NNT : 2015SACLS123

THESE DE DOCTORAT
DE L'UNIVERSITE PARIS-SACLAY,
préparée à l'Université Paris-Sud

ÉCOLE DOCTORALE N°570
EDSP - Santé publique

Santé publique - épidémiologie

Par

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Epidemiological study of workers employed in the French nuclear fuel industry and analysis of the health effects of uranium compounds according to their solubility

Thèse présentée et soutenue à Villejuif, le 30 novembre 2015 :

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The PhD thesis was prepared in the Laboratory of Epidemiology of the Institut de Radioprotection et de Sûreté Nucléaire (IRSN) in the frame of the doctoral network of the École des Hautes Études en Santé Publique (EHESP).

The three-year scholarship was provided by the « Health, Environment, and Toxicology » scientific program of the Région Île-de-France.

Additional funding was provided by DoReMi (European Commission-funded network of excellence), the EHESP, and the Université Paris-Sud.

A two-month internship was performed at the University of California, San Francisco (UCSF).

In memory of my grandmother, Taïsiya Kalyaseva,

and my aunt, Valentina Zhivina.

«И нам ведь друг от друга ничего не надо, ведь верно, да? Давай мы с тобой запомним это лето…просто запомним и всё, ладно?»
(фильм Сергея Соловьёва «Сто дней после детства», Мосфильм, 1975 год).

«Был шторм, унесло сети… Это стихи, а не запись…»
(телевизионная повесть Эдварда Радзинского «Ольга Сергеевна», Мосфильм, 1975 год).

ACKNOWLEDGMENTS

I would like to begin by thanking my supervisor, Dominique Laurier, for always believing in me and letting me grow both professionally and independently, for your constant guidance and thoughtful advice despite your many competing commitments, for carefully reviewing and proofreading tons of my French and English drafts, and for presenting me to members of your broad network of collaborators.

My deepest gratitude is to Irina Guseva Canu, who was my supervisor during the pre-doctoral internship at IRSN. Thank you for selecting the CV of a Russian MPH student from Israel despite never meeting me in person, for introducing me to the field of radiation research and to the passionate topic of internal contamination, for your enormous help with French bureaucratic procedures, and for your insightful comments through all these years despite leaving your job at IRSN. I am still remembering our telephone interview before Shabat in June 2011 that later profoundly changed by life and allowing me to become who I am now.

Special thanks go to my mentor Lydia Zablotska at UCSF. Who would believe that our conversation during the HEIR 2013 conference in Berkeley could lead to such fruitful collaboration? It was a real pleasure working with you in San Francisco, learning your first-hand experience of constructing and analyzing cohorts of Canadian nuclear workers and Chernobyl populations. Thank you for your help in statistics and with the famous EPICURE, and for helping me to gain more confidence in myself.

Thank you to my internal dosimetry mentors Eric Blanchardon and Estelle Davesne at IRSN. I am grateful to all our numerous exchanges. Thank you for sharing your experience with me, and be patient with all my amateur questions. I remember how I was happy calculating internal doses for several workers by myself.

I am very grateful to Eric Samson, the principal investigator of a cohort of French nuclear fuel cycle workers at IRSN. Thank you for your always rapid help with databases, and for the ability to share some concerns and uncertainties during my PhD project. Thank you for giving me a strong hand during validations and verifications of medical files at Pierrelatte, and for our jokes and funny stories in the rather obscure setting of archives with mice and spiders.

I was very fortunate to collaborate with James Grellier from CREAL. Your comments, frequent feedback, and your English proofreading have improved my work immensely. Thank you for our

discussions on how to handle analyses in EPICURE. I wish you all the best in your new role of father!

I would like to thank David Richardson from UNC. Thank you for our exchanges on statistics during your stays at IRSN and beyond. I am sure that your comments on the drafts of my articles have improved their quality and impressed reviewers during the peer-review process. Our summer jokes on the way to the Clamart swimming-pool was an essential break from the intense writing of this manuscript.

Some data for this PhD thesis were collected with the help of Philippe Collomb and Christine Niogret from the AREVA NC Pierrelatte Occupational Health Department and Pascale Scanff and Hervé Roy from IRSN. I really appreciate the time that you spent on helping me to advance my work.

Feedback from my PhD thesis committee (Dominique Laurier, Irina Guseva Canu, Pascal Wild, Eric Samson, Eric Blanchardon, Estelle Davesne, Sophie Ancelet, Iris Jovanovic) was a great support during these three years. I am thankful to them for their time investment and support.

This PhD thesis benefited from a number of experts in radiation research. I am very grateful to comments and questions of the ICRP TG64 group (Margot Tirmarche, Dominique Laurier, James Marsh, François Paquet, Mikhail Sokolnikov, and Richard Wakeford) on my work. Specifically I would like to thank some experts to share with me their deep knowledge on uranium exposure and dosimetry: Jeri Anderson (NIOSH), Maia Avdandilashvili (USTUR), Derek Bingham (AWE), and Iulian Apostaei (SENES Inc.). My participation in the presentations of Elisabeth Cardis (CREAL), Richard Haylock (PHE), Janet Hall (Institut Curie), Michaela Kreuzer (BfS), and Tamara Zhunussova (NRPA) allowed putting my research into a broader perspective. I am very thankful to Dale Preston for his detailed and quick help with analyses in EPICURE, and to Philippe Bérard (CEA) for the ability to follow his internal dosimetry course. Thanks to Aušra Kesminienė and Evgenia Ostroumova from IARC for our exchanges about their research on the Semipalatinsk cohort.

I would like to thank my rapporteurs Prof. Elisabeth Cardis (CREAL), Prof. Catherine Luccioni (CNAM), and examiners Dr. Jean Bouyer (Université Paris-Sud), Dr. Michaela Kreuzer (BfS), Dr. Philippe Bérard (CEA), and Prof. Jean-Christophe Amabile (SRPA) to taking time from their busy schedules to review this work. Thanks to Elisabeth Cardis and Catherine Luccioni for their comments and the thorough proofreading of the whole manuscript!

I would like to express my gratitude to those who participated in critical reading of this manuscript: Dominique Laurier, Estelle Davesne, Eric Blanchardon, Eric Samson, Olivier Laurent, Martin Blair, Daniel Schereck, Alex Franco, Michael Coleman, Joseph Dumetz, Lydia Zablotska, and Irina Guseva Canu.

These three years would not have been possible without my background in medicine and public health acquired at the I.M. Sechenov Moscow Medical Academy, the Hebrew University of Jerusalem, and the Université Paris-Sud. In particular, I owe my gratitude to my Moscow mentors and professors Zhanna Vakurova, Maria Nadinskaya, Dmitry Napalkov, Marina Borlakova, Irina Kosagovskaya, Ludmila Syrtsova, Kirill Danishevsky, Irina Ilchenko, and Artyom Gil. Thanks to my Israeli professors to give me a broad perspective of public health that I use incessantly: Ora Paltiel, Milka Donchin, Gina Leib, Yehuda Neumark, and Jeremy Kark.

Thank you to all my LEPID colleagues for your everyday support and nice discussions: Hélène Baysson, Marie-Odile Bernier, Sylvaine Caër-Lorho, Enora Cléro, Jérôme-Philippe Garsi, Sophie Jacob, Iris Jovanovic, Olivier Laurent, Klervi Leuraud, Béatrice Nkoumazok, Irwin Piot, Tristan Roué, Sara Villeneuve, Lucy Fournier, Sabine Hoffmann, Sophie Ancelet, and Estelle Rage. Thanks to my two fellow PhD students (already graduated) Damien Drubay and Neige Journy for sharing the office and very positive atmosphere.

I am very grateful the IRSN direction (Jocelyne Aigueperse, Philippe Voisin, Marc Benderitter, Laurence Roy, Véronique Joffrès, Malika Abdelsadok, Patricia Brunet, Gauzelin Barbier, Mathieu Schuler, and Patrick Laloi) for allowing me to pursue this PhD degree at one of the world's leaders of the radiation field.

Thanks to the many friends I met and learned from in Moscow, Vilnius, Jerusalem, Paris and San Francisco. Special thanks to Bruno, Domenico, Sergey, Gildas, Violeta, Marius, and Tomas for sharing moments of joy and uncertainty.

I would finally like to thank my parents, Irina and Vladimir, for having always encouraged and supported my choices.

ABSTRACT

External γ-radiation exposure has been shown to be associated with mortality risk due to leukemia, solid cancer, and, possibly, circulatory diseases (CSD). By contrast, little information is available on health risks following the internal contamination, especially the inhalation of uranium compounds with respect to their physicochemical properties (PCP), such as solubility, isotopic composition and others.

The aim of this PhD thesis was to estimate mortality risk of cancer and non-cancer diseases in French nuclear fuel cycle workers and comprises three objectives: (1) evaluation of the impact of uranium on mortality through a critical literature review, (2) analysis of cancer and non-cancer mortality in a cohort of uranium enrichment workers, (3) analysis of the relationship between CSD mortality and internal uranium dose in AREVA NC Pierrelatte workers.

