumour progression: **Mme Pflumio – INSERM** • Identification of a molecular signature of thyroid cancer caused by radiation: **Mme Chevillard – CEA** • Review of the CLIC meeting: **J.Clavel**
Tuesday 3rd November, 2009 Luxembourg European Commission	EU Scientific Seminar 2009 **Childhood leukaemia : Mechanisms and causes**	Presentations on the theme of "Childhood leukaemia – general overview and ongoing studies in France". • The heterogeneity of acute lymphoblastic leukaemia - **D. Sommelet** • Review of research in France – **J. Clavel**
Tuesday 24th November, 2009	WG	Report on the seminar held in Luxembourg on 3rd November - **D Sommelet - D. Laurier** • Work of the "sites" sub-group: list of additional information on sites (location, characteristics), to be obtained from the relevant organisations (ASN, Ministries, etc.) • Discussion on the participation of new, qualified experts in the WG • Drawing up of the WG progress report
Monday 14th December, 2009	"Sites" sub-group	Finalisation of the memorandum for the above-mentioned organisations
Tuesday 2nd February, 2010	WG	Drawing up of the WG progress report
Thursday 15th April, 2010	WG "Sites" sub-group	• Drawing up of the WG progress report • **Meeting of the "sites" sub-group / ASN** (DIS-DEU-DRD)
Thursday 20th May, 2010	WG	Drawing up of the progress report
Thursday 17th June, 2010	WG	Drawing up of the progress report
Monday 28th June,	WG ASN, DGS, DGPR,…	Presentation of the preliminary report
Wednesday 1st September	WG	Finalisation of the preliminary report

1.3.3. Important points to remember from the working group meetings

The following points will be addressed in the next chapters:

▲ The multifactorial nature of leukaemia

▲ The differences in the findings of German and French epidemiological studies (methodology, nuclear plant operating conditions: installation type, location, installation and population density, authorised and actual gas and liquid discharge, quantity and type of discharge, etc.).

▲ Presentation of genetic and environmental risk factors for childhood cancer, besides ionising radiations: genetic predisposition, hydrocarbons, dioxin and polychlorinated biphenyls, radon, pesticides, electromagnetic fields, etc.

▲ The benefits of improving the characterisation of childhood exposure to environmental pollution (through studies such as the French longitudinal study of children, ELFE) and of investigating events occurring before birth. In this respect, storing samples of umbilical blood and taking samples at birth could provide a valuable source of information.

▲ The need to take into account the specific characteristics of nuclear sites: definition of a list of sites and their characteristics (type of site, source of emissions, site history, type of discharge, type of human exposure, waste management strategy). The issue of how to deal with liquid discharge has been raised. Although the issue is relevant, investigating it may not be feasible.

▲ Germany and other countries have been asked to extend studies such as KIKK to other sites (research centres or sites close to the French and Swiss borders) > the Swiss study, CANUPIS, involves all the children born in Switzerland over a period of 6 years (it is due to be published in 2011).

▲ It should be pointed out that discussions are underway in Germany regarding the creation of a prospective cohort, along with the recording of all potential aetiological factors, the storage of blood samples at birth and the genomic characterisation of leukaemia. Furthermore, the development of animal models should be encouraged.

▲ On 9th April 2009, the WG suggested setting up sub-groups in order to:

1) review and update the knowledge of the factors responsible for childhood leukaemia;

2) establish the genomic characteristics of leukaemia occurring in clusters, in order to determine whether there is a link with nearby nuclear installations;

3) create a list of French nuclear sites to be included in current studies; draw up specifications and assess the resources needed.
At a meeting on 8th June 2009, the "sites" sub-group began to discuss the objectives and methodology of the approach proposed, and what resources would be needed to implement the approach successfully.

Objectives: creation of a list of sites (installations that produce or have produced radioactive discharge, and nuclear sites that do or do not produce radioactive discharge); characterisation of these sites, with a view to:
- informing the public (publication of the list of sites and explanation of the possible role of site characteristics);
- conducting various epidemiological studies (selection of sites and identification of characteristics).

Approach: the approach adopted must be exhaustive, selective and iterative: draw up an initial list of sites, identify the characteristics of

interest, gather all the necessary data, draw up a list of the sites finally selected, use this list and publish the results.
The proposals put forward by the "sites" sub-group are presented in chapters V.1. and VIII.2. of the report.

▲ The importance of establishing the genomic characteristics of leukaemia and of identifying a possible link with radiation were addressed by Ms. Pflumio (INSERM) and Ms. Chevillard (CEA); the goal is to identify the molecular signature of ionising radiations (thyroid model) and to help improve the understanding of leukemogenesis (animal models, leukemic stem cells).

1.3.4. Seminar on "Childhood leukaemia, mechanisms and causes", 3rd November 2009

This scientific seminar, hosted by the Group of Experts referred to in article 31 of the Euratom treaty, took place in Luxembourg on 3rd November 2009.

France was represented at this seminar by Danièle Sommelet, Jacqueline Clavel, Dominique Laurier, Margot Tirmarche (IRSN), Alain Rannou (IRSN), Jean Piéchowski (CEA) and Jean Luc Godet (ASN).

Each presentation has been published in the form of an article in the European Commission's "Radiation Protection" review.
Danièle Sommelet and Jacqueline Clavel addressed the subject of "Childhood leukaemia – general overview and ongoing studies in France". Danièle Sommelet focused on the heterogeneity of acute lymphoblastic leukaemia and Jacqueline Clavel presented a review of French studies in this field.

The risk factors for leukaemia were presented by Herbert Jürgens, Germany. He focused in particular on the links between leukaemia and infection/the immune system, and on the theory that the disease develops in several stages, especially *in utero*.
WU Müller's presentation on "Leukaemia and nuclear installations" emphasised the uncertainty and mediocre quality of studies on this subject.

The round table and the ensuing presentations addressed the link between leukaemia and infection. The studies presented by R. Wakeford show that population movements increase the risk of leukaemia in children between 0 and 4 years old in rural areas, especially those living in the vicinity of nuclear power plants. On the other hand, no such increase has been observed in urban areas. The theory that infection is a causal factor has once again been put forward, but no virus has been identified to date.

In his conclusion to the seminar, Patrick Smeesters went back over several points: the heterogeneity of leukaemia, the wide variety of factors suspected of causing the disease (infection, environment, ionising radiations, etc.) and the multi-step development theory. He underlined the necessity of conducting large-scale multidisciplinary studies, which do not focus exclusively on ionising radiations from nuclear installations, but also on gene-environment interactions.

ACUTE CHILDHOOD LEUKAEMIA: A HETEROGENEOUS DISEASE

2

2.1. Introduction

Acute leukaemia accounts for almost all cases of childhood leukaemia. It results from a malignant process occurring in a multipotent hematopoietic stem cell or already taking place in a lymphoid or myeloid differentiation pathway. In addition to the role played by cell-cell interaction and communication, structural and numerical genetic abnormalities cause a dysregulation of the proliferation, maturing, differentiation, senescence and apoptosis processes, in which pre-existing and/or acquired anomalies (for example hypersensitivity to triggering factors and cell repair disorders) play a part.

2.2. Epidemiology: incidence, survival rates

The creation of a national registry of childhood cancers in 1990 has facilitated the development of descriptive epidemiology studies (Clavel et al. 2004). Leukaemia is the most frequent form of cancer in children and adolescents, accounting for 30% of cases. Between 1990 and 1999, 470 new cases were reported per year in children between 0 and 14 years of age, and 80 new cases were reported per year in young people between 15 and 19 years of age. Acute lymphoblastic leukaemia (ALL) accounts for 85% of cases, with a peak age of 2 to 4 years for B precursor cell ALL (excluding Burkitt's Lymphoma). The incidence of leukaemia in Europe may have risen by 0.6% per year over the last 30 years, bearing in mind the possibility of reporting bias (table II).

Cure rates have improved considerably over the last few decades. At present, the cure rates for ALL and AML in children between 1 and 15 years old are 80-85% and 60% respectively.

This progress can be explained by the automatic enrolment of patients in national and international protocols and trials. As a result, the use of chemotherapy has improved and new approaches can be tested (targeted therapies for example). Thanks to these trials, prognostic factors can be more clearly defined and patients can be stratified on diagnosis and during chemotherapy according to clinical, cytological, immunologic, cytogenetic and molecular data (Pui et al. 2008).

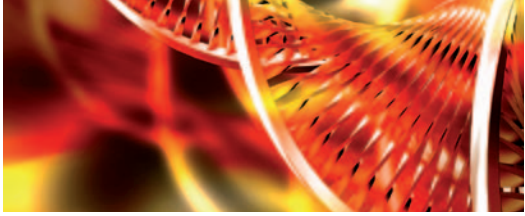


Table 2 : Incidence rate of childhood blood malignancies in France (RNHE, 2000-2004)

Diagnostic groups	N	%	Incidence rate (/10%)			M/F
			Crude	Standardised	Cumulative	
I. Leukaemia, myeloproliferative and myelodysplastic syndromes	**2435**	**28.7**	**43.8**	**45.9**	**659.9**	**1.2**
Ia. Lymphoid leukaemias	1882		33.8	35.7	511.2	1.2
Ia1. Immature cell leukaemias	1799		32.3	34.2	488.7	1.1
Ia2. Mature B-cell leukaemias	82		1.5	1.5	22.3	3.8
Ia3. Mature T-cell and natural killer cell leukaemias	1		0.0	0.0	0.3	-
Ia4. Lymphoid leukaemias not otherwise specified	0		0.0	0.0	0.0	-
Ib. Acute myeloid leukaemias	393		7.1	7.2	105.7	1.1
Ic. Chronic myeloproliferative syndromes	45		0.8	0.7	12.0	1.0
Id. Myelodysplastic syndromes and other myeloproliferative syndromes	68		1.2	1.3	18.4	1.7
Ie. Leukaemias not otherwise specified	47		0.8	0.9	12.7	2.6
II. Lymphomas and reticulo-endothelial neoplasms	**1011**	**11.9**	**18.2**	**17.1**	**270.7**	**1.8**
IIa. Hodgkin's lymphomas	423		7.6	6.7	112.1	1.2
IIb. Non-Hodgkin's lymphomas (except Burkitt's lymphoma)	296		5.3	5.1	79.5	1.7
IIb1. Immature cell lymphomas	122		2.2	2.1	32.7	2.7
IIb2. Mature B-cell lymphomas (except Burkitt's lymphoma)	74		1.3	1.2	19.8	1.5
IIb3. Mature T-cell and natural killer cell lymphomas	92		1.7	1.6	24.8	1.2
IIb4. Non-Hodgkin's lymphomas, not otherwise specified	8		0.1	0.1	2.2	1.0
IIc. Burkitt's lymphomas	255		4.6	4.5	69.2	5.4
IId. Reticulo-endothelial neoplasms	36		0.6	0.7	9.7	1.1
IIe. Lymphomas not otherwise specified	1		0.0	0.0	0.3	0.0

2.3. Stratification of acute leukaemia

At present, stratification is based on the following criteria, regardless of the type of leukaemia: clinical data (age, leukocytosis, impairment of the central nervous system), cytology and cytochemistry, immunophenotyping, cytogenetics, molecular typing and early response to chemotherapy (evaluation of the residual illness). (Pui et al. 2008, Vrooman and Silverman, 2009).

2.3.1. Acute Lymphoblastic Leukaemia (ALL)

In ALL, the leukaemia cells show rearrangements of the immunoglobin and/or T-cell receptor (TCR) genes and, on their surface, express proteins corresponding to the early stages of maturation of normal T or B lymphocyte cells. However, they contain genomic anomalies which cause maturation arrest at a variable stage.

The identification of abnormalities in the number and structure of chromosomes has improved the understanding of some leukemogenesis mechanisms. Human genome sequencing, new biotechnologies such as transcriptome analysis using microarrays, comparative genomics and the full sequencing of the tumour cell genome using microarrays that explore variations in genetic polymorphisms, have led to rapid progress in the knowledge of leukaemia cells.

Chromosome accidents (deletions, translocations, mutations, etc.) lead to the

accumulation of genetic abnormalities. Chromosome translocations activate transcription factors, the aberrant expression of which in the leukaemia cells either induces or represses target genes involved in differentiation, proliferation, cell death, and self-renewal and quiescence properties.