Existing epidemiological data on uranium PCP and associated health outcomes are scarce. Studies of nuclear fuel cycle workers by sub-groups within the specific stage of the cycle (e.g., uranium enrichment and fuel fabrication) are considered the most promising to shed light on the possible associations, given that such sub-groups present the advantage of a more homogenous uranium exposure.

To study the mortality risk associated with exposure to rapidly soluble uranium compounds, we set up a cohort of 4,688 uranium enrichment workers with follow-up between 1968 and 2008. Individual annual exposure to uranium, external γ-radiation, and other non-radiological hazards (trichloroethylene, heat, and noise) were reconstructed from job-exposure matrixes (JEM) and dosimetry records. Over the follow-up period, 131,161 person-years at risk were accrued and 21% of the subjects had die. Analysis of Standardized Mortality Ratios (SMR) showed a strong healthy worker effect (SMR all deaths 0.69, 95% confidence intervals (CI) 0.65 to 0.74; n=1,010). Exposures to uranium and external γ-radiation were not significantly associated with any cause of mortality in log-linear and linear excess relative risk models. A monotonic decreasing trend was observed for lung and lymphohematopoietic cancers across uranium exposure categories.

Previous analysis of a cohort of AREVA NC Pierrelatte uranium processing workers suggested that exposure to uranium may increase CSD mortality. A nested case-control study was set up to analyze the dose-response relationship and adjust for major CSD risk factors (smoking, blood pressure, body mass index, total cholesterol, and glycemia) collected from medical files. The study included 102 CSD cases and 416 controls matched on attained age, gender, birth cohort, and socio-professional status. Absorbed dose was calculated taking into account the solubility of uranium compounds extracted from the JEM. CSD risk was analyzed by conditional logistic regression. A positive but imprecise association was observed (excess odds ratio per mGy 0.2, 95% CI 0.004 to 0.5). None of the considered CSD risk factor confounded this association.

Compared to previous studies, our work provided important methodological improvements: consideration of specific uranium PCP, calculation of uranium organ doses, and adjustment on potential confounding factors (non-radiological exposures and CSD risk factors). The absence of association between exposure to rapidly soluble uranium compounds and mortality in the cohort of uranium enrichment workers may be indicative of the effective elimination of uranium from the human body. Analysis within the nested case-control study confirmed an association between uranium exposure and CSD mortality, not confounded by CSD risk factors. Our results should be confirmed in further studies. Future work should focus on uncertainties associated with internal uranium dose estimation, on nature of association with CSD mortality, and on temporal relationships between radiation and CSD risk factors.

Key words: uranium; epidemiology; cohort study; nested case-control study; internal dose estimation.

SCIENTIFIC PRODUCTION

Publications

Zhivin S, Guseva Canu I, Samson E, Laurent O, Grellier J, Collomb P, Zablotska LB, Laurier D. Mortality (1968–2008) in a French cohort of uranium enrichment workers potentially exposed to rapidly soluble uranium compounds. *Occupational and Environmental Medicine* (accepted 28/10/2015).

Garsi JP, Samson E, Chablais L, **Zhivin S**, Niogret C, Laurier D, Guseva Canu I. Half-century archives of occupational medical data on French nuclear workers: a dusty warehouse or gold mine for epidemiological research? *Archives of Industrial Hygiene and Toxicology* 2014;65:407-416.

Zhivin S, Laurier D, Guseva Canu I. Health effects of occupational exposure to uranium: Do physicochemical properties matter? *International Journal of Radiation Biology* 2014;90:1104-1113.

Guseva Canu I, **Zhivin S**, Garsi JP, Caër-Lorho S, Samson E, Collomb P, Acker A, Laurier D. Effets de la contamination chronique à l'uranium sur la mortalité : bilan d'une étude-pilote chez les travailleurs de l'industrie nucléaire en France [in French]. *Revue d'Epidémiologie et de Santé Publique* 2014;62:339-350.

Zhivin S, Laurier D, Caër-Lorho S, Acker A, Guseva Canu I. Impact of chemical exposure on cancer mortality in a French cohort of uranium processing workers. *American Journal of Industrial Medicine* 2013;56:1262-71.

Oral presentations

Zhivin S, Laurier D. Étude épidémiologique des travailleurs du cycle du combustible nucléaire et analyse des effets sanitaires des composés uranifères en fonction de leur solubilité. *Journées des Thèses IRSN (http://www.irsn.fr/FR/Larecherche/Formation_recherche/Theses/Pages/Les-theses-a-l-IRSN-5224.aspx),* Isle-sur-la-Sorgue, March 2015.

Zhivin S, Guseva Canu I, Samson E, Laurent O, Grellier J, Collomb P, Laurier D.French cohort of uranium enrichment workers: first results of mortality analysis. *The 2014 Conference on Radiation and Health & Radiation Research Society (http://www.radres.org/?page=CRHRegOpen),* Las Vegas, USA, September 2014.

Zhivin S, Laurier D. Occupational exposure to uranium in nuclear fuel cycle workers and veterans of wars. *Periodic meeting of the International Commission on Radiological Protection (ICRP) task group 64 "Cancer risk from alpha emitters"*, Paris, June 2014.

Zhivin S, Laurier D.Étude épidémiologique des travailleurs du cycle du combustible nucléaire et analyse des effets sanitaires des composés uranifères en fonction de leur solubilité. *Journées des Thèses IRSN (http://www.irsn.fr/FR/Larecherche/Formation_recherche/Theses/Documents/Livret%20Journ%C3%A9es%20des%20th%C3%A8ses%20IRSN%202014.pdf)*, Paris, March 2014.

Zhivin S, Laurier D, Caër-Lorho S, Acker A, Guseva Canu I.Doit-on prendre en compte l'exposition chimique chez les travailleurs français du nucléaire? *15ème colloque de l'Association pour le Développement des Études et des Recherches Études Épidémiologiques sur la Santé et le Travail (ADEREST)*, Paris, November 2013. *Archives des Maladies Professionnelles et de l'Environnement*2013;74(6):669-670.

Zhivin S, Laurier D, Guseva Canu I. Health effects of occupational exposure to uranium: does physicochemical characterization matter? The 11th International Conference on the Health Effects of Incorporated Radionuclides (HEIR), Berkeley, USA, October 2013. *International Journal of Radiation Biology* 2014;90(11):945-7.

Zhivin S, Laurier D, Caër-Lorho S, Acker A, Guseva Canu I. Chemical exposure and cancer mortality in a French cohort of uranium processing workers. *23rd International Epidemiology in Occupational Health (EPICOH) Conference*, Utrecht, the Netherlands, June 2013. *Occupational and Environmental Medicine* 2013;70(suppl 1):A83.

Zhivin S, Laurier D. Review of recently published epidemiological studies on uranium processing workers.*Periodic meeting of the International Commission on Radiological Protection (ICRP) task group 64 "Cancer risk from alpha emitters"*, Paris, April 2013.

Poster presentation

Zhivin S, Guseva Canu I, Samson E, Laurent O, Grellier J, Collomb P, Laurier D.French cohort of uranium enrichment workers: first results of mortality analysis. Poster presentation for the Early Stage Radiation Investigator Session.*The 2014 Conference on Radiation and Health & Radiation Research Society (http://www.radres.org/?page=CRHRegOpen)*, Las Vegas, USA, September 2014.

Technical documentation

Zhivin S, Blanchardon E. Critical reading of an epidemiological study among Fernald Feed Materials Production Center workers. Note technique IRSN, October 2013.