The heterogeneity of ALL is confirmed by the existence of homogeneous transcriptional profiles in the sub-categories defined for the purpose of adapting the treatment strategy.

Prognostic classification of ALL

Cooperative groups recognise four prognostic groups. It should be noted that the FAB 3 sub-type (Burkitt's lymphoma) is not included in this classification. The four groups are as follows:

▲ **children below 1 year old (2% of ALL).** 80% present a severe form of ALL (especially those below the age of 6 months, with a white cell count above 300,000/mm3): pro-B (CD19+, CD10-) with rearrangement of the MLL gene located in 11q23.

▲ **children presenting a standard risk pre-B ALL (54% of ALL)**. 1 to 10 years old, white cell count below 50,000/mm3, cytogenetic or molecular abnormalities with a good prognosis: hyperploidy above 50 chromosomes, trisomy of chromosomes 4, 10 and 17, translocation t(12;21) / TEL-AML1 t(1;19) / E2A-BPX1 and absence of poor prognosis cytogenetic or molecular abnormalities (Rubnitz et al. 2008).

▲ **children presenting a high risk pre-B ALL (30% of ALL)**. Above 10 years old, white cell count above 50,000 / mm3 and cytogenetic or molecular abnormalities such as t(4 ;11) / TEL-AF4 and other rearrangements of the MLL gene, hyperploidy below 45 chromosomes, t(9; 22) / BCR-ABL (Philadelphia chromosome), mutation or deletion of the IKZF1 gene occurring even in the absence of a BCR-ABL fusion gene (Mullighan et al. 2009).

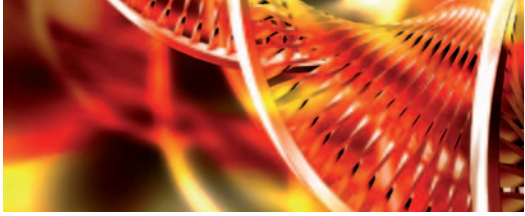
▲ **children presenting a T-cell ALL (14% of ALL)**. More effective therapeutic protocols have improved their prognosis, especially in the case of hyperleukocytosis (above 200,000/mm3), t(5 ;14)/ TLX3-HOX11, certain rare rearrangements of the T receptor, and del(9p) (Borowitz et al. 2008).

It is also important to mention the key role played by the early detection of residual disease using flow cytometric and molecular methods: it is measured either in the blood (8 days after a single corticotherapy session) or in the bone marrow (15-20 days and 30-40 days after starting polychemotherapy). The protocol may be continued or intensified according to the level of residual illness, regardless of the initial prognostic factors.

Furthermore, the response to treatment is related to the level of expression of apoptosis-facilitating genes (quick response to treatment) or of genes involved in cell adhesion, proliferation or anti-apoptosis (slow response or resistance to treatment) (Bhojwani et al. 2008).

2.3.2. Acute myeloblastic leukaemia (AML)

Due to the complexity of AML, it must be carefully diagnosed according to the 7 cytological types in the FAB classification and the associated genetic abnormalities; this is crucial to defining an appropriate treatment strategy and to continuing to improve the cure rate (without systematically resorting to hematopoietic stem cell transplantation after the post-chemotherapy remission period).

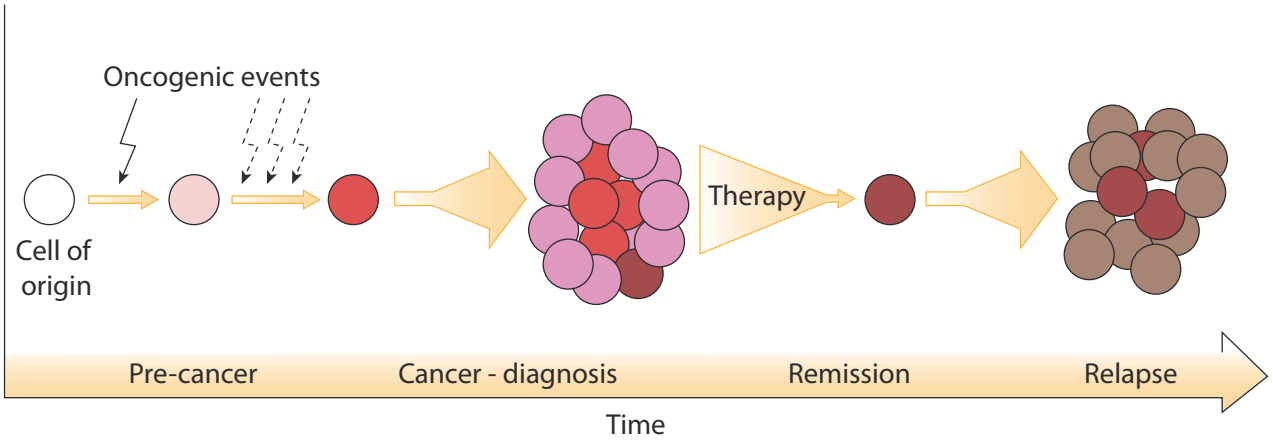


The prognosis is favourable in children below the age of 1, especially those with a white cell count greater than 50,000 / mm3, monosomy 7, deletion 7q, t(9;11)(p21-22;q23) or other MLL rearrangements. The existence of a residual illness after two programmes of chemotherapy is a highly unfavourable prognostic factor.

The prognosis is favourable in patients with t(8 ;21)(q22;q22)/AML1-ETO, t(15;17)(q22;q12-21) and inv(16)(p13;q22).

The prognosis is average in patients with acute megacaryoblastic leukaemia, trisomy 21 and normal karyotype AML.

2.4. The multi-step development of leukaemia



Bomken et al, 2010 *- From the stem cell to the development of cancer and possible relapse. An initial oncogenic event (solid arrow) occurring in a normal cell can create a precancerous cell or lead directly to malignant transformation. The oncogenic event is likely to feed on a certain number of genetic or epigenetic events (dotted arrows). From clinical diagnosis onwards, the heterogeneous tumour contains cells that have produced or can produce stem cells, and therefore do not respond to standard therapy. These stem cells can divide and differentiate to replenish the tumour.*

Several studies conducted over a period of more than ten years have confirmed the multi-step development of both ALL and AML (Bomken et al, 2010). **The initial event (most often a translocation) may be inherited or occur in utero. It leads to the development of a preleukaemia clone, which carries one or more characteristic genomic abnormalities** (Wiemels et al. 2008).

The arguments behind this theory are as follows: the very short latency between birth and the onset of ALL (age peak between 2 and 4 years); the extreme cellular kinetic stress of the foetus; the high rate of concordant leukaemia in twins (thanks to placental anastomosis); and, above all, the discovery of preleukaemia clones in archived blood samples from around 1% of newborns. The development of these preleukaemia clones (initial event) results from:

- Rearrangements of the MLL gene at 11q23 and of chromosomes 4, 9 and 19 (observed in 80% of AML cases and 60% of ALL cases in infants below the age of 1).

These MLL rearrangements are also observed in cases of acute leukaemia occurring after treatment with topoisomerase II inhibitors. This suggests that fœtal exposure to such substances, combined with the reduced ability of the fœtus and/or the mother to catabolise them, may play a role in the development of acute leukaemia in infants;

- Rearrangements of the ETV6 gene at chromosome 12 and of RUNXI at chromosome 21 (TEL-AML1 observed in 25% of ALL cases); (Hong et al. 2008).
- Rearrangements of RUNX1/ETO at chromosome 8 in 15% of AML cases;
- Trisomy 21;
- Notch 1 mutation in T-ALL (Armstrong et al. 2009 ; Eguchi-Ishimae et al. 2008).

Except perhaps for a few cases of acute leukaemia developing during the first year of life, one or more secondary events are required to induce leukaemia (as indicated by the occurrence of additional genetic abnormalities in 1% of the children monitored from birth due to the presence of a preleukaemia clone). (Kinlen, 2004; Greaves and Buffer, 2009).

Hence, TEL-AML1 gene fusion (associated with pre-B ALL) generates a population of persistent preleukaemia cells *in utero*. These cells proliferate slowly due to the inhibition of the TGFß pathway by the TEL-AML1 protein, which also interferes with the regulation of immunologic and inflammatory reactions. Therefore, the malignant progression of the preleukaemia clone (generally observed after chromosome 12p deletion) can be explained by a dysregulation of the immune response system, which leaves the organism vulnerable to the consequences of a second event. It has been suggested that this second event may have an infectious origin, but this has not been proven.

The multi-step development of leukaemia reflects the complexity of the events occurring and underlines the need to better understand the leukemogenesis process and hence the action mechanisms of potential risk factors (Wiemels, 2008; Bernt and Armstrong, 2009, Sipkins, 2009; Barber et al. 2009).

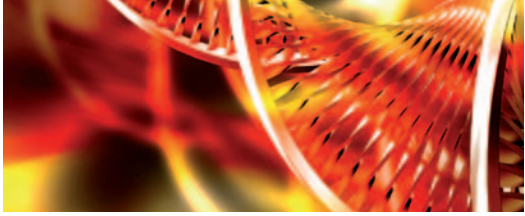
Leukaemia and the immune system, ionising radiations, infections, other factors

The effects of ionising radiations on the functional expression of the immune system have been documented in many studies. However, it is difficult to compare the results of these studies due to differences in the methodologies used and the modalities of exposure to ionising radiations (dose, dose rate, radiation type, cell type).

Note: the occurrence of immuno-suppression and immuno-modulation, especially following exposure to **high doses**, causing cytotoxicity and cell signalling abnormalities. Therefore, cancer can develop due to a defect in the immunological surveillance system or to chronic inflammatory reactions associated with the activation of cells involved in immune defence or in the inhibition of cell-mediated cytotoxicity.

Following atomic bomb blasts and nuclear accidents such as Chernobyl, hematopoietic regeneration occurs after several months or years. This regeneration includes the immune functions. However, a few abnormalities and senescence phenomena persist, which can lead to pathological outcomes. It should also be noted that chromosome abnormalities continue to exist for a long time after exposure to high doses of radiation.

The persistence of immune system abnormalities associated in particular with the T-cell line, the abnormal production of cytokines



and chronic inflammatory processes can also cause non-malignant diseases (due to a failure to control infections and to autoimmune mechanisms). Such diseases (e.g. heart disease) have recently been reported in atomic bomb blast survivors.

There is still much controversy as to the effects of **low doses** (< 100 mGy) and **low dose rates** (< 100 mGy/h) of ionising radiations on the immune system. In animals, either immune cell depletion or a stimulation effect is observed. Clinical studies are still rare, and should be pursued.
Also, following exposure to low doses, indirect "bystander" effects, genomic instability and adaptation phenomena should be taken into consideration, in addition to the direct effects of ionising radiations on the cells.

What impact do ionising radiations have on the immune system? The question is still open to debate.

A possible dysregulation of the immune response to common (viral?) infections in children has been under discussion since the late 1980s:

- the Kinlen hypothesis, based on a glut of leukaemia cases in the population around Sellafield;
- The Greaves hypothesis based on a correlation between lifestyle (day-care attendance), the peak in leukaemia incidence at 2 to 5 years old and delayed immune stimulation. However, unlike in animal models, no specific infectious agent has been isolated. Viral genome research using potential preleukaemia cells has not identified any such agents either.
- The Smith hypothesis: an initial infectious event in utero (preleukaemia clone), followed by one or more post-natal mutations.

While the infection theory cannot be discarded, the idea that exposure to ionising radiations causes an immune imbalance requires further investigation. Moreover, such imbalances are observed in some genetic illnesses.

The research could focus on the following points:

- detailed analysis of radiation-induced immune disorders;
- the effects of low doses and low dose rates vs. medium and high doses;
- the combined effects of ionising radiations and other genetic and environmental factors;
- the impact of external and/or internal radiation;
- immune disorders caused by ionising radiations and secondary illnesses (long-term health effects).