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AMAD	Activity median aerodynamic diameter
ALARA	As Low as Reasonably Achievable
AOR	Adjusted odds ratio
BMI	Body mass index
BNFL	British Nuclear Fuels Limited
BP	Blood pressure
Bq	Becquerel
CANDU	CANada Deuterium Uranium
CEA	Commissariat à l'énergie atomique et aux énergies alternatives
CépiDC	Centre d'épidémiologie sur les Causes Médicales de Décès
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CMR	Carcinogenic, mutagenic or toxic for reproduction
CSD	Circulatory diseases
CT	Computerized tomography
CURE	Concerted Uranium Research in Europe
CVD	Cerebrovascular diseases
DNA	Deoxyribonucleic acid
DOE	US Department of Energy
DoReMi	Low Dose Research towards Multidisciplinary Integration
DU	Depleted uranium compounds
EC	European Commission
EOR	Excess odds ratio
ERR	Excess relative risk
EU	Enriched uranium compounds
Gy	Gray
HATM	Human Alimentary Tract Model
HDL	High-density lipoprotein
HLEG	High level and expert group on European low dose risk research
HR	Hazard ratio
HRTM	Human Respiratory Tract Model
HWE	Healthy worker effect
ICD	International Classification of Diseases
ICP-MS	Inductively coupled plasma-mass spectrometry
ICRP	International Commission on Radiological Protection
IDEAS	General guidelines for the estimation of committed effective doses from the incorporation data
IHD	Ischemic heart diseases
IL	Interleukin
ILO	International Labour Organization
INSEE	Institut National de la Statistique et des Etudes Economiques
INSERM	Institut National de la Santé et de la Recherche Médicale
IR	Ionizing radiation
IRSN	Institut de Radioprotection et de Sûreté Nucléaire
ISCO	International Standard Classification of Occupations
JEM	Job-exposure matrix
KIM	Kidney injury molecule
KPA	Kinetic phosphorescence analyzer

LDL	Low-density lipoprotein
LET	Linear energy transfer
LHP	Lymphohematopoietic
LLR	Long-lived radionuclides
LN	Intra-thoracic lymph nodes
LOD	Level of detection
LRT	Likelihood ratio test
LSS	Life Span Study
MM	Multiple myeloma
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular Disease
MOX	Mixed oxide fuel
NCI	National Cancer Institute
NCRP	United States National Council on Radiation Protection and Measurements
NHL	Non-Hodgkin's lymphoma
NIOSH	National Institute for Occupational Safety and Health
NU	Natural uranium compounds
OR	Odds ratio
PPE	Personal protection equipment
RBE	Relative biological effectiveness
RBM	Red bone marrow
RDP	Radon decay products
RNIPP	Répertoire National d'Identification des Personnes Physiques
RPU	Reprocessed uranium compounds
RR	Relative risk
SI	International System of Units (Système International d'Unités)
SIR	Standardized Incidence Ratio
SISERI	French national database of occupational external exposure to ionizing radiation
SMR	Standardized Mortality Ratio
SNIIRAM	Système National d'Informations Inter-Régimes de l'Assurance Maladie
Sv	Sievert
TCE	Trichloroethylene
TNF	Tumor necrosis factor
TRACY U	TRAvailleurs du CYcle du combustible potentiellemment exposés à l'Uranium
UCSF	University of California San Francisco
UF_6	Uranium hexafluoride
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
UO_2F_2	Uranyl fluoride
UV	Ultraviolet
WHO	World Health Organization
WLM	Working-level month

INTRODUCTION

Humans are constantly exposed to naturally occurring ionizing radiation such as cosmic radiation and radon gas. On a global level, major artificial exposure comes from medical X-ray examinations and nuclear fallout after nuclear accidents (e.g., Chernobyl, Fukushima) and weapons testing. The occupational radiation exposure occurs in some occupations, such as medical personnel and nuclear workers.

While extensive data are available on long-term health effects of acute high-dose γ-radiation, less is known about low-dose internal α-radiation exposure following inhalation. These α-emitters tend to accumulate in particular tissues and emit a very dense type of radiation. Uranium is a ubiquitous α-emitter whose toxicity depends on its physicochemical properties, notably solubility and isotopic composition.
Nuclear workers involved in the nuclear fuel fabrication and reprocessing (hereafter referred to "nuclear fuel cycle workers") attract a great deal of scientific attention due to their protracted exposure to various uranium compounds and the availability of monitoring data. However, internal radiation exposure assessment is subject to large uncertainties, and recent reviews have suggested performing studies within sub-groups of workers with homogenous uranium exposure or collection of accurate data on physicochemical properties of uranium compounds.

In 2005 a pilot study of AREVA NC Pierrelatte uranium processing workers was set up by the Institut de Radioprotection et de Sûreté Nucléaire (IRSN) to study potential associations with internal uranium exposure. This pilot study led to the construction of a cohort of more than 12,000 French nuclear fuel cycle workers (TRACY cohort).

My PhD project integrates the continuation of these works. In particular, I focused on studying the impact of uranium physicochemical properties on the risk of possible health effects by means of a critical literature review (Objective I), the construction of the French cohort of uranium enrichment workers and the analysis of mortality (Objective II), and the analysis of the relationship between circulatory disease mortality and internal uranium radiation dose in the nested case-control study of AREVA NC Pierrelatte workers (Objective III).

This PhD manuscript consists of six chapters.

Chapter 1 provides a general background on human exposure to ionizing radiation, describes concepts of radiation damage and dose, and highlights current focus of radiation research.

Chapter 2 introduces the different stages of the French nuclear fuel cycle. It places importance on a variety of radiological and non-radiological hazards encountered by workers. The current state of the internal uranium monitoring system used by occupational health departments is described.

Chapter 3 presents evidence of the chronic health effects of uranium in toxicological and epidemiological studies. It presents critical literature review of the association between mortality and internal uranium exposure analyzed in the frame of this PhD. This chapter highlights the influence of uranium physicochemical properties, identifies current gaps, and proposes areas of improvement for future studies of nuclear fuel cycle workers.

Chapter 4 presents the mortality analysis of the French cohort of uranium enrichment workers. A unique feature of this population is exposure to rapidly soluble uranium compounds. Chapter 4 provides details on the cohort construction and the methodology of reconstruction of reconstruction of occupational exposure for radiological and non-radiological hazards. Mortality was analyzed in comparison with the general French population. Exposure-response analyses were performed for selected causes of death.

Chapter 5 considers the relationship between circulatory disease mortality and uranium radiation dose. Analyses rely on a nested case-control study of AREVA NC Pierrelatte workers. An internal dosimetry protocol was developed specifically for this study that allowed estimation of individual radiation doses based on monitoring data and uranium compound solubility. Major classical circulatory disease risk factors were extracted from medical files. Dose-response analyses, adjusted on these risk factors, suggested an independent effect of internal uranium exposure.

Chapter 6 presents a general discussion of the limitations and advantages of the performed work. This chapter discusses questions raised by this work, and open perspectives for future research.

Chapter 1. HUMAN EXPOSURE TO IONIZING RADIATION

1.1. Ionizing radiation

Ionizing radiation refers to radiation that carries sufficient amount of energy to free electrons from atoms and molecules. Ionizing radiation consists of electromagnetic waves and subatomic particles. Higher ultraviolet portion, gamma rays, and X-rays are the electromagnetic spectrum of ionizing radiation (Figure 1). Subatomic particles include α-particles, β-particles, and neutrons.

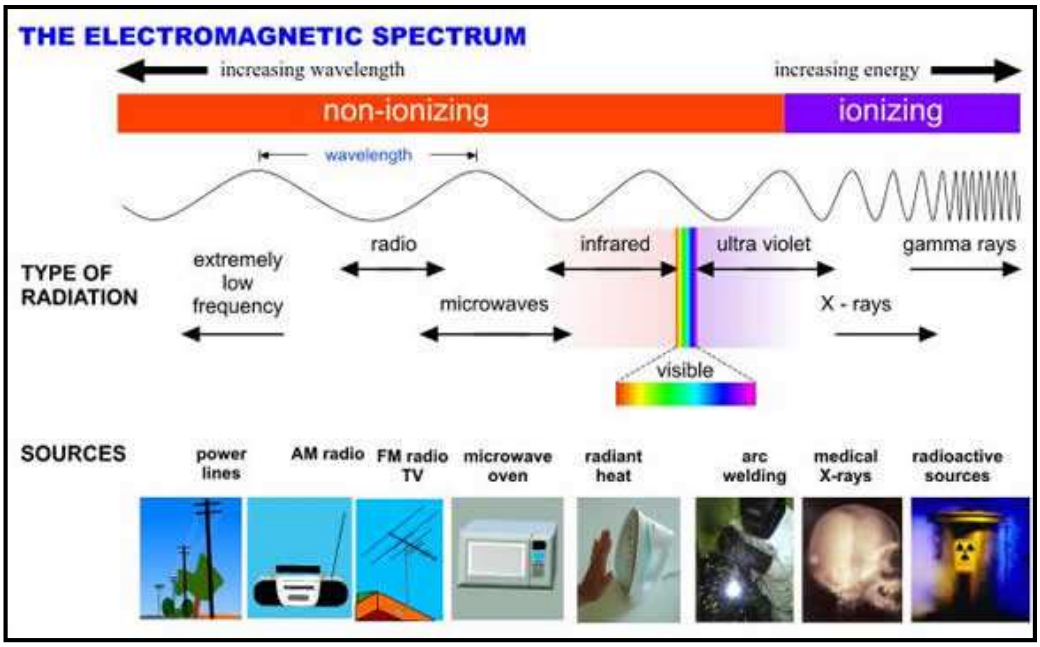

Figure 1. Electromagnetic spectrum of ionizing radiation. Source: Australian Radiation Protection and Nuclear Safety Energy, accessed from http://www.arpansa.gov.au/radiationprotection/basics/ion_nonion.cfm [26 May 2015]

Certain atoms are unstable and refer to **radionuclides**. They emit ionizing radiation (IR) that can break the bounds between electrons and the nucleus so that atoms become charged (ionized) (Alpen, 1998).