2.5. Questions

At the end of this chapter, several questions remain open:

▲ *How can we improve the assessment and understanding of childhood acute leukaemia, bearing in mind its heterogeneity and genetic complexity? Genomic sequencing of tumour cells, role of the medullary stroma, pharmacogenetic study of children and parents, transfection to animal models, long-term in vitro culture of leukaemia cells, etc.;*

▲ *How can we improve the knowledge of the causes of leukaemia, especially in children? Link between leukaemia stem cells, preleukaemia clones, pre-existent cell abnormalities or cell abnormalities occurring at leukaemia transformation, and the associated genetic and/or environmental causes?*

▲ *How should new aetiological factors be taken into account (concept of confusion factors)?*

▲ *How can we reconcile the study of a large number of potential aetiological factors with all the molecular biology studies needed to understand the complexity of the disease? Is there a link, at least with certain aetiological factors or sub-types?*

▲ *Can we carry out a retrospective study of the possible links between leukaemia type (immunophenotype, cytogenetics, molecular signature) and exposure to such and such a potential risk factor (especially ionising radiations from nuclear installations)?*

▲ *How do we address the problem of the statistical power of studies, given the rarity of the disease and the large number of abnormalities that may or may not confirm the role of such and such an aetiological factor?*

KNOWLEDGE OF THE RISK FACTORS FOR CHILDHOOD LEUKAEMIA

3

The causes of leukaemia are still unclear (Rossig and Juergens, 2008). Less than 5% of cases are associated with a genetic disposition, such as trisomy 21, chromosome instability, a DNA-repair disorder, a systemic immune deficiency, type-I neurofibromatosis or Li-Fraumeni syndrome. We know that previous exposure to a confirmed environmental risk factor plays a role (high doses and high dose rates of ionising radiations, topoisomerase II inhibitors, aldylating agents, benzene); the role of other (potential) risk factors is still only more or less strongly suspected: very low doses and low dose rates of ionising radiations, including natural radiation, extremely low-frequency magnetic fields (high-voltage lines), pesticides and traffic pollution. Infections during infancy and the factors contributing to their occurrence (breastfeeding, day-care, etc.) should also be taken into consideration. The fact that these factors can intervene not only in the infant, but also in the foetus or in the mother or father prior to conception, only adds to the complexity of the problem.

The first genome-wide association studies have revealed associations with SNPs within the ARID5B, IKZF1, CEBPE and CDKN2A genes. The significance of this is currently being investigated. Few studies have been conducted on gene-environment interactions, which lead to polymorphisms in the genes involved in the metabolism of aromatic polycyclic hydrocarbons, benzene and alcohol, and in DNA repair.

The morphological, immunophenotypical, cytogenic and molecular heterogeneity of leukaemia probably reflects its aetiological heterogeneity. We can therefore expect to discover specific links between certain types of exposure and certain leukaemia sub-types. The more the affected cell is differentiated, the more specific the link will be. For reasons of participant numbers, the studies published to date have concentrated essentially on separating cases of ALL, AML and pre-B ALL in order to establish such links. Considering the period at which they were carried out, they rarely took molecular characteristics into account. The theories regarding a molecular signature are still very tenuous. One research paper addressed the possibility of there being specific links between 11q23 rearrangements and the consumption of foods with topoisomerase II inhibition properties. These findings have never been reproduced. In France, the National Registry of Childhood Blood Malignancies has concentrated on recording a large number of the cellular and molecular characteristics of leukaemia in a standardised manner, so that specific links can be identified when statistical power permits.

3.1. Exposure to ionising radiations

3.1.1. Knowledge of the link between ionising radiations and childhood leukaemia

It has already been established that high doses of ionising radiation play a role in most childhood cancers (Unscear 2008). However, the bone marrow seems to be more sensitive to ionising radiations than other organs, and leukaemia is now regarded as being one of the cancers most frequently induced by high doses of ionising radiation.

Compared with solid cancers, the increased risk of developing leukaemia emerges much more quickly following exposure (within a few years rather than a few decades). Leukaemia was the first type of cancer to be associated with external exposure to ionising radiations in the Hiroshima and Nagasaki survivors' cohort (Folley 1952). Furthermore, at a given dose, the risk of developing leukaemia increases much more significantly than that of developing a solid cancer (ICRP 2007). Lastly, the excess risk per unit dose is higher if exposure occurs in childhood than if it occurs in adulthood (Preston et al 1994; Preston et al 2004).

These findings have been confirmed by several studies, not only in Hiroshima and Nagasaki survivors but also in subjects exposed to medical or accidental radiation. It has now been acknowledged that individuals who have been exposed to radiation doses above a few hundred millisieverts are at risk of developing leukaemia (IARC 2000; IARC 2001; NRC 2006; Unscear 2008). Given these findings, the model currently used to estimate the radiation-induced risk of leukaemia is based on a linear-quadratic bone marrow dose-response relationship, and takes into account the modifying effects of sex, age at exposure and time since exposure (Unscear 2000; NRC 2006).

It is more difficult to accurately quantify the risk of leukaemia associated with lower radiation doses and with chronic exposure to low doses. The Oxford Survey of Childhood Cancer, which focused on the risk of childhood cancer from pre-natal X-ray exposure, revealed an excess of leukaemia cases in children exposed *in utero* to doses above 10 mGy (Doll and Wakeford, 1997; Wakeford and Little, 2003). This study included over 10,000 matched case/control pairs of children born between 1943 and 1976. However, more recent studies concentrating on lower doses of *in utero* radiation did not show an excess of cases (Ron, 2003). It is also worth mentioning a very recent publication by Noshchenko et al., indicating an increased risk of leukaemia at bone marrow doses of only 10 mGy, in Ukrainian children below the age of 5 at the time of the Chernobyl accident (Noshchenko et al 2010).

3.1.2. Exposure to natural ionising radiations

In France, the average individual effective dose of natural radiation is 2.4 mSv per year. This dose can be lower by a factor of 2 or higher by a factor of 5 depending on the region: from 1.2 mSv to 12 mSv per year (Rannou et al 2006). Natural radiation includes radon (58%), gamma rays emitted from the earth's surface (telluric radiation) (21%), cosmic radiation (13%) and radiation from water and food (8%).

Since the late 1980s, around 20 ecological

studies have linked regional variations in leukaemia incidence with variations in domestic radon concentrations. Most of these studies conclude that there is a positive correlation between the two [Laurier et al. 2001]. A recent review, focusing specifically on infant leukaemia, reached a similar conclusion (11 positive correlations – 8 of which are significant – in 12 ecological studies [Raaschou-Nielsen 2008]). An ecological study conducted in France has revealed a moderate but significant correlation between exposure to domestic radon and AML incidence in children: the incidence rate was 24% higher in areas with the highest radon levels (on average, there was a difference of 100Bq/m3 between the highest exposure quintile and the lowest exposure quintile serving as the referent) [Evrard et al 2005]. This correlation was still evident after exposure to telluric radiation had been taken into account (Evrard et al 2006).

On the other hand, case-control studies conducted in the general population have produced contrasting and, for the most part, insignificant results [Raaschou-Nielsen 2008]. The expected correlation (based on the findings of the ecological studies) is low, and it would require a much bigger case-control study than those which have been conducted to date to confirm it. Nevertheless, a recent Danish study has revealed a correlation between model-estimated domestic radon concentrations and the risk of ALL [Raaschou-Nielsen et al. 2008]. It has recently been estimated that 8 to 30% of infant leukaemia cases in Great Britain could be attributable to natural radioactivity [Wakeford et al. 2009]. This estimation takes telluric and cosmic radiation into consideration, which were not always taken into account in the studies referred to above. [Laurier et al. 2001].

3.1.3. Medical diagnostic exposure to ionising radiations

Medical procedures are the primary artificial source of ionising radiations. In France, they account for around 40% of annual exposures (Billon et al, 2005; IRSN/InVS report, 2010). The vast majority of these procedures are for diagnostic purposes and they expose large numbers of people to low doses of ionising radiations (70 million X-rays are performed every year in France, and this number is increasing by 5 to 8% per year). On the other hand, therapeutic procedures expose individual people to much higher doses, mainly for the purpose of treating cancer. Such exposures involve only a small proportion of the French population (around 180,000 people per year).

Approximately 3.6 million CT scans are performed every year. Due to technological progress, the doses delivered to patients have increased: the ease and rapidity of image acquisition has lead to a rise in the number of exposures. The doses delivered to patients during diagnostic examinations vary from a fraction of a millisievert (mSv) for a thorax scan to around 10 mSv for an abdominal/pelvic scan. Scans account for only 5% of X-ray examinations, but they represent 40 to 67% of total medical radiation exposure, depending on the country (UNSCEAR 2000).

Brenner and his colleagues argue that CT scans increase the lifetime risk of death from cancer in paediatric subjects living in Anglo-Saxon countries. The mortality risks associated with abdominal and brain scans in one-year-old children are 0.18% and 0.07% respectively (Brenner 2001). In France, X-ray examinations are performed less frequently on children than on adults,

so the collective dose associated with them is lower. Nevertheless, there are several problems specific to paediatric radiology: the tissue of children is more sensitive to radiation than adult tissue, children have a longer life expectancy and are therefore more likely to develop a risk of cancer, and X-ray procedures are not technically adapted to their needs.

The IRSN has launched a large-scale study in France to assess the risk of cancer in children who have had a CT scan (Bernier et al 2010). Recommendations have been made to reduce the dose per scan.

3.2. Exposure to non-ionising radiations

A large number of studies have been conducted on exposure to **extremely low frequency electromagnetic fields** (ELF-EMFs). Meta-analysis results [Ahlbom et al. 2000] [Greenland et al. 2000] have lead the IARC (International Agency for Research on Cancer, WHO) to class exposure to magnetic fields of 0.4 µT or more as "a possible human carcinogen" (2B) [IARC, 2002]. It is believed that this level of exposure doubles the risk of childhood leukaemia and affects around 1% of the paediatric population. Magnetic fields do not seem to be associated with other forms of cancer. High- and very high-voltage power lines can only partly explain high exposure levels. However, this type of exposure can be identified, whereas transformer stations and other network set-ups that generate this level of electromagnetic field strength are more difficult to locate and quantify. The percentage of children exposed to electromagnetic fields of 0.4 µT or more is much higher in populations living within 30 metres of high-voltage lines than in the rest of the population.

3.3. Infectious factors

Viral infections are at the root of several animal cancers and have been suspected of causing childhood leukaemia for many years. This theory, which has been put forward to explain the development of some spatiotemporal leukaemia clusters [Kinlen 1988], has been reinforced by the repeated observation of incidence rate increases in areas subject to large population movements [Kinlen et al. 1995]. Building on this theory, a link has been identified between childhood leukaemia incidence and population movements in the child's place of residence at birth [Rudant et al. 2006] or at diagnosis [Bellec et al. 2008]. The leukaemia incidence rate appears to be significantly higher in remote areas experiencing large movements of population. However, the search for leukemogenic viruses in cases of childhood leukaemia has not produced any results.

Common infections occurring in the first few months of life seem to play a key role in the maturation of the immune system. In the absence of adequate stimulation, the preleukaemic lymphocytes that develop in around 1% of foetuses are more subject to leukaemic transformation during childhood infections [Greaves 2006]. Several studies have revealed a negative correlation between childhood leukaemia and a high number of common infections occurring within the first 12 months of life or early entry into day-care.

3.4. Exposure to pesticides

Several authors have linked domestic exposure to **pesticides** with the risk of childhood leukaemia [Lowengart et al. 1987; Buckley et al. 1989; Leiss and Savitz 1995; Infante-Rivard et al. 1999; Ma et al. 2002; Menegaux et al. 2006; Rudant et al. 2007].

3.5. Exposure to hydrocarbons

A great deal of research has been conducted into **parental occupational exposure**, but the type of exposure is poorly defined in most cases. Maternal exposure to organic solvents during pregnancy could be a risk factor for childhood leukaemia and brain tumours.