1.1.1. Main types of ionizing radiation

Different types of IR are divided into non-penetrating (α- and β-particles) and penetrating (X- and γ-rays, and neutrons) (Figure 2). The difference is that non-penetrating IR quickly ionizes numerous cellular molecules once in the tissue, while penetrating IR may travel large distances in human tissue without interacting with electrons (NRC, 2006). The types of IR are distinguishable as follows:

- ***α-particles*** are heavily charged helium atoms ($^4_2$He). In the air they can travel a few centimeters and can be stopped by a sheet of paper. These particles have a range of tens of μm in biological tissues and thus cannot penetrate the epidermis. Therefore, α-emitting radionuclides are only hazardous when inhaled or ingested.
- ***β-particles*** are lighter than α-particles, and are composed of either positrons (β^+) or electrons (β^-). In the air, they travel tens of centimeters and can be stopped by a thin sheet of metal or wood.
- ***X***-and ***γ-rays*** are represented by photons that have both particle and wave characteristics. In the air, they may travel many meters, and can be attenuated by a thick lead layer.
- ***Neutrons*** are uncharged particles released during nuclear fusion and fusion. They may react with other atoms and make them radioactive (neutron activation). In the air, neutrons travel great distances and require several meters of water or cement to shield against them.

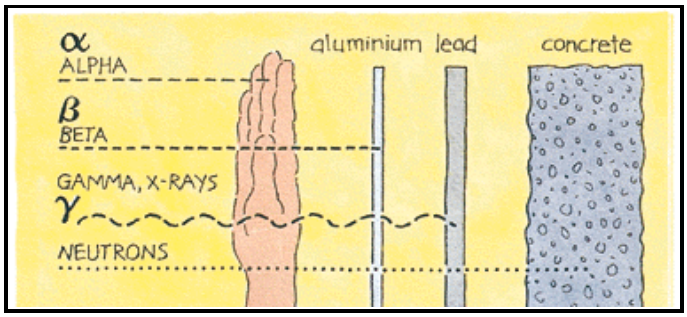

Figure 2. Penetration activity of the four main types of ionizing radiation. Source: World Nuclear Association, accessed from http://www.world-nuclear.org/info/Safety-and-Security/Radiation-and-Health/Radiation-and-Life/ [26 May 2015]

1.1.2. Radiation measurements

A measurable quantity of IR exposure, referred to as a **dose**[1], is the ratio of the energy deposited in a volume by IR-matter interactions to the mass of this volume. A branch of physics (dosimetry) quantifies the dose from IR in different situations of exposure. Biological effects generally increase with the dose absorbed by biological tissues.

Radiation protection is a set of practices, tools and regulations aimed at avoiding unacceptable health hazards while allowing the use of IR for economically or medically beneficial applications. The different quantities used to characterize radiation exposure are: radioactivity, absorbed dose, equivalent dose, and effective dose (ICRP, 2007). Equivalent and effective doses were specifically developed for radiation protection purposes by the International Commission on Radiological Protection (ICRP) (ICRP, 2007).

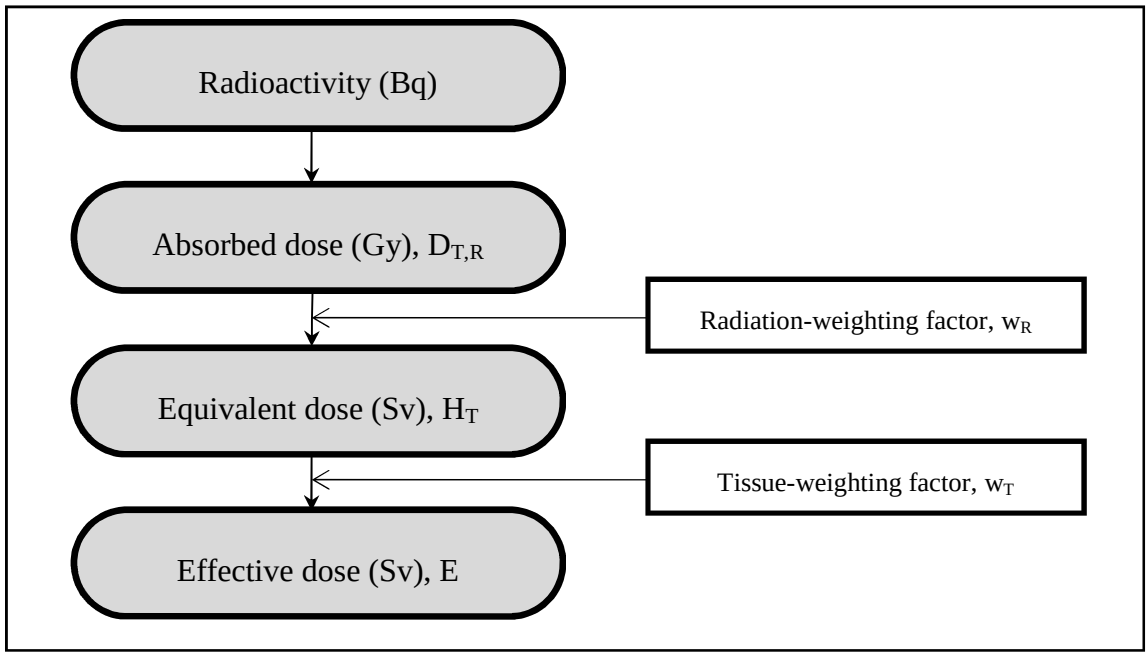

Figure 3. Main indicators of exposure in radiation protection

Radiation quantities are further described below:

- **Radioactivity** of the source is the number of nuclear transformations per second. Some atoms are more radioactive than other because they require less time (smaller half-life) to undergo radioactive decay. The International System of Units (SI) unit for radioactivity is Becquerel (1 Bq=1 disintegration.second^{-1}).

[1] In exposure science, a xenobiotic dose is its quantity divided per unit mass of tissue or body. In radioprotection, this unit (Bq/kg) is not sufficient because of the physicochemical properties of various radioelements, and because of various body tissues' radiosensitivity.

- **Absorbed dose** is the quantity of imparted energy per unit of mass. The SI unit is the Gray (Gy, 1 Gy=1 $J.kg^{-1}$). In radiation protection, this dose is averaged over the target organ (e.g., liver) or is estimated for sensitive target cells within the tissue (e.g., basal and secretory cells of the bronchi, stem cells of the alimentary tract, red bone marrow, etc.).
- **Equivalent dose** in a tissue *T* is defined as $H_T = \sum_R w_R D_{T,R}$, where $D_{T,R}$ is the absorbed dose in a tissue *T* of the radiation type *R*, and w_R is the radiation-weighting factor, a dimensionless expert judgment based on the relative biological effectiveness (RBE) of different types of IR (more on the RBE in Chapter 1.1.3). It equals one for photons of γ-radiation, one for β-particles, and 20 for α-particles (ICRP, 2007).
- **Effective dose** is a weighted average of equivalent doses to radiosensitive tissues, $E = \sum_t w_R H_T = \sum_T \sum_R w_R D_{T,R}$, where w_T is the tissue-weighting factor for a tissue T, and the sum of w_T equals one. The values of w_T are essentially derived from the frequency of appearance of stochastic effects (cancer and hereditary diseases) in the cohort of atomic bomb (A-bomb) survivors of Hiroshima and Nagasaki. Stochastic effects are further described in Chapter 1.1.6.
- **Committed effective dose** is a quantity specifically related to internal exposure due to the retention of a radionuclide in the body. It is defined as the effective dose delivered over 50 years in adults, and until the age of 70 years in children due to the retention of a radionuclide in the body following internal contamination.

A body organ dose is not a directly measurable quantity. For external exposure, it is usually estimated from badge dosimeters. The dosimetry of internal exposure is more indirect, because it is based upon direct measurements of radioactivity (e.g., lung counting) or measurements in excreta (e.g., urine and feces). As time passes, incorporated radioactivity in different tissues lowers depending on the radioactive decay and the biokinetics of a radionuclide. Thus, internal dose needs to be interpreted using dedicated biokinetic and dosimetric models, combined with an appropriate exposure scenario.

1.1.3. Concept of radiation damage

Radiation damage from the same absorbed dose may be different for various types of IR (UNSCEAR, 2006). Thus, the concept of linear energy transfer (LET), the energy deposited

per unit distance over the path of a particle, is used to describe the capacity of different types of IR to transfer energy to a body's tissues. A high-LET IR (α-particles and neutrons) tends to produce more damage to the cells, for example in terms of DNA double-strand breaks compared to low-LET IR (γ-radiation).

The difference in radiation quality for a given biological organism is known as the RBE. The RBE of α-radiation can be calculated as the absorbed dose of α-radiation required to produce a specified biological response (often, cell killing or late effects) divided by the absorbed dose of the reference γ-radiation. Because the RBE is calculated for a specified outcome in a specific population and for specific exposure scenarios, the studies of the RBE of α-radiation for different outcomes are still ongoing (Durante, 2014; Marsh *et al*, 2014; Zhukovsky *et al*, 2015).