It has been established that **benzene** is leukemogenic in adults [IARC 1982]. It is therefore beneficial and important to investigate its effects on children. Although studies of the relationship between exposure to **traffic pollution** and the risk of childhood leukaemia are very few, most of them conclude that living in high traffic areas increases the risk of leukaemia [Savitz and Feingold 1989] [Pearson et al. 2000] [Nordlinder and Järvholm 1997] [Feychting et al. 1998] [Crosignani et al. 2004] [Visser et al. 2004]. The Lombardy cancer registry has firmly linked the risk of leukaemia with the estimated amount of benzene produced by road traffic at the place of residence at diagnosis, with an odds ratio of almost 4 where estimated benzene exposure levels reach 10 µg/m3 or more [Crosignani et al. 2004]. Two successive and convergent case-control studies conducted within the team have reached similar conclusions in regard to benzene exposure. They both suggest a possible increase in the risk of leukaemia, associated with immediate proximity to garages and petrol stations (odds ratio between 2 and 4, concerning 3 to 6% of the paediatric population) [Steffen et al. 2004][Brosselin et al. 2009]. A third study also reports an increased risk in children living within 100 metres of a petrol station [Harrison et al. 1999].

3.6. Proximity to non-nuclear industrial installations

Very few studies have explored the possible impact of pollution from **non-nuclear industrial installations** on the risk of childhood cancer. The methodology employed in the Knox and Gilman study [Knox and Gilman 1997], which suggests that there is a higher incident rate in the vicinity of oil refineries and metallurgy plants, has been widely criticised. Two other studies found no evidence of a higher incidence rate around petrochemical plants [Sans et al. 1995] [Wilkinson et al. 1999]. No data is available yet on the risk of childhood cancer in areas close to incinerators and to industrial sources of dioxin and PCB.

4 PROXIMITY TO NUCLEAR INSTALLATIONS AND ACUTE CHILDHOOD LEUKAEMIA: RECENT REVIEW OF EPIDEMIOLOGICAL STUDIES

The question as to whether or not there is a greater risk of developing childhood leukaemia in the vicinity of nuclear installations has been raised repeatedly since the 1980s, and many descriptive epidemiological studies have been carried out on the subject.

In April 2008, the IRSN conducted a critical review of the studies published (IRSN 2008) (Laurier et al. 2008a). Since then, the IRSN has also been monitoring publications relating to this theme. At the start of 2008, descriptive data were available for 198 nuclear sites in ten different countries: Great Britain, Germany, France, Sweden, Spain, the United States, Canada, Japan, Switzerland and Israel. Local studies focusing on a specific site were considered separately from multi-site studies investigating a group of sites within one country.

According to the report, three sites could be considered as confirmed clusters: Sellafield in England, Dounreay in Scotland and Kruemmel in Germany. A number of sites, such as Aldermaston and Burghfield in Great Britain or the La Hague reprocessing plant in France, were classed as possible clusters because, while the findings relating to them were equally well-documented, they were insufficient to prove the existence of an excessive number of cases. Although many studies have been carried out to determine the possible causes of leukaemia clusters around certain sites, none of the theories put forward so far (cf. Chapter III) have been able to explain them.

The review of all the multi-site studies conducted to date, including in France, has not produced any evidence of an increase in overall leukaemia frequency in the 0-14 and 0-24 age groups. Nevertheless, a German study (KIKK Study) described an excessive number of leukaemia cases in children between 0 and 4 years old living in the vicinity of German nuclear power plants (Kaatsch et al. 2007; Spix et al. 2007). Bearing in mind that this very narrow age bracket was not widely studied prior to the publication of these results, primarily due to the small number of subjects involved, these findings are not supported by any other study, including the most recent French study on the subject (Laurier et al. 2008b) and a British study (Bithell et al. 2008). Moreover, although one of the original objectives of the German study was to provide additional information which could have explained the excessive number of cases (for example, information on lifestyle, the children's medical history, potential exposure during childhood or pregnancy, etc.), it failed to do so (Grosche 2008; Nussbaum 2009).

Finally, this critical review showed that the limits inherent to descriptive studies are substantial and that they make it difficult to interpret the results. Under these circumstances, each new result had to be compared with existing scientific knowledge (IRSN report, 2008). This report gave rise to a number of letters and observations (Mangano and Sherman 2008; Fairlie 2008, 2009a, b, c; Fairlie and Körblein 2010; Laurier et al. 2010), illustrating the difficulty of interpreting results and the importance of considering the quality of studies when assessing the risk of childhood leukaemia in the vicinity of nuclear sites. For example, the results obtained in a recent multi-site study in America (Mangano and Sherman 2008) seem to be arguable from a methodological point of view. Indeed, most of them can be explained by a single site, and "proximity" to this site was defined as being within 150 km.

A meta-analysis has also been carried out to try to combine the results of the various descriptive studies (Baker and Hoel 2007). To summarise, the results (based on 17 of the 37 studies originally identified) showed standardised mortality ratios (SMR) and standardised incidence rations (SIR) that were greater than 1 and significant. However, this meta-analysis was methodologically limited, which meant that the results were relatively unreliable (Spix and Blettner 2009).

Finally, a study was conducted recently in Finland (Heinavaara et al. 2009), where there are currently 2 nuclear power plants in operation. Based on a rigorous methodology involving 3 different approaches, this study did not find any evidence of an increased risk of childhood leukaemia around nuclear power plants, regardless of the age group (0-4; 5-9; 10-14; 19-19; >=20) or the size of the area studied (0-4 km, 5-9.99 km, etc). However, it involved a very small number of subjects and therefore had a limited ability to identify any excesses.

NUCLEAR INSTALLATIONS AND RADIOACTIVE DISCHARGE

5

5.1. The identification of sites of interest

5.1.1 Needs

At the very first meetings of the pluralist working group on the risk of leukaemia around nuclear installations (leukaemia WG), questions were raised as to the type of installations to include. The discussions led to the following conclusions:

- "nuclear installations", i.e. sites or facilities operating in the nuclear sector, vary greatly in terms of their purpose, characteristics and discharge;
- there are many sites and facilities operating outside of the nuclear sector which also release radioactive material into the environment and are therefore likely to cause similar concerns;
- therefore, the sites and installations in these two groups had to be prioritized and selected according to their relevance to the subject in hand (childhood leukaemia);
- this proved to be difficult for several reasons:
  - the selection process must take into account a broad range of relevant criteria relating to the characteristics of the installations, the assessment of risks and the concerns of the general public,
  - non-specialists, including those in the working group, are largely unfamiliar with the diversity of the installations potentially concerned,
  - there is no centralised database of information on the installations potentially concerned, and the amount of information available on the different categories covered varies greatly,
  - the initial discussions revealed no existing, straightforward set of criteria for drawing up a single list of installations.

The working group concluded that the rigorous identification and selection of sites of interest and their discharge is an essential part of its mission to review the current knowledge and propose the studies and research needed to improve it.

5.1.2. Objectives

The objective identified by the working group is to draw up a list of sites of interest, in terms of the risk of leukaemia in the surrounding area. This list is to be accompanied by an explicit set of criteria and an explanation of the selection process.

This task is important in regard to both methodology and results:

- from a scientific viewpoint: it will make the site selection process more efficient

and facilitate the characterisation of discharge from these sites and hence the assessment of risks. This approach could be used in the short term to revise the list of sites selected for INSERM's georeferenced epidemiological study (Géocap). A more precise site selection process and a more detailed characterisation of discharge could then be developed for use in subsequent studies;

- from an information viewpoint: the process, which consists in drawing up an inventory of potential sites of interest before making a selection based on relevant criteria, will clarify the issues involved and hence make it easier to explain them to the stakeholders, the media and the general public.

Besides being essential to the successful completion of the working group's mission, this approach to assessing the risk of childhood leukaemia has a much broader advantage in that it could be adjusted, if necessary, to address other risks associated with nuclear installations.

5.1.3. Creation of a sub-group

In July 2009, the working group decided to set up a sub-group tasked with defining selection criteria and drawing up the list of sites of interest. The creation of a sub-group was a necessary step, in order to:

- maintain as close a link as possible between the "technical task" of identifying and selecting sites, and the discussion of risk factors within the WG,
- ensure a pluralist approach, taking into account the concerns of each different member of the WG (nuclear installation specialists, health risk specialists, experts from various associations and patients' representatives) at every stage.

The sub-group has met 3 times since it was created (8th June and 14th December 2009, 15th April 2010) and, on 28th June 2010, it presented the approach it would be taking to the working group.

5.1.4. The sub-group's approach and the steps involved

The approach adopted by the sub-group consists of two phases, based on 2 successively-established lists:

- The first list will provide an exhaustive selection of nuclear sites and installations that have produced or still produce radioactive discharge, based on existing, generic lists of sites (BNIs, mines, hospitals, SBNIs, ICPEs, etc.).
- The second list will contain only the sites that are relevant in terms of the risk of leukaemia in neighbouring populations. It will be based on (i) the first list and (ii) selection criteria relating to the risk of leukaemia in neighbouring populations.

This approach is in keeping with the aim to control costs and avoid delays. Note that:

- the sub-group's work will be based as far as possible on information provided by relevant parties within the organisations responsible for controlling the installations concerned. These parties may be consulted by means of hearings, prepared for in advance by a questionnaire and followed up, if necessary, by an exchange of written documents;
- the goal is to establish a list of information of interest and to verify the availability of this information without going so far as to systematically collect it. Any easily accessible information will be collected, and requirements regarding the identification of less accessible information will be defined with a view to collecting it further down the line.

Four key steps can be identified:

▲ *Establishment of an initial list of sites*

At this stage, existing lists will be used without taking into consideration the importance or even the relevance of the different categories. The proper authorities and organisations will be contacted to obtain a list for each category and to verify the type of information available (ASN, DSND, DGPR, IRSN, ANDRA[14], DREAL[15], etc.). Sites throughout mainland France will be counted.

▲ *Identification of characteristics of interest, selection*

A general list of the information necessary/relevant to characterising each of the potential installations will be drawn up. This information will pertain to the site (geographic and socio-economic characteristics, etc.), the installation itself (type of activity, size, etc.), and the discharge from the site or installation (type, volume, etc.). A preliminary list of the information required is provided in chapter 5.1.6.

On the basis of this information, a set of criteria will be defined with a view to selecting the most relevant sites in terms of their characteristics and of the public's perception of the threat they pose to neighbouring populations. The sub-group has suggested extending the criteria to include the risk of cancer and childhood leukaemia. Lastly, an explanation will be provided of the criteria selected and of the sites selected on the basis of these criteria.

▲ *Collection of the information needed to define site characteristics*

At this stage, the inventory of available information sources put together during the preceding steps will be completed. Wherever possible, this inventory will be updated with additional information requested from relevant organisations, which may include those involved in the preceding stages or other players such as nuclear operators.
In addition to identifying accessible information, this step may lead to recommendations regarding further research.

▲ *Use of the list and publication on the selection procedure*

The completion of the previous steps should result in a list of installations. The process of producing this list is just as important as the list itself, so an explanation of the objectives and limits of the list and of the selection process and criteria will also be provided. Prior to publication, the legitimacy of the list will be verified by consulting the organisations concerned.
It will then be used, as planned, in epidemiological and public health research projects, and distributed to various groups of people (general public, intermediary bodies, radiation protection and public health organisations, etc.) via the most appropriate media (web, articles, conferences, etc.).

5.1.5 Resources and time frames

The work is being carried out by the "sites" sub-group of the leukaemia working group. This sub-group is made up, as far as possible, of representatives of the different groups in the working group.
The resources and support needed to carry out the work include:

- technical secretarial support for the sub-group, ensured by the ASN with the assistance of the working group's technical secretariat,
- coordination of the sub-group, ensured by WISE-Paris,
- data analysis and editorial work, shared between the representatives of the various institutes in the leukaemia working group

14 ANDRA: French National Agency for Radioactive Waste Management
15 DREAL: Regional Directorate for the Environment, Land-Use Planning and Housing

(IRSN, INSERM, InVS) and non-institutional experts (WISE-Paris, ACRO, etc.),

- the cooperation of the authorities concerned in providing the necessary information.

5.1.6 Identification of site characteristics of interest

The sub-group has drawn up a preliminary list of characteristics of interest, which has been discussed with representatives of the relevant departments within the ASN.

The information put together will enable us to identify, select, prioritise and characterise installations of interest. Hence, each installation will be characterised by a set of information, ranging from the trivial to the highly complex. Although not exhaustive, this information will cover the following points:

▲ *sites:*

- location,
- type: single installation or a group of installations on the same site,
- the economic environment: industrial environment or remote site, presence of chemical plants, high-voltage power lines, etc.,
- demographic environment: population density, urban/rural area,
- geography and climate (wind rose, etc.).

▲ *installations:*

- characterisation of the installation:
- type of installation,
- type of activity,
- administrative category,
- period of operation: start-up phases, significant modifications, end of operation (if appropriate), etc.,
- operator,
- environmental monitoring: is there an environmental monitoring programme or not? who is in charge of it? what criteria is it based on, etc.

▲ *discharge:*

- is there any radioactive discharge, managed in accordance with discharge standards?
- type of discharge: gaseous and/or liquid, radionuclides, etc.,
- volume,
- characterisation of discharge outlets: height of chimney for gaseous discharge, type of receiving environment for liquid discharge (river, basin, wastewater treatment plant, etc.),
- characterisation of the rate of discharge: frequency, flow rate, etc.
- period of discharge, changes in discharge during operation,
- history of incidents,
- are impact calculations carried out, what is the basis of measurement (real data, regulatory data, etc.).
- combined discharge of chemical substances, etc.

The initial objective is not to gather detailed information on all of the installations concerned and all of the characteristics defined. The main focus will be on whether such information exists and if it is accessible.

For each point, the aim is to determine:

- if the information exists (in some cases, the answer is obvious), and if the authority in question has access to it,
- if yes, what form does the information come in (level of detail, type of document, format, etc.),
- and how accessible is it (confidentiality, physical access, etc.)? If necessary, what is the access procedure?

5.2. Discharge in France

5.2.1 Radionuclides

Installations can emit a wide variety of radionuclides, which are generally organised into categories. For example, they can be broken down into three categories: tritium (which, for various reasons, is always in a separate category), beta emitters and alpha emitters. As far as discharge from nuclear installations is concerned, limits are generally established for more specific categories: tritium, carbon-14, iodines, other fission and activation products, beta emitters and alpha emitters for liquid effluents, and the same categories plus rare gases for gaseous effluents. Restrictions are also imposed on radionuclides (uranium, radium, etc.) from some installations upstream of the nuclear fuel cycle, for example uranium mines.

It is important to note that the activity released by each radionuclide differs, so they do not all have the same bearing on the leukaemia issue. In fact, some radionuclides are more likely to affect the bone marrow than others. The breakdown into categories does not, therefore, adequately reflect the importance of a radionuclide, so all that really needs to be known is the exact composition of each category.

The composition of the categories varies over time. Even where the installations concerned are similar (for example, plants of the same type and the same power), it varies from one installation to another.

Lastly, it should be noted that carbon-14 emissions have only been monitored for a short time (except for those from the reprocessing plant in La Hague), so there is obviously very little feedback. Nevertheless, it should be possible for nuclear power plants to extrapolate recent results, as they have always discharged 100% of their carbon-14. On this subject, it should be noted that simple calculations have shown that carbon-14 now accounts for a significant proportion of radiation doses due to gaseous discharge from power plants (its contribution was smaller 20 years ago, when other radionuclides were discharged in greater quantities).

5.2.2 Radionuclide release

The volume of radionuclides released by different installations varies enormously, from zero discharge (irradiators for example) to a very high volume of discharge (the reprocessing plant in La Hague). Power plants, factories, research installations, storage centres, etc. all produce varying volumes of discharge. It should be noted that some very specific installations (nuclear medicine departments for example) also produce liquid discharge at least. Situations therefore vary greatly, and it is impossible to generalise (except for some types of installation, such as nuclear power plants).

With the exception of a few, clearly-identified radionuclides (tritium, carbon-14, iodine-129 and krypton-85) the overall volume of radionuclides released has dropped significantly since about 1985. However, this reduction has followed a fluctuating rather than linear pattern. Any reconstruction of exposure patterns in populations living close to installations must therefore be based not only on current discharge, but also on an analysis of previous discharge levels and the variations in them.

It should be noted that the very nature of secret nuclear installations (concerning national defence) can give rise to questions regarding discharge and, above all, the radionuclides released.

Moreover, knowledge of the radionuclides released is closely linked with the method used to quantify discharge. This will be discussed further in the next section.

5.2.3 Measurement of radionuclides

Since the overall radionuclide release rate has dropped, the volume of some radionuclides is very often lower than the measurement threshold. This means that it is difficult to quantify the amount of these "undetectable" radionuclides released. Since 2002, a "reference spectrum" of radionuclides has been defined for each individual installation. The discharged volume of these radionuclides is not recorded as zero, but as a value equal to half of the detection limit multiplied by the overall volume of effluent released. Therefore, the values for some radionuclides are artificially over-estimated: the actual discharge levels are lower than the figures published.

It is important to note that measurement rules have changed several times over time. Therefore, it is sometimes difficult, if not impossible, to accurately compare temporal variations.

Lastly, this measurement method is used for civil BNIs, but not necessarily for installations classified on environmental protection grounds (ICPEs) - which are controlled by the Regional Directorates for the Environment, Land-Use Planning and Housing (DREAL) - or for secret BNIs (under the authority of the DSND).

All the information on discharge from civil BNIs has been archived. The oldest information is kept in the national archives, while information from the past ten years is more easily accessible at the ASN. The question of accessibility to information on ICPE discharge is still under discussion.

5.2.4 The discontinuous nature of discharge

Most discharge data are published on an annual basis. These data are usually sufficient to estimate annual doses, based on the assumption that the rate of discharge remains constant throughout the year. However, while this assumption is valid for some types of atmospheric discharge, it reflects only the average situation for other forms of discharge which are released discontinuously, for example liquid discharge.

Discharge is regarded as a by-product of normal plant operation. However, accidents can occur, albeit rarely. The discharge resulting from these accidents can be measured using the systems already in place, or may be impossible to measure by the usual means (this situation being even more rare). In this case, the volume of activity released can sometimes be estimated retrospectively.

5.3. A comparison of France and Germany

Although the design of French and German installations is quite similar in some cases, the situation in these two countries cannot be compared directly for the reasons described below.

5.3.1 The different types of installation

France's nuclear power plant population is made up of 58 pressurised water reactors of three types (900, 1300 and 1450 MW).

Of the 17 reactors currently in operation in Germany, 65% are pressurised water reactors and 35% are boiling water reactors.
A pressurised water reactor uses nuclear fuel, which is engaged in a fission chain reaction that heats the water in the primary coolant loop.
The hot primary coolant heats the so-called "secondary" coolant via a heat exchanger or steam generator. In the steam generator, the secondary coolant turns into steam, which drives a turbine connected to a generator, thereby producing electricity.

A boiling water reactor operates in a similar manner, the difference being that the water in the primary loop, which is heated by the nuclear fuel, is transformed directly into steam.

The radionuclides in the two loops are primarily released through the building's ventilation system, during the scheduled draining of the treatment reservoir (gaseous discharge) or during the exchange between the primary coolant and the secondary coolant (liquid discharge).

5.3.2 Discharge testing

In Germany, only gamma radiation (reference radiation) is measured initially. Other analyses are performed subsequently. Moreover, the German authorities believe that the amount of carbon-14 discharge in liquid effluents is negligible. This assumption is based on the fact that the majority of liquid effluents are processed by evaporation prior to being released, but no verification tests are performed.

5.3.3 Discharge measurement

The main differences between France and Germany lie in their discharge measurement systems:

- in Germany, all discharge below the measurement threshold is recorded as zero (iodines for example). As a result, the discharge figures published tend to be under-estimated.
- in France, such discharge is quantified by multiplying the measurement threshold by the overall volume of discharge. Hence, unlike in Germany, the discharge figures published tend to be over-estimated.

Germany, unlike France, does not take into account radionuclides with a half-life < 8 days (with the exception of Iodine-131). This reinforces the tendency to under-estimate discharge values in Germany, compared with France where the figures are more realistic.

6 ONGOING EPIDEMIOLOGICAL STUDIES

6.1 French epidemiological studies

For the last 15 years, the Environmental Epidemiology of Cancer unit headed by Jacqueline Clavel at the CESP[16], UMRS-1018 (ex-U754) has been developing a research programme on the risk factors for childhood cancer. This programme is based on the national registration and the precise, standardised classification of childhood cancer cases. Since 1990, cases of haematological malignancy have been registered at Inserm by the National Registry of Childhood Blood Malignancies (RNHE), which is run by J. Clavel. Since 2000, solid tumours have been registered at Nancy University Hospital by the National Registry of Childhood Solid Tumours (RNTSE), which is run by B. Lacour. The 2 registries operate jointly and have just published national figures on the incidence of childhood cancer between 2000 and 2004 (Lacour et al, 2010). Their methodology complies with international rules and their certification by the National Committee of Registries is reviewed every 4 years following an audit by Inserm and the InVS. The unit also uses complementary methods to identify risk factors but, regardless of its approach, always aims to be precise and accurate in the classification of diagnoses, the selection of cases and the assessment of exposure.

The IRSN's epidemiology laboratory is conducting studies on the effects of exposure to low doses of ionising radiation. The recently-established "enfant scanner" cohort study aims to reproduce the doses delivered to children under 5 during CT-scans, and to analyse the potential link with the subsequent development of cancer or leukaemia in these children.

Lastly, it is worth mentioning the French longitudinal study of children, ELFE, coordinated by Inserm and the INED.

6.1.1. Case-control studies

Case-control studies are particularly well suited to studying rare diseases. The unit has conducted several such studies. The national registry-based studies ESCALE (2003-2004) and ESTELLE (2010-2011) involve standardised interviews with parents and the collection of DNA samples. Hence, they provide individual information on the children's socio-demographic background, their personal and family medical histories, their environment and their lifestyle. As a result, several environmental and genetic factors can be investigated at the same time. A genome-wide association study (GWAS) is currently being carried out, based on the case subjects used in ESCALE and a group of Caucasian control subjects.

16 CESP: Centre for Research in Epidemiology and Population Health

Previous studies conducted by the unit have strengthened the theory that there is a link between leukaemia and (i) exposure to household pesticides (Menegaux et al, 2006; Rudant et al, 2007), (ii) proximity to petrol stations (Steffen et al, 2004; Brosselin et al, 2009) and (iii) the delayed occurrence of common childhood infections (Perrillat et al, 2002 ; Rudant et al, *under revision*). They also suggest a possible link with passive smoking, in association with certain genetic polymorphisms (Clavel et al, 2005).

The ESTELLE study is a national study of cancer patients below the age of 15. The study schedule varies according to the type of cancer: 2010 for acute leukaemia, 2006 (retrospectively) to 2011 for Hodgkin's lymphoma, and 2010 to 2011 for non-Hodgkin's lymphoma, malignant brain tumours, neuroblastoma and nephroblastoma. Control subjects of the same average age and sex have been recruited from the general population. In all, the study should include 2000 case subjects and 1600 control subjects. Data are being collected via telephone interviews with the mothers and self-surveys of the fathers. A DNA bank is being set up, consisting of blood samples from the case subjects and saliva samples from the control subjects, the parents of the case subjects and other relatives. The interviews are being carried out by IPSOS.

6.1.2 Ecological studies

Ecological studies do not deal with individual data (they study the link between the incidence rate and exposure in a given geographic unit (*département*[17], *commune*[18] or employment area) and they can take into account only a small number of co-exposures. Their advantage, however, is that they can compare exposed and unexposed areas on a large scale. The past and present ecological studies performed by the unit have focused on population movements (in partnership with INSEE[19]), exposure to ionising radiations of natural origin (radon and telluric gamma) and exposure associated with proximity to nuclear sites (in partnership with IRSN).

These studies have shown a higher rate of incidence among children living in remote areas subject to significant population movements (Rudant et al, 2006; Bellec et al, 2008). On the other hand, there is no evidence that the risk of leukaemia is higher in areas close to civil nuclear installations (670 cases observed out of 720.1 expected cases); neither does it increase with the distance to the centre of the site or with the power of the plant (White-Koning et al, 2004; Laurier et al, 2008). In the second stage of the programme, the IRSN estimated the level of exposure to discharge from civil nuclear installations, based on the number of applications for discharge permits and on climate data. No link was revealed (Evrard et al, 2006).