1.1.4. Routes of exposure

Radiation exposure can derive from an external source beaming from outside the body (**external exposure**), but also from the incorporation of radionuclides, leaving their energy in internal organs once absorbed (**internal exposure** or **internal contamination** or **intakes of radionuclides**). Internal contamination by radioelements emitting α-radiation is particularly dangerous because of the high energy of α-particles. Different radionuclides tend to cumulate in particular organs: ^{131}I (thyroid gland), ^{90}Sr (bone), ^{235}U (bone and kidney). Internal contamination can occur by different routes: inhalation, ingestion, injection, skin absorption, and wound contamination. In occupational settings, the main route is inhalation of radioactive aerosols and dusts (Figure 4).

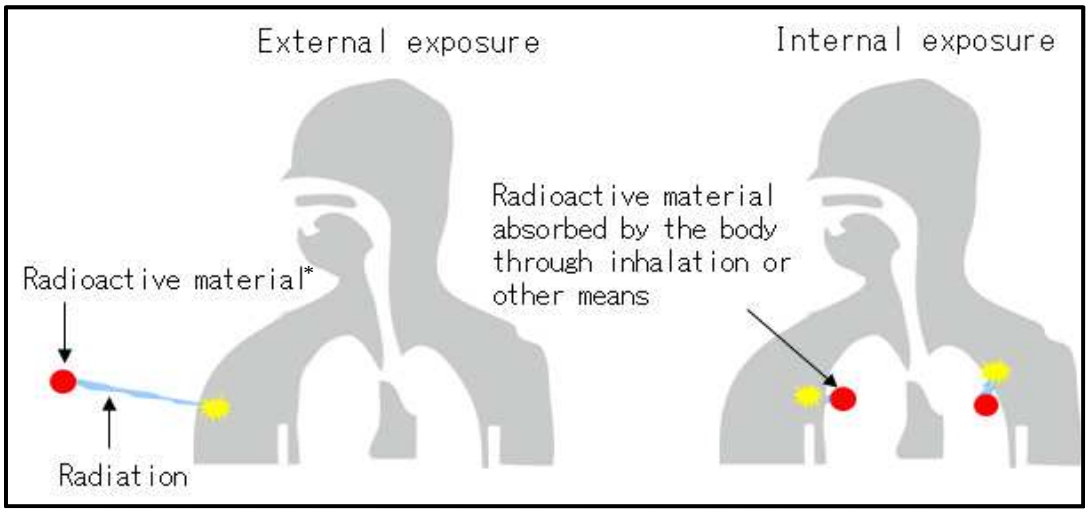

Figure 4. External vs. internal radiation exposure. **Source: National Institute of Radiological Sciences of Japan, accessed from http://www.nirs.go.jp/db/anzendb/NORMDB/ENG/1_yougosyuu.php [28 May 2015]**
*Radioactive material or X-ray generator

In the general population, ingestion by the gastrointestinal tract occurs through ingestion of food and water (UNSCEAR, 2008). In the occupational settings, a radioactive material enters the gastrointestinal tract in two ways: (1) directly through unintentional hand carriage of radioactive material, and (2) undirectly through the mucociliary clearance of the material towards pharynx where it is swallowed.
While the duration of external irradiation is dependent on the presence of the external source, internal exposure may continue a long time after an intake if a radioelement is accumulated by the body and not excreted effectively (e.g., insoluble uranium, plutonium, and strontium).

Both external and internal exposure can be long-term (**chronic**) and short-term (**acute**). For instance, populations can be chronically exposed to IR if radioactive materials are constantly present in the soils or at the workplace. In nuclear workers, chronic exposure is often more important because it accumulates over the long period of work. In contrast, a known example of acute external exposure over several seconds is the atomic bombings of the Japanese cities of Hiroshima and Nagasaki in 1945 (Ozasa *et al*, 2012).

1.1.5. Sources of human exposure

Public exposure to IR is from two main sources: natural and artificial (man-made) (UNSCEAR, 2008). In France, according to IRSN, the mean effective radiation dose is 3.7 mSv per year (Figure 5). The major part of this dose is due to natural sources (65%) and

medical X-ray examinations (35%). Exposure from industrial artificial sources, including nuclear accidents, is less than 1% (Figure 5).

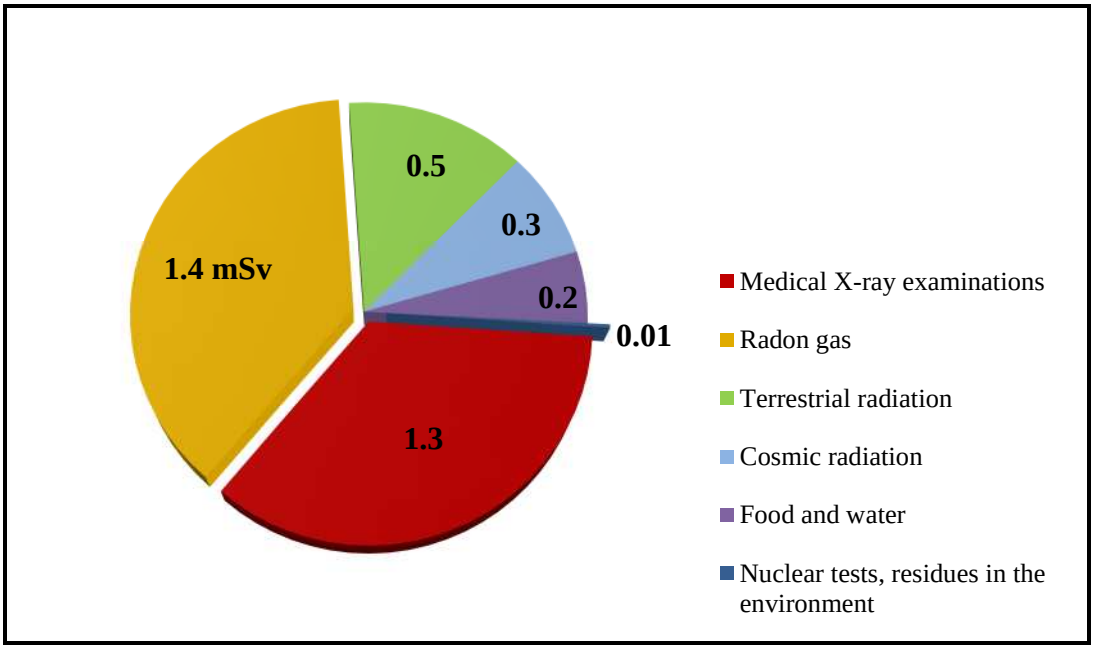

Figure 5. Main sources of exposure to ionizing radiation (mean annual effective dose) in the general French population. Source: Institut de Radioprotection et de Sûreté Nucléaire (IRSN), 2010.

While exposures from artificial industrial sources of IR (excluding medical examinations) represent low proportion of the mean annual effective dose in the general population, there may still be non-negligible contributors to effective doses in the certain occupational sectors, such as radiology and nuclear medicine, nuclear fuel cycle and nuclear power production, metal mining and smelting, phosphate industry, coal mining, oil and gas drilling, rare earth, and titanium oxide industries. All these occupations are subject to dosimetry monitoring, meant to keep IR exposure as low as reasonably achievable (ALARA), and in accordance with legal requirements. At present, the majority of French workers monitored for exposure to IR receive effective doses less than 1 mSv per year, and less than ten workers exceeded the 20 mSv radiation annual effective dose limit in 2013 (IRSN, 2014).

1.1.6. Stochastic and deterministic health effects of ionizing radiation

Ionization of atoms in the deoxyribonucleic acid (DNA) or nearby may cause lasting biochemical damages, possibly leading to the lost of tissular function (hematopoiesis) or tissue reactions, mutations, and, eventually, to the initiation of cancerogenesis.

Health effects after exposure to IR are divided into two broad groups: **deterministic (**also known as **tissue reactions)** and **stochastic** (Stewart, 2012). Deterministic effects occur after exposure to high doses of IR that exceed a certain threshold. Such high exposure causes massive cell death and is manifested by radiation sickness syndrome (nausea, weakness, hair loss, skin burns, and diminished organ function, etc.). Deterministic health effects are thought not to appear below a certain dose threshold level, unique to each tissue. Circulatory effects are currently considered as deterministic with a threshold of 0.5 Gy (AGIR, 2010; Stewart, 2012).

Stochastic effects—associated with statistical likelihood—reflect long-term disease occurrence probability and depend on the radiation dose received even after low-level IR exposure in the range of several tens to hundreds mSv. In contrast to deterministic effects, increased levels of exposure make the stochastic effects more likely to occur, but do not influence the severity of the effect. Stochastic effects consist primarily of cancer and hereditary effects. Although never observed in humans, hereditary effects of IR in the form of germline mutations may be transmitted to the offspring. Very recently, biological (AGIR, 2010) and epidemiological (Little *et al*, 2012a) data appeared showing a dose-response for circulatory diseases below a threshold of 0.5 Gy. This points out a changing paradigm with respect to the deterministic effect of IR on the circulatory system.