A very moderate link between domestic exposure to radon and the incidence of childhood AML was observed over the same period (24% increase in incidence for 100 Bq/m3) (Evrard et al, 2005). On the other hand, exposure to telluric gamma rays was not associated with leukaemia (Evrard et al, 2006).

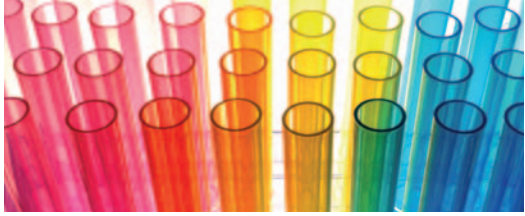
These studies will be repeated for the period from 1990 to 2009.

6.1.3 GEOCAP

GEOCAP is a national case-control study, which does not draw on any individual information besides age, sex and georeferenced address. Exposure and socio-demographic data derive from this address.

GEOCAP includes 8,000 case subjects and 30,000 control subjects from the general

17 Département: administrative region headed by a préfet
18 Commune: smallest administrative subdivision, administered by a mayor and a municipal council
19 INSEE: National Institute for Statistics and Economic Studies



population (children below 15 years old, living in mainland France). Exposure is determined according to the distance between the place of residence and the exposure source (estimated by georeferencing) and by the semi-quantitative modelling of exposure levels.
The project focuses in particular on (1) the proximity of high-voltage power lines and exposure to extremely low frequency electromagnetic fields; (2) proximity to road traffic and environmental exposure to benzene; (3) exposure of places of residence to natural ionising radiations, especially radon (in collaboration with IRSN); (4) proximity to nuclear sites; (5) proximity to other industrial sites.
The addresses of 6,500 case subjects and 15,000 control subjects have already been georeferenced, with an uncertainty of less than 100 metres for 96% of them and 15 metres for 80% of them. The georeferencing process should be completed by March 2010. The list of civil nuclear installations to be considered is currently being established.

6.1.4 Study of spatio-temporal clustering and identification of clusters

Lastly, **the study of spatiotemporal clustering and the identification of clusters** provide a different view of the distribution of cases, without any assumptions regarding potential risk factors. A systematic tendency towards spatiotemporal clustering can argue for an infectious aetiology and localised clusters can point to environmental factors.

Previous analyses have revealed an extremely moderate overdispersion of childhood leukaemia incidence between 1990 and 1994 (Bellec et al, 2006). Further investigations are underway, to identify clusters of varying shapes and size across France.

In addition to studies **that actively aim to identify clusters**, investigations are regularly conducted in response to concerns from the public or the authorities about a health-related situation which they perceive as abnormal, or about a suspected environmental hazard (Laurier et al, 2000). Even where there is an excess of cancer cases, these studies do not usually result in any aetiological assumptions (Gagnière et al, 2010). In addition, more often than not, the design and statistical power of the studies do not allow for the analysis of dose-effect relationships.
Variations in the exhaustiveness of case ascertainment between areas close to nuclear sites and the rest of the country can distort risk assessment (when the number of cases observed in the vicinity of a site is compared with the number of cases that might be expected to be found there if the incidence rate were identical to that in the rest of the country). The purpose of a registry is to prevent these differences in case ascertainment.
The exhaustiveness of registries is assessed using several indicators, the main one being the average number of independent sources per case. There were differences between regional registries when they were first established (Desandes et al, 2004). Now that case ascertainment is organised on a national basis, local differences should have been eliminated. The overall findings of the national registry of childhood leukaemia are accessible (Clavel et al, 2004). However, it should be verified that inter-regional disparities no longer exist, and that there are no differences between areas close to nuclear sites and areas further away.

6.1.5 The "enfant-scanner" cohort study

In 2007, the IRSN and the French-speaking society for paediatric and prenatal imaging set up a study of a cohort of children in France, having had one or more CT-scans before the age of 5. CT-scans are a diagnostic tool, which has become more and more widely used over the last decade and which contributes significantly to the level of exposure in France (5% of all examina-

tions and at least 40% of the overall dose in France in 2002). Eighteen major paediatric radiology centres, based in university hospitals across France, are taking part in the study. Recruitment for the study began in 2000. The cohort will be extended between 2006 and 2013 within the framework of the joint European project, Epi-CT, which is underway now. At present, the cohort includes over 30,000 children, and this figure is ultimately expected to rise to around 90,000. An accurate, dosimetric reconstruction of the doses received, based on the image acquisition protocols and the machines used, is currently being undertaken. By checking the cohort against the registries of childhood blood malignancies and childhood cancers, it will be possible to determine the incidence of cancer and leukaemia within the cohort. Monitoring the causes of death within the cohort will also facilitate follow-up in adulthood. In short, the purpose of this study is to assess the risk of childhood leukaemia and cancer in the cohort, associated with exposure to radiation from CT-scans during childhood. The first analyses will be carried out from 2012 to 2013.

6.1.6 The French longitudinal study of children (Elfe)

The French longitudinal study of children (Elfe), coordinated by the INED and Inserm, aims to analyse the impact of various environmental, family, social, educational, behavioural, health and nutritional factors on the physical, psychological and social development of children, based on a representative cohort of 20,000 children born in France in 2009 (https://www.elfe-france.fr/). One of the objectives of the study is to investigate the relationship between environmental exposure and childhood illness, by evaluating the exposure of children to environmental pollution. It will determine the level of exposure of the 20,000 children in the cohort to known or suspected risk factors for leukaemia, such as: natural or medical ionising radiations, pesticides, etc. Hence it will provide fresh information on childhood exposure to certain known or suspected risk factors for leukaemia. On the other hand, this study does not aim to investigate the relationship between risk factors and the development of leukaemia. However, it may shed some light on this as part of a joint analysis.

6.2. Ongoing studies abroad and on an international scale

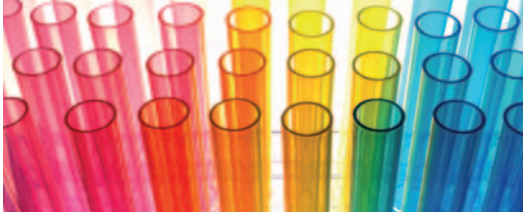
6.2.1. The Childhood Leukaemia International Consortium - CLIC

http://clic.berkeley.edu/

Led by Patricia Buffler of the University of Berkeley, CLIC coordinates case-control studies of childhood leukaemia in around fifteen different countries. It does not address the issue of ionising radiations. The "pooled" studies focus on perinatal characteristics, infections, maternal tobacco use, exposure to pesticides and genetic factors. Jacqueline Clavel is on the steering committee. She is responsible for the "pooled" study of premature common infections, and is co-responsible for analysing gene-tobacco interactions. The results are expected to be published within the next few years.

6.2.2. The International Childhood Cancer Cohort Consortium I4C

Several aetiological assumptions are difficult to test retrospectively, once the cancer has developed, because parental recollec-



tions are the only source of information and these are likely to become less reliable as time passes and, more problematically, as the parents' anxiety grows. Given its prospective nature and the wealth of data collected, ELFE, a French longitudinal study of 20,000 newborns recruited in 2001-2012 (http://www.elfe2009.fr/), is an ideal source of information on the pre-natal period. Unfortunately, the size of the study does not allow the investigation of rare diseases such as childhood cancer. However, the I4C (International Childhood Cancer Cohort Consortium), which is an international project bringing together cohort studies across the world, has been set up precisely for this purpose. I4C should therefore encompass around 1 million children, and describe their pre-natal characteristics in detail.

6.2.3. European cohort project on CT-scan exposure during childhood

The "Epi-CT" project is a European research project. Coordinated by the International Agency for Research on Cancer, it is backed by the EC and is scheduled to start in 2011. It involves 17 teams from 11 different countries. Its objective is to determine the risk of childhood cancer and leukaemia associated with CT-scan exposure. A joint protocol has been defined, enabling the integration of several national cohorts of children exposed to CT examinations into a global analysis. These national cohorts include existing cohorts like the French "enfant scanner" cohort and the British cohort, as well as new cohorts in other countries. Hence, around 1.5 million children will be included in the analysis. This should provide sufficient statistical power to identify any possible risk of leukaemia associated with CT radiation, even if this risk is very small. The first results are expected to be published in 2016.

6.2.4. Ongoing studies in Germany

Following numerous studies, in-depth discussions have been held regarding the potential impact of radioactive discharge from nuclear installations on the risk of childhood leukaemia. The conclusion is that, given the doses involved, this discharge alone cannot affect the incidence of childhood leukaemia. A similar conclusion has been reached in Germany, based on a less detailed assessment than that conducted in the United Kingdom, but nevertheless taking the current knowledge of radiation effects into consideration. The German KIKK study cannot be repeated in the near future, given the small number of new cases occurring annually in the vicinity of nuclear installations. The results, which take into account exposure to electromagnetic fields of less than 50 Hz, are compatible with those produced by other studies, but cannot be explained at present. Under these circumstances, the BfS decided to develop a research programme to improve the understanding of the pathogenesis of childhood leukaemia. In 2008, it teamed up with the ICNIRP (International Commission on Non-Ionizing Radiation Protection) and the WHO (World Health Organisation) to set up a think tank on the causes of childhood leukaemia. Hence, in 2009, a small group of experts were appointed and assembled; they will meet again in 2010 to outline their proposed research programme. This confidential meeting will not focus exclusively on ionising radiations. It will include specialists in other fields, who will pool their experience to identify knowledge gaps and propose possible ways of filling them in. The fields covered will range from immunology to stem cell research, animal models, molecular genetics, virology, epidemiology, molecular epidemiology, modelling and paediatric oncology.

6.2.5. Other studies

Several studies are underway in various countries, which, in the coming years, should provide new information on the risk of leukaemia in children living close to nuclear installations.

The American Academy of Science and the Office of Nuclear Regulatory Research are setting up a study on the risk of cancer in populations living in the vicinity of nuclear installations in the United States. This involves:

- making an inventory of current knowledge and defining a study methodology (for mid-2011);
- then, over two or three years, implementing the methodology and analysing the data gathered. A committee of independent experts will define the exact scope of the study. One of the objectives is to meet the public's need for information. The preliminary discussions underlined the necessity of taking other potential aetiological factors into consideration and the benefits of targeting children, not only because they are more vulnerable but also because they are easier to monitor.

In Switzerland, the **CANUPIS** study was launched in 2008 with a view to analysing the risk of childhood cancer in areas close to Swiss nuclear power plants. This study is being carried out by the Institute of Social and Preventive Medicine at the University of Berne. It is a so-called "cohort study", within which all the children in Switzerland who were born between 1985 and 2007 are being monitored. The precise identification of each child's place of residence will enable the researchers to determine if the cancer incidence rate is higher in the vicinity of nuclear power plants than in other places. In addition, the full residential history of children diagnosed with cancer will be established as part of the study. Hence, the possible influence of place of residence during the first few months and years of life will be taken into consideration. Another advantage of the study design is that it allows other environmental factors, such as high-voltage power lines and industrial areas, to be taken into account. However, the small number of subjects included in the study is a major drawback (around 3,000 cases of cancer, including 980 cases of leukaemia). The results will be published in 2011.

In late 2008, the **Belgian** Ministry of Social Affairs and Public Health commissioned the Scientific Institute of Public Health (IPH) to conduct a nationwide epidemiological study of the state of health of people living within the vicinity of nuclear installations. The purpose of this study is to describe geographic variations in cancer incidence in Belgium, and to investigate the theory that local excesses exist, particularly in areas close to nuclear sites. Although this study does not focus exclusively on childhood leukaemia, it should provide data on this population. The final results should be published during the course of 2011.

7 INFORMATION AND COMMUNICATION

7.1. Background

The question of the risk of leukaemia in the vicinity of nuclear sites stands at the crossroads between several disciplines and areas of interest: radiation protection, health risk assessment, oncology, environmental monitoring, nuclear physics and chemistry, dosimetry, industry, energy production, etc. Furthermore, it involves people from various walks of life: institutional experts, doctors, researchers, experts from non-profit organisations, patient representatives, etc. The communication difficulties encountered by the WG at the beginning of its mandate underline the need to work on sharing knowledge, clarifying specialist terms and "translating" them into everyday language, and effectively conveying information to non-specialists.