1.1.7. Radiation protection and individual risk assessment

The use of equivalent and effective doses in radiation protection provides a simple and convenient quantity helpful in controlling exposures, but does not provide accurate estimates of individual risk (EC, 2013). Radiation-weighting factors w_R, based on the RBE, were not produced to distinguish between scenarios of exposure (acute and chronic) and different outcomes (immediate and late) (Harrison & Day, 2008; ICRP, 2007). Tissue-weighting factors w_T were produced to represent contributions of doses to individual tissues on the risk of cancer and hereditary effects (ICRP, 2007). Moreover, these w_T are based on sex- and age-averaged data of A-bomb survivors of Hiroshima and Nagasaki. Thus, effective dose should be used only for radiation protection purposes (ICRP, 2007). Although, ICRP recommends using absorbed doses weighted by appropriate RBE in epidemiologic studies to avoid misuses of radiation protection quantities (ICRP, 2007), it can become problematic in a view of uncertain RBE values.

1.1.8. Key epidemiologic studies of cancer and circulatory disease risks

The key epidemiologic studies of cancer and circulatory diseases after exposure to IR are regularly reviewed by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (UNSCEAR, 2006).

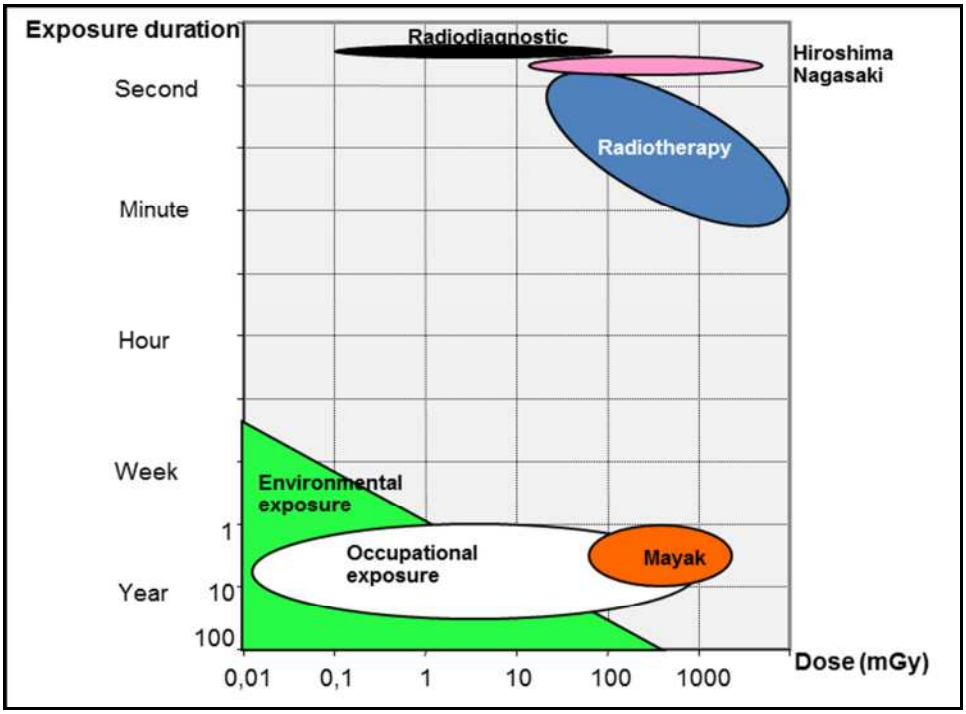

Figure 6. Dose levels and duration of exposure to ionizing radiation in epidemiologic studies of the health effects of ionizing radiation. Source: (Laurier & Hill, 2013).

There is an important variability of dose levels and duration of exposure among human populations, which are reflected by existing epidemiological studies (Figure 6).

In general, epidemiologic studies can be divided into three major groups based on exposure place: **occupational**, **environmental, and medical**.

In occupational settings, the major studies are the studies of uranium miners, Mayak Production Association plutonium workers in Russia, and other nuclear and clean-up workers, and medical personnel chronically exposed to internal or external IR. The advantages of these studies are their very well-defined study populations and the availability of individual radiation monitoring data.

Studies of environmental exposure to IR are concentrated on different scenarios of exposure in the general population: external exposure (A-bomb survivors of Hiroshima and Nagasaki), internal exposure (ingestion of radioactive water, residential exposure to radon), and mixed

internal and external exposure (populations residing near the Techa river, consequences of explosions of the nuclear reactors in Chernobyl and in Fukushima).
In medical settings, higher dose diagnostic IR procedures in the form of computerized tomography (CT) scans raise concerns for late health effects, in children and adolescents particularly (Bosch de Basea *et al*, 2015; Journy *et al*, 2015; Pearce *et al*, 2012).

1.1.8.1. Cohort of A-bomb survivors as a basis for current radiation protection standards

The risks estimates obtained in one study are difficult to extrapolate to another one due to different levels and dose rates of exposure, and differences in baseline risks of diseases attributed to diet, lifestyle and genetic background. Nevertheless, modern radioprotection standards are mainly based on large cohort prospective studies of A-bomb survivors of Hiroshima and Nagasaki exposed to flash external IR in 1945 and, to a lesser extent, on studies of radiotherapy patients.

The study of A-bomb survivors of Hiroshima and Nagasaki is known as Life Span Study (LSS), set up in 1950. LSS includes approximately 120,000 persons: 93,000 A-bomb survivors and 27,000 unexposed persons not present in Hiroshima and Nagasaki during the bombing (Grant *et al*, 2015; Ozasa *et al*, 2012). The major source of exposure in this cohort is external IR; radiation doses from residual radioactivity (induced radioactivity of soils and buildings through neutron activation, and radioactive fallout in the form of "black rain") were considered negligible. Among the in-city A-bomb survivors in the LSS, 87,000 had an estimated radiation dose to the colon. Among these, 69,000 subjects received colon dose[2] below 100 mGy.In the recent analysis with follow-up on 31 December 2003 and the updated dosimetry system DS02, the overall mortality risk was increased by 22% per Gy, and by 47% per Gy for solid cancers (Ozasa *et al*, 2012). Cause-specific mortality was associated with radiation exposure for the following cancers: non-chronic lymphocytic leukemia (non-CLL), breast, bladder, lung, esophagus, stomach, and colon cancers (Ozasa *et al*, 2012). The LSS was among the first studies that found a positive association between radiation and mortality due to circulatory diseases (Kodama *et al*, 1996; Preston *et al*, 2003; Shimizu *et al*, 1992; Wong *et al*, 1993); in the most recent cohort update, the increase is 11% per Gy (Ozasa *et al*, 2012).

[2] Colon dose is considered sufficiently representative of radiation exposure to internal organs in the LSS (Ozasa *et al*, 2012).

Studies of the LSS cohort also described major effect modifiers of radiation-induced mortality, such as age at exposure, attained age, and time since exposure (Ozasa *et al*, 2012; Thompson *et al*, 1994).

1.2. Current issues for radiation protection research

Current radiation protection standards rely mainly on knowledge gained from studies of A-bomb atomic survivors and radiotherapy patients. Because substantial uncertainty exists for long-term health effects of low-level IR of below 100 mGy, the High Level and Expert Group on European Low Dose Risk Research (HLEG) identified the key priorities for future low-dose research in Europe (HLEG, 2009):

- **Shape of the dose-response relationship**
- **Tissue sensitivity and individual variability in cancer risk**
- **Non-cancer health effects**
- **Impact of radiation quality**
- **Internal exposure (intake of radionuclides) risk**

Knowledge regarding long-term health risks from intakes of radionuclides is underpinned by important damages to cells by α-particles, widespread exposure, and possible use of nuclear terrorism ("dirty bombs") (Boice, 2014). Assessment of the internal dose is subject to uncertainties due to a large number of parameters of associated biokinetic and dosimetric radionuclide-specific models (Etherington *et al*, 2006). This assessment, however, could be more reliable for populations with well-characterized exposure and monitoring data, such as diagnostic investigations and therapeutic treatments (^{131}I and other radionuclide-labelled monoclonal antibodies), and cohorts of workers chronically exposed to uranium, plutonium, tritium, strontium, cesium, and polonium (HLEG, 2009).

Several workshops and editorials reiterated that studies of nuclear fuel cycle workers are considered to be among the most promising for studying chronic disease mortality association with internal uranium exposure because of the availability of the monitoring data and the long duration of follow-up in most of the existing cohorts (Boice, 2014; Cardis & Richardson, 2000; Cardis *et al*, 2001; Laurier *et al*, 2012).

Chapter 2. NUCLEAR FUEL CYCLE WORKERS: INTERNAL URANIUM EXPOSURE MONITORING

2.1. Uranium and its critical role in the atomic energy

Uranium is the 92th element of the Dmitry Ivanovich Mendeleev's periodic table, and the heaviest naturally occurring element. It was discovered in 1789 by the German chemist Martin Heinrich Klaproth who had precipitated the yellow salt as the product of dissolving pitchblende in nitric acid. In its pure state, uranium is a silver-colored dense metal with a melting point of 1133 °C. It occurs in soil, rocks, water, plants, animals, and humans. The most elevated uranium concentrations are found in phosphates, and in igneous rocks such as granite (Morvan, 2004).

The most common oxidation states of uranium are uranium (IV) and uranium (VI). In an aqueous solution, uranium is usually in the oxidative state VI, known as uranyl ion UO_2^{2+}. Uranium is radioactive with six major isotopes being ^{232}U, ^{233}U, ^{234}U, ^{235}U, ^{236}U, and ^{238}U. Uranium decays mainly by emitting α-particles. Natural uranium consists of three isotopes: ^{234}U, ^{235}U, and ^{238}U. The key radioactive properties of natural uranium are shown in Table 1.

Table 1. Key radioactive properties of natural uranium

Isotope	Half-life (years)[†]	Mass in natural uranium (%)	Specific activity ($Bq.g^{-1}$)[‡]	Radiation energy (MeV)
^{234}U	2.5×10^5	0.0055	2.32×10^8	4.8 α
^{235}U	7.0×10^8	0.72	8.0×10^4	4.4 α, 0.21 γ
^{238}U	4.5×10^9	99.27	1.25×10^4	4.2 α

[†]Half-life is the time that it takes for half of the atoms to decay and the activity to be proportionately reduced.
[‡]Activity is the rate at which the nuclei in the isotope decay.

^{238}U is a **fertile** isotope because after absorbing one neutron it becomes ^{239}U. ^{239}U is a beta-emitter that decays to produce ^{239}Np, which, in turn, also decays producing ^{239}Pu. ^{239}Pu is a source used in atomic weapons (e.g., the "Fat Man" bomb detonated over Nagasaki in 1945).

^{235}U is the only naturally present **fissile** isotope. The neutron can split its nucleus into several parts (fission products). The fission is accompanied by a large release of energy and a release of several neutrons. During so-called chain reaction, the free neutrons can hit other ^{235}U nuclei, producing more and more neutrons. Due to its fission characteristics, ^{235}U-containing fuel (3-5% enrichment in civil applications) is the main nuclear fuel used in the nuclear industry.

2.2. French nuclear fuel cycle

The **nuclear fuel cycle** is a series of industrial processes that leads to energy generation from uranium and other materials in nuclear reactors. It starts in the front end (uranium mining and preparation) part, and it ends in the back end (fuel reprocessing or disposing) part of the nuclear fuel cycle. If spent fuel is reprocessed, the nuclear fuel cycle is referred to as a closed fuel cycle; otherwise, a cycle is referred to as an open fuel cycle. The French nuclear cycle is a partly closed fuel cycle, as shown in Figure 7.

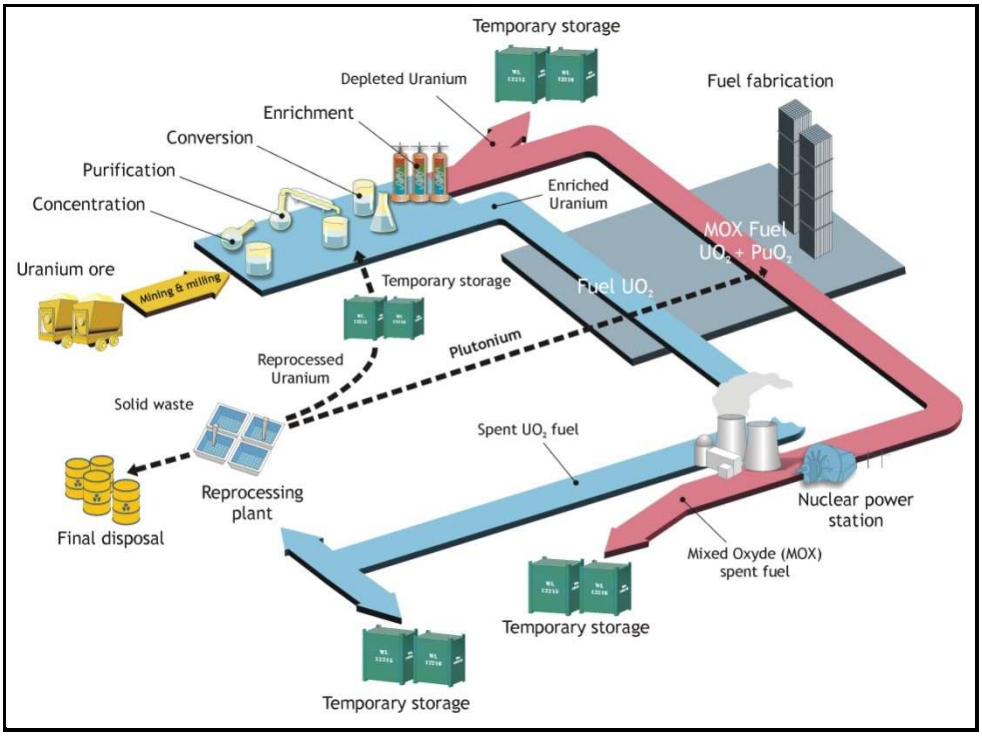

Figure 7. French nuclear fuel cycle. Source: Institut de Radioprotection et de Sûreté Nucléaire (IRSN), 2015.

It includes the following stages:

1) **Uranium mining.** In order to extract uranium ore, open pit, underground mines, and *in-situ* recovery is used. Open pit mining is used when the uranium deposits are close to the surface; underground mines are used in case of deeper uranium deposits. *In-situ* recovery (dissolving uranium in the ground and pumping the solution to the ground) is the new predominant technology in some countries, such as Kazakhstan.
2) **Uranium milling and processing.** During the milling process, uranium is extracted from crushed ore by leaching with strong acid or alkaline. Uranium oxide is then precipitated from the solution, dried, heated, and packed as “yellow cake” powder. Yellow cake is a mixture of uranium oxides that contains up to 96% of uranium in the

form of triuranium octoxide (U_3O_8), uranium trioxide (UO_3), and ammonium diuranate $(U_2O_7)(NH_4)_2$ (Pinkerton *et al*, 2004).

3) **Chemical conversion.** Because only ^{235}U is fissile, the fuel should have increased ^{235}U content. At this step, the"yellow cake" is purified and transformed successively into uranyl nitrate ($UO_2(NO_3)_2$), $(U_2O_7)(NH_4)_2$ and then into UO_3, and, finally, into uranium dioxide (UO_2). UO_2 is then converted into uranium tetrafluoride (UF_4). Finally, the reaction of UF_4 with fluorine gas provides uranium hexafluoride (UF_6). UF_6 is solid at ambient temperature, but becomes gas at temperatures above 60 °C.
4) **Enrichment.** The enrichment separates gaseous UF_6 into two streams: one enriched in ^{235}U, and another depleted in ^{235}U. Uranium enriched up to 3-5% is used in nuclear reactors for most civil applications. Uranium enrichment is described further in Chapter 2.2.2 because of the focus on French uranium enrichment workers in Chapter 4.
5) **Fuel fabrication.** Reactor fuel is in the form of ceramic pellets. These are formed from defluoridation of UF_6 into UO_2, and baking of UO_2 at a high temperature (800 °C). The pellets are encased into metal tubes, and arranged into a fuel assembly ready for introduction into a nuclear reactor. One water-pressurized-water nuclear reactor usually contains around 200 fuel assemblies.
6) **Energy production.** Energy in the form of heat is produced by neutron induced fission of ^{235}U atoms. This heat then transforms water into steam. The steam drives a turbine connected to an energy generator.
7) **Fuel reprocessing.** After four years in a nuclear reactor, fuel contains 5% waste and 95% potentially recycled products. The latter can be extracted by chemical separation. Plutonium (up to 1%) is recycled as Mixed Oxide (MOX) fuel. MOX is a mixture of depleted uranium and plutonium oxides, whose manufacture is similar to that of uranium oxide fuel. MOX fuel is used in 21 existing French nuclear reactors. The uranium is recovered in the form of uranyl nitrate and is referred to as reprocessed uranium. It remains slightly more enriched (1%) than natural uranium and could be used in the manufacture of new fuel.

2.2.1. Comparison with the Canadian nuclear fuel cycle

Nuclear fuel cycles are often country-specific. The information below briefly discusses Canadian nuclear fuel cycle in a view of constant collaboration between French and Canadian nuclear industries.