In view of the controversy surrounding the possible link between BNIs and childhood leukaemia, the WG's task is to propose lines of research into the causes of childhood leukaemia, and to help ensure the transparency of information distributed to the general public, the public health authorities and healthcare professionals.

The context may vary:

- it may be a crisis situation, in which a rapid response is expected to questions such as: what is the risk? to whom? why? how can possible consequences be prevented? who is responsible? who is involved? how is the situation being monitored?
- fundamental questions may also be raised outside of emergencies.

In any case, scientists must be attentive to the public's deep concern about the impact of the environment on health, and especially on the development of childhood cancers. However, establishing environmental impact is not an easy task, depending on whether this impact is regarded as **exclusive** or **contributive** and on the methodological difficulties encountered.

The goal is to build and maintain confidence through a combination of education, technical know-how and humanity. Effective communication in this area of public health raises challenges of a human, scientific, economic, social and political nature.

7.2. The need for information among parents of children with cancer and paediatric oncologists

- The National Union of Associations for Parents of Children with Cancer or Leukaemia (UNAPECLE) (see Appendix 2).

The following key points must be taken into consideration:

- 90% of parents are concerned about the causes of their child's cancer: the role of heredity and genes, exposure to carcinogenic factors during or after pregnancy.

- The role of ionising radiations: yes (depending on the place of residence), but it is not a major issue compared with other environmental factors.

- Note: the concerns raised by media coverage.

- The French Society of Paediatric Oncology (SFCE) (see Appendix 3)

This appendix shows the questions faced by paediatric oncologists. They reflect the need to provide paediatric oncologists with precise information. Moreover, such information would be useful to all paediatric healthcare professionals and to all doctors (basic training and continuing education).

7.3. The point of view of ACRO: clarity and transparency

The data suggesting a possible link between the risk of leukaemia and proximity to nuclear installations have always provoked strong public concern. True, it is genuinely difficult to separate the concept of danger (which is easier to identify) from the concept of risk (which is based on probability and is less perceptible). Moreover, epidemiological studies are based on different scientific tools designed to meet different objectives (case-control studies, descriptive studies, geographic studies, etc.), which are difficult for non-specialists to understand.

Of course, feelings and impressions can vary greatly, and no doubt reflect to a certain extent the very different opinions of members of the public regarding the nuclear programme. Yet the concerns voiced by certain parts of the population, especially those living close to nuclear installations, are very real. Therefore, the belief that there may be a risk cannot be ignored, as it leads to (often repressed) feelings of anxiety and unhappiness.

The response to these concerns should be completely transparent, not only in regard to the risks associated with nuclear installations – and, in particular, with the discharge from these installations – but also the scientific research into these risks and its objectives.

The goal, therefore, is to ensure the accessibility of all data and improve the ability to interpret them or even, in some cases, to analyse them in relation to clearly-explained objectives. However, at this stage, confidence cannot be decreed, especially where the highly-sensitive issue of nuclear risk is concerned. It must be earned. And it often takes a very long time to do so.

Plenty of opinion surveys have revealed not only the lack of public trust in nuclear operators, but also the limited confidence in institutional organisations. The credibility of scientists, associations and independent experts has certainly improved, but none of them can claim to enjoy the sort of large-scale confidence that is still lacking today.

Although it is not the only solution, all or some of these players must be able to sit down around a table with the firm intention of producing a comprehensible review of the problems raised. This review would reflect the differences of the participants and would not necessarily aim to be consensual; however, it would be as widely informative as possible and would highlight points of agreement and disagreement, as well as areas of uncertainty and knowledge gaps.

In all likelihood, confidence will only arise from a pluralist approach, provided that the objectives are clearly defined and that the resources invested are commensurate with the stakes. It will certainly not stem from the convictions of any one party.

7.4. Information and communication: a few principles

"Clearly communicating the message of uncertainty" (E. Hirsch, 2009, on the influenza pandemic) is essential to maintaining the cooperation and confidence of the parents of sick children and of the rest of the population.

We must learn how to effectively explain the concept of low potential risk, which, in an area where suspicion prevails, may be acceptable for a community but is considered unacceptable for the individuals affected and their families.

Making sure that information is **transparent** and **accessible** should prevent distrust, anxiety and panic. Issuing a press release or a document based on a scientific concept (regardless of its worth) is not really providing information, unless there is a preliminary debate between scientists and the civil society, giving everyone an opportunity to voice their opinion and to absorb the information little by little, not only on an individual basis but above all collectively.

Observing good practices is a necessity for everyone, including the media. The circulation of complex and uncertain information requires an ethical approach, defined in cooperation with human and social scientists.

8 OBJECTIVES DEFINED BY THE WG IN TERMS OF FOLLOW-UP STUDIES

8.1. Support for studies on the risks associated with low-doses of ionising radiations

The WG recommends that Requests for Proposals should focus primarily on studies aiming to improve the knowledge of the risks associated with low doses of ionising radiations (Cancer Plan, ANR[20], environment, etc.).

The WG is issuing guidelines and supporting ongoing studies relating to the role of low doses of ionising radiations:

- of medical origin [studies underway on the impact of CT-scans, both in France ("enfant scanner" cohort) and on the international level (European project "Epi-CT")],
- of natural origin [studies underway both in France (as part of the GEOCAP project coordinated by Inserm and the IRSN) and abroad, for example in Great Britain),
- of medical and natural origin (the Elfe cohort study, which aims to document levels of exposure to ionising radiations during childhood).

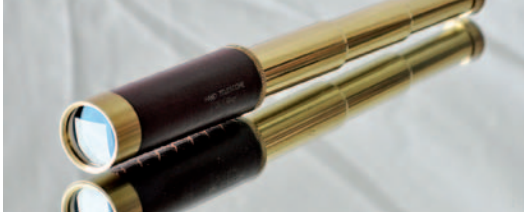
It also recommends follow-up studies to build on current work:

- improve knowledge of exposure (taking geology into consideration),
- target the prenatal period too, which means that the address of the parents at the time of birth must be recorded,
- investigate cumulated exposure to radiation, which means that the child's full residential history (from the time of conception) must be recorded,
- take into account genetic factors which contribute to radiocarcinogenesis (polymorphisms in the repair genes and in the cell cycle),
- take into account the environmental and demographic factors associated with environmental exposure to radiation.

8.2 Identification and characterisation of nuclear sites of interest

The WG has emphasised the need to progress discussions regarding the typology and selection of installations and sites of interest, considering the concerns about the health impact of radioactive discharge from industrial facilities. Given the diverse range of sites, activities and discharge involved, and the need to select sites that are relevant in terms of both the questions raised and the methodology of the studies being implemented, there is no single, straightforward answer as to which sites are of interest. Therefore, a multicriteria analysis framework must be developed, in order to establish a list of sites of interest and of their relevant characteristics.

20 ANR: French National Research Agency



A sub-group of the working group has already identified the installation categories, the criteria to be taken into account and the information sources that are accessible. This sub-group has proposed a four-step approach, the details of which are described in chapter V-1:

- establishment of an initial list of sites, based on lists already drawn up by the proper authorities for each category of installations potentially concerned;
- identification and selection of characteristics of interest, distinguishing between information on the site and its environment, on the installation itself and on discharge; explanation of the selection criteria;
- collection of the data needed to complete the selected characteristics, from accessible information sources;
- use of the list in the development of epidemiological and public health studies, and publication of the selection process alongside public information and awareness guidelines.

The WG recommends implementing a study to identify and characterise sites of interest operating in the nuclear sector or producing radioactive discharge. The WG believes that, given the nature of the study, it will require pluralistic leadership.

8.3. Clinical and biological characterisation of leukaemia

Epidemiological studies must be able to investigate the cytological, cytogenetic, immunophenotypical and molecular **heterogeneity** of leukaemia in greater detail than they do at present. It is important to **document** cases of leukaemia in as detailed a manner as possible, in order to identify underlying aetiological heterogeneity. This documentation must be fully **standardised**, so that it is not impacted in any way by the place of treatment or by environmental exposure factors. Such studies must be **large enough** to support specific classifications with sufficient statistical power. This can be achieved by developing international studies, which implies that the quality of case characterisation must be homogenous and reproducible from one country to another.

At present, there is no known molecular signature of environmental exposure. However, it is possible that current molecular biology and toxicology research will identify specific profiles or new nosological classifications over the next few years, which could be taken into consideration. Having a **biological resource centre** would allow cases to be defined according to potential new criteria. Therefore, the paediatric oncology community is planning to develop a national virtual biobank over the next few years, alongside epidemiological and clinical research projects (the SFCE's HOPE project and the HOPE-Epidemiology research platform).

The working group stresses that this strategic approach (detailed characterisation of leukaemia) is absolutely crucial to fulfilling the mission statement. Therefore, the working group believes that the supervisory authorities must support the implementation of the above-mentioned measures.

8.4. Research into the causes of leukaemia – other aetiological factors and mechanisms

As mentioned several times in this report, leukaemia is a multifactorial, multi-step and heterogeneous disease. Aetiological research must therefore address a broad spectrum of environmental and genetic factors at the same time, using appropriate and complementary approaches (ecological, case-control and cohort studies).

Some environmental factors (such as exposure to pesticides, environmental benzene and natural ionising radiations) seem to be risk factors and should be explored in greater depth. The theory that early stimulation of the immune system (through infections and allergies) plays a protective role must also be investigated further. Research into

genetic factors of predisposition must be reviewed through GWAS[21], and the regions of the genome associated with the risk of leukaemia must be sequenced in detail over the next few years. The mechanisms of gene-environment interactions are still unclear, and the candidate gene approach adopted in the last decade must be reviewed in order to take into account the complete mechanisms of immune response and of xenobiotic repair or metabolism. The possibility of studying (i) the expression of certain genes (rather than genotypes) in case-control studies and (ii) epigenetic factors must be discussed.

The WG recommends that large-scale genetic analyses be conducted and appropriately funded.

8.5. How to improve training, information and communication

With scientific progress, a demand for public information, debate and the social control of science has emerged.

Given the possible link between nuclear power plant and the risk of cancer (particularly childhood leukaemia), the combination of uncertainty, confusion factors and methodological limits can lead to overreaction, unrealistic demands for explanations and suspicions of manipulation. These issues interfere with public information efforts and with the privileged relationship between doctor and patient. .

We have already stressed the difficulties involved in communicating with the public, and also the overriding necessity of doing so (Chap. VII). This means identifying all the parties in a position to contribute to the communication process, and setting up information channels while being willing to consider other options, as communication on such subjects should not be restricted to specific channels. The Nuclear Transparency and Safety Act of June 2006 established the High Committee for Transparency and Information on Nuclear Safety (HCTISN) and, in addition, injected fresh impetus into the local information committees (CLIs), most of which belong to the ANCCLI[22]. It should also be pointed out that local information and monitoring committees (CLISs) have (or are being) set up specifically for facilities other than BNIs, such as former uranium sites (which are governed by the regulations on ICPEs).

These structures – which generally have a pluralist membership – have to deal with a very broad range of questions from the public. However, the "health impact" issue is a common theme. This theme emerged again recently in the survey conducted by the Regional Health Observatory (ORS) on the incidence of cancer around the Tricastin site[23]. This survey was commissioned by the local CLI (CLIGEET), at the suggestion of FRAPNA[24].

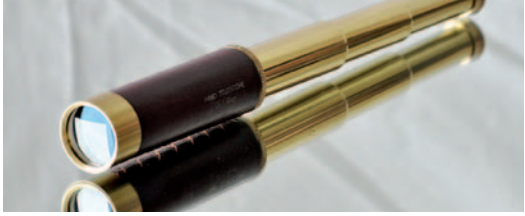
We are recommending that a system for scientifically monitoring leukaemia and nuclear installations be set up (see below). The additional information thus provided will probably help the above-mentioned structures in their appointed task of providing answers, in both everyday and crisis situations.