In contrast to the French nuclear fuel cycle, the Canadian nuclear fuel cycle is open, because it does not include fuel reprocessing (Figure 8). In addition, Canada does not have enrichment facilities, and all enriched uranium is imported from other countries. While France ceased its mining activities in 2001, Canada is the second world's largest producers of uranium in 2014[3]. Today, the majority of uranium mines is concentrated in the provinces of Saskatchewan (Cluff Lake, Key Lake, McArthur River, Beaverlodge, Cigar Lake, Midwest Project, McClean Lake, Rabbit Lake), Northwestern Territories (Port Radium), and Ontario (Blind River, Elliot Lake, Bancroft). The Port Hope uranium milling and processing facility was operated in 1940–1950s under the auspices of the US Department of Energy (DOE) (L.B. Zablotska, personal communication). An important Canadian invention is the CANDU (CANada Deuterium Uranium) nuclear reactor that uses natural unenriched uranium and is operated under heavily-pressurized water. There are currently 19 operating CANDU reactors. Figure 8 presents the CANDU fuel cycle.

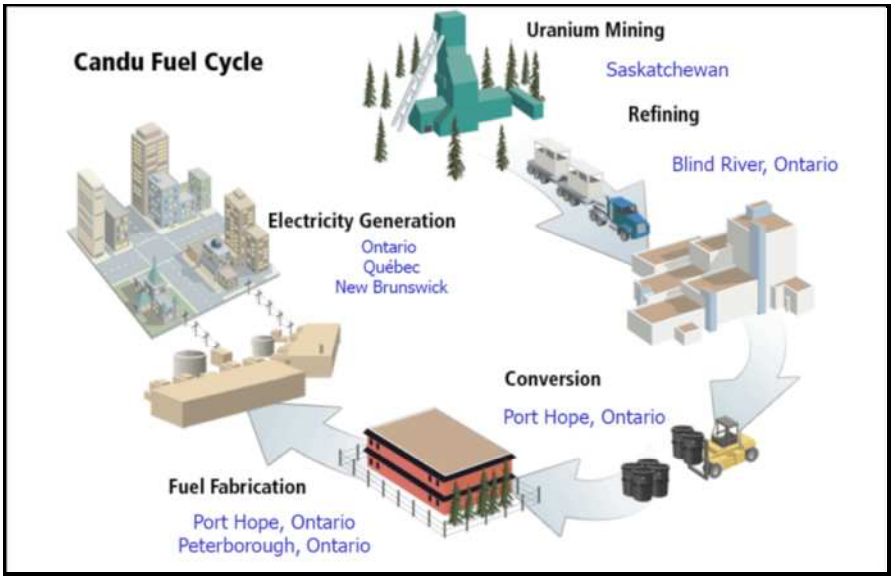

Figure 8. Canadian Candu nuclear fuel cycle. Source: Canadian Nuclear Waste Management Organization, assessed from http://www.nwmo.ca/uploads_managed/MediaFiles/1162_nwmo-nuclearfuelcycleandusedfu.pdf [19 June 2015].

[3] World uranium mining, 2014. Source: World Nuclear Association, assessed from: http://www.world-nuclear.org/info/Nuclear-Fuel-Cycle/Mining-of-Uranium/World-Uranium-Mining-Production/ [04 November 2015].

2.2.2. Enrichment by gaseous diffusion technology

The main purpose of uranium enrichment is to increase the ^{235}U content. Because the mass of ^{235}U and ^{238}U differ very slightly, specific separation technologies that take into account physical properties of the two isotopes are needed. These technologies separate the incoming feed into two streams relative to ^{235}U concentration: enriched and depleted. Table 2 lists commercial and research uranium enrichment technologies based on physical and chemical separation methods.

Table 2. Main commercial and research uranium enrichment technologies

Technology	Examples
1. Diffusion in a pressure gradient	Gas centrifuge Separation nozzle Vortex tube
2. Diffusion principles	Gaseous diffusion Mass diffusion Thermal diffusion
3. Phase equilibrium principles	Chemical exchange Ion exchange
4. Photo excitation principles	Atomic vapor laser isotope separation Molecular laser isotope separation
5. Electromagnetic principles	Plasma separation process Electromagnetic isotope separation Plasma centrifuge

Source: (Whitaker, 2005).

Nowadays, the two main commercial technologies based on physical separation are gaseous diffusion and gas centrifugation. Both technologies use highly soluble UF_6 gas as a feed material. The world's major uranium enrichment plants are situated in:

- France (AREVA NC, CEA, and Eurodif plants)
- Netherlands (Almeco plant)
- UK (Capenhurst plant)
- USA (Paducah, Portsmouth, and Oak Ridge K-25 gaseous diffusion plants)
- Russia (Novouralsk, Seversk, Angarsk, and Krasnoyarsk enrichment plants)

In France, the main technology of commercial enrichment between 1964 and 2012 was gaseous diffusion. This technology utilizes the separation effect arising from the flow of UF_6 gas through small tubes (Figure 9). Lighter ^{235}U are more likely to escape through porous membranes compared to heavier ^{238}U. By repeating this process a number of times, one can obtain more and more enriched product.

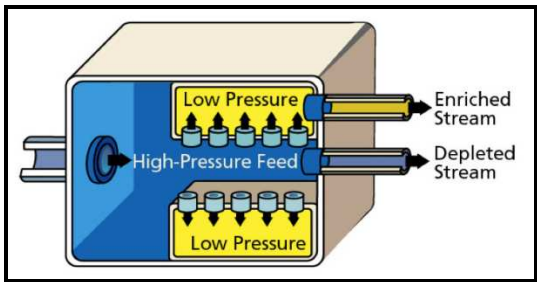

Figure 9. Gaseous diffusion technology. Source: Yale Scientific, assessed from http://www.yalescientific.org/2012/12/enriching-uranium/ [17 June 2015]

Gaseous diffusion was the first commercial-scale technology developed in the 1940s during the Manhattan Project. Relative to other enrichment technologies, gaseous diffusion has very high energy consumption, and a small separation factor requiring many repeated stages to obtain sufficiently enriched uranium. By contrast, gas centrifugation has lower energy consumption and requires less time to enrich uranium. That was the reason why France phased out its gaseous diffusion plants in 2012, and switched to gas centrifugation by opening the new Georges Besse II uranium enrichment facility.

2.2.3. Exposures in French nuclear fuel cycle workers[4]

The subject of this PhD project is internal uranium exposure; however, French nuclear fuel cycle workers can also be exposed to non-radiological hazards (Table 3).

Together with uranium compounds, chemical and physical (noise, heat, etc.) hazards are a part of the nuclear fuel cycle industrial process. For example, the major non-radiological exposures at uranium enrichment plants are noise (due to the working enrichment cascades), heat (to maintain UF_6 gaseous state), and trichloroethylene (TCE, heat transfer fluid).
Major occupational hazards are regulated by the European Commission (EC) regulation 2004/37 (EC, 2004); in this regulation, substances are classified into three groups as carcinogenic, mutagenic or toxic for reproduction (CMR): (1) substances known to have CMR effects, (2) substances that are strongly suspected to trigger or increase the frequency of

[4] Impact of non-radiological (chemical) exposure on mortality of AREVA NC uranium processing workers was a subject of Sergey Zhivin's pre-doctoral internship at IRSN. This research was conducted under the supervision of Dr. I. Guseva Canu and Dr. D. Laurier, and published in the American Journal of Industrial Medicine (Zhivin *et al*, 2013).

the occurrence of CMR effects, and (3) substances that raise concern for their possible mutagenic effects, but in relation to which there is insufficient scientific evidence.

Table 3. Major groups of industrial hazards at French uranium processing and enrichment plants

Hazard group	Examples
Uranium compounds	Natural
	Enriched
	Depleted
	Reprocessed
External γ-radiation	
Chemical hazards	Metal dusts
	Hydrazine and hydrocarbon fuels
	Acids
	Trichloroethylene
	Chlorinated and fluorinated products
Physical hazards	Welding fumes
	Silica and rock/wool fibres
	Asbestos
	Heat
	Noise
	Electromagnetic fiels

Source: adapted from (Guseva Canu *et al*, 2013b; Guseva Canu *et al*, 2009).

Until recently, little attention was paid to assessing exposure to non-radiological hazards in the French nuclear industry due to sparse and often unusable monitoring data. However, chemical and physical hazards at uranium plants have been studied at similar U.S. and UK nuclear facilities: Rocketdyne/Atomics International (Ritz *et al*, 2000), Oak Ridge gaseous diffusion plant (Yiin *et al*, 2009), Paducah gaseous diffusion plant (Chan *et al*, 2010), Fernald Feed Materials Production Center (Anderson *et al*, 2012), and the British Nuclear Fuels Limited (BNFL) plants (McNamee *et al*, 2006).

2.2.3.1. Personal protective equipment

Collective protection measures (ventilation, engineering controls, and worker sensibilization) against occupational hazards are the most important; however, personal protective equipment