The objectives defined by the WG are as follows:

1. ***Discuss ways of delivering intelligible and honest information to the public, which meets both collective and individual expectations (determine the most appropriate language, educational media, etc). The organisations authorised to respond in both everyday and crisis situations should be involved in these discussions.***
2. ***Take into account the ethical issues involved in circulating information that is sensitive, uncertain and very often fragmented.***
3. ***Introduce healthcare professionals to effective methods of communication, and think about incorporating such methods into their basic training. This subject also concerns local players responsible for risk management.***

Hence, the working group recommends the creation of a new pluralist WG focusing on information and communication. This new working group should include more skill sets than the current WG: human and social sciences, philosophy, ethics, new technologies, etc.

21 GWAS: Genome-Wide Association Studies
22 ANCCLI: National Association of Local Information Commissions and Committees
23 Study of the incidence of cancer around the Tricastin nuclear power plant, ORS Rhône-Alpes, June 2010
24 FRAPNA: Rhône-Alpes Federation for the Protection of Nature



8.6. Promoting the development of a scientific monitoring system and of international cooperation

▲ *The scientific monitoring of leukaemia and nuclear installations*

The IRSN has been monitoring the risk of leukaemia in the vicinity of nuclear installations for many years. This has resulted in the publication of several summaries of the literature (Laurier et Bard 1999, Laurier et al 2002, Laurier et al 2008). Other organisations also monitor leukaemia cases around nuclear installations, both in France (INSERM, Wise, Acro, InVS) and abroad (BfS in Germany, COMARE in Great Britain, NRC in the United States). Nevertheless, many studies are either being planned or are already underway in various countries, and it is often difficult to obtain detailed and comprehensive information.

▲ *The stepping up of international research efforts*

There are two explanations as to why the findings relative to the risk of leukaemia around nuclear installations are difficult to interpret: firstly, studies of leukaemia clusters are inherently limited, as they focus on a small geographic area and a small number of subjects; secondly, the causes of childhood leukaemia are still unclear.

Descriptive studies: many studies have or are being conducted with a view to describing the frequency of childhood leukaemia in the vicinity of nuclear installations. Some of these studies focus on a single site, others focus on a group of sites in a given region or country. Such studies are often small, which makes it difficult to interpret the findings (this is particularly true for local studies involving very small geographic areas, but it is also applicable to multi-site studies focusing on a specific age group, for example children below the age of 5). Furthermore, the methodologies employed vary greatly (choice of geographic area, reference rates, statistical method, etc.), making it difficult to compare results. Finally, some studies are limited by a border effect (the scope of the study may be reduced if the installation is located at the edge of the study region). One solution is to harmonise or coordinate national research (conduct multi-site studies rather than numerous local studies) and international research (coordinate the methods used in neighbouring countries to allow for the joint analysis of data). This solution could be extended to include the metrology aspect of studies, in order to improve the compatibility of international data.

Aetiological studies: many studies have or are being conducted with a view to identifying the causes (risk factors) of childhood leukaemia. More and more of these studies are being carried out within the framework of international collaborative projects, such as CLIC, I4C or Epi-CT. Several French research teams are already involved in this international cooperation effort (INSERM, IRSN, InVS), either by participating in international consortiums or by conducting contributing studies in France. Nevertheless, although these research projects are one of the most promising means of gaining new knowledge on the causes of leukaemia, they require a substantial, long-term investment from research teams. One solution is to provide financial support for research teams participating in international projects.

The WG recommends improving the organisation of scientific monitoring, with 2 objectives in mind:

- ***Update scientific knowledge more efficiently;***
- ***Be more responsive to questions raised by the media and the public when the publication of new findings triggers fresh concern.***

This organisational effort could be backed by the Heads of the European Radiological Protection Competent Authorities (HERCA); it could be based on a rapprochement of the various organisms concerned, through the development of a network of correspondents for example. The creation of annual seminars could also help to improve the circulation of information.

Le groupe de travail recommande le renforcement des efforts de recherche au niveau international.

APPENDIX

APPENDIX 1: Mission statement sent to Ms. D. SOMMELET

RÉPUBLIQUE FRANÇAISE

AUTORITÉ DE SÛRETÉ NUCLÉAIRE

DEPARTMENT OF IONISING RADIATIONS AND HEALTH

Paris, 18th August 2008

DEP-DIS-No. 0124-2008
Project coordinated by: Chantal Bardelay
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Ms. Daniele Sommelet
Hopital de Brabois – Hopital d'Enfants
Rue du Morvan
54511 Vandoeuvre CEDEX

Subject: Creation of a pluralist working group on "the risk of childhood leukaemia in the vicinity of nuclear power plant."

Dear Ms. Sommelet,

In March 2008, following the publication of the German study on the occurrence of childhood leukaemia in the vicinity of nuclear plants at the end of 2007, the Institute for Radioprotection and Nuclear Safety (IRSN) published a summary of the epidemiological studies already conducted in this field. The National Institute of Health and Medical Research (INSERM) also launched a research and surveillance programme on the subject.

These publications and research programmes are appearing at a time when associations – in particular the Local Information Committees – are repeatedly petitioning the authorities about the effects of discharge from nuclear installations on the health of the neighbouring populations.

Under these circumstances, we have decided to appoint you as Chairperson of a pluralist working group, responsible for analysing the current knowledge of the risk of leukaemia in children living close to nuclear power plant. Based on an inventory of the possible causes of childhood leukaemia, the working group will also be tasked with proposing the studies and research necessary to improve the current state of knowledge.

We would like you to select the members of this working group, making sure that it includes scientific experts from the fields of medicine, epidemiology and radiation protection, as well as individuals whose personal experience will enable them to make a valuable contribution to the debate. The participation of foreign experts and personalities would also be appreciated.

The InVS, the IRSN, INSERM and AFSSET will assist you in putting together the group and monitoring its work.

www.asn.fr
6, place du Colonel Bourgoin • 75572 Paris cedex 12
Téléphone 01 40 19 86 00 • Fax 01 40 19 86 69

We would also like to inform you that we have decided to create a national committee for planning and monitoring the measures needed to improve the current knowledge of the effects of discharge from nuclear power plant on the health of people living nearby. The goal is to be able to answer the public's frequent questions about the potential risks and illnesses associated with the nuclear power industry. Acting under the authority of the ASN's Chief Executive Officer, this committee will comprise representatives of the Ministry of Health, Youth, Sport and Associations, the Ministry of Ecology, Energy, Sustainable Development and Land Use Planning and the above-mentioned institutes, along with members of the medical community and of various associations.

Given the recent publication of the German study, the risk of leukaemia in children living close to nuclear installations will be the first subject examined by this committee. Therefore, you will be invited to present the committee with your programme, working methods, regular progress reports and the conclusions and recommendations of the working group. The work carried out by the working group will be made public, in accordance with procedures established in conjunction with the monitoring committee.

We hope to receive a draft work schedule before the end of December 2008.

We would like to thank you for your personal commitment to this task.

Yours sincerely,

Chief Executive Officer of the Nuclear Safety Authority

Director General of Health,

Professor Didier Houssin

Director General of Pollution and Risk Prevention

CC:

Mr. Jacques Repussard, Director General of the IRSN
Ms. Francoise Weber, Director General of the InVS
Mr. Andre Syrota, Director General of Inserm
Monsieur Henri Poinsignon, Director General of Afsset

APPENDIX 2: Contribution of the UNAPECLE[25]

NATIONAL UNION OF ASSOCIATIONS FOR PARENTS OF CHILDREN WITH CANCER OR LEUKAEMIA

Parental concerns regarding research

90% of the questions asked by parents have to do with the causes of their child's illness, whether this is leukaemia or a solid tumour.
Indeed, adult cancer is often connected with a person's habits or lifestyle over many years (cigarettes, asbestos, pesticides, etc.). As the development of cancer in children or young people cannot be caused by this sort of long-term exposure, parents find it difficult to understand and this serves to increase their feelings of guilt.
The most frequently-discussed issues are:

- Heredity, genetics: do cancer genes exist? Are some families "prone" to cancer? If I have other children, are there any particular genes that we should be looking for? Could the child's brothers and sisters develop cancer too? Several people in my husband's family or my own family have had cancer; is there a connection?
- Pregnancy and cancer: what did I do during my pregnancy that could have caused my child to develop cancer?
- Genes and pregnancy: what could have caused my child to develop cancer (diet, alcohol, cigarettes, medication, high-voltage power lines, mobile phone masts, etc.)? There have never been any questions relating directly to nuclear power plants, except in the event of an accident or incident.

However, one subject is frequently raised, which does bear some relation to the issue of proximity to nuclear power plants: that of the rays used in radiotherapy or for diagnostic purposes.

- What sorts of rays are used? Is there any analogy with the effects observed after nuclear tests?
- What are the side effects?
- Is radiotherapy a localised treatment? To what extent? How does it affect parts next to the tumour or the irradiated area?
- Are my other children in danger when I come back from a radiotherapy session with their brother or sister?

On the basis of these facts, it would appear that parents ask general questions about the causes of childhood cancer, and that concerns about nuclear power stations are on a par with those about environmental factors. Nuclear installations are not a major concern in themselves, but fall under suspicion in the same way as mobile telephones and colorants!
Radiation in general is a common factor but, as most parents have little knowledge of the subject, it is impossible to provide them with clear and comprehensible information. In fact, the type of radiation involved and the equipment used are very complex.
Some parents ask for information that may, in some respects, be connected with nuclear power plants. For example, they may ask about figures published in the press regarding the increasing number of leukaemia and cancer cases in children, teenagers and young adults. Once again, environmental factors are referred to, but not nuclear power plants in particular.

All in all, the above remarks come from parents who do not live particularly close to a nuclear power plant. The questions asked by parents who do live close to a nuclear power plant may be different, but the responses analysed do not provide any information on this.

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25 UNAPECLE: National Union of Associations for Parents of Children with Cancer or Leukaemia

APPENDIX 3: Contribution of the SFCE[26]

- Are children who live close to nuclear power plants and installations at greater risk of developing acute lymphoblastic leukaemia?
- If yes:
  - How large is the area affected by (or what is the scope of) this excess risk?
  - Can this excess risk be attributed to population movements, radioactive emissions or another factor of confusion? To what extent can this be proved?
  - Does this excess risk relate to specific forms of cancer, in terms of their cyto-immuno-cytogenetic-molecular identity?
  - How can the risk of developing ALL (which is not usually a radio-induced illness) and the specific risk to children (rather than adults) be explained?
- Is there an excess risk of developing other childhood or adult cancers?
- What is the level of exposure to radioactive substances in areas close to nuclear installations (during ordinary operation and following incidents such as that which occurred at Tricastin?) What is the usual means of exposure (air, drinking water, fruit and vegetables, etc.)?
- Does environmental exposure to radioactive substances affect pregnant women differently? Do pregnant women metabolise these substances differently?
- Is this information available? Has it been verified? Is it reliable? Have all civil and military nuclear installations been located and registered? Are they all being monitored?

26 SFCE: French Society of Paediatric Oncology

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LIST OF ACRONYMS

ACRO	Association for the Control of Radioactivity in the West
Afsset	French agency for environmental and occupational health safety
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloblastic Leukaemia
ANCCLI	National Association of Local Information Commissions and Committees
ASN	Nuclear Safety Authority
BfS	Federal Office for Radiation Protection
BNI	Basic Nuclear Installation
CLIC	Childhood Leukaemia International Consortium
DGPR	General Directorate of Risk Prevention
DGS	General Directorate of Health
DSND	Delegate for Nuclear Safety and Radioprotection on Defence Sites
GWAS	Genome-Wide Association Studies
I4C	International Childhood Cancer Cohort Consortium
ICNIRP	International Commission on Non-Ionizing Radiation Protection
ICPE	Installation classified on environmental protection grounds
INCa	National Cancer Institute
INED	National Institute of Demographic Studies
Inserm	National Institute of Health and Medical Research
InVS	Institute for Public Health Surveillance
IRSN	Institute for Radiation protection and Nuclear Safety
KiKK	Epidemiologische studie zu kinderkrebs in der ungebung von kernkraftwerdern (epidemiological study of childhood cancer in the vicinity of nuclear power plants)
SBNI	Secret Basic Nuclear Installation
SFCE	French Society of Paediatric Oncology
UNAPECLE	National Union of Associations for Parents of Children with Cancer or Leukaemia
WG	Working group
WHO	World Health Organisation
WISE	World Information Service on Energy

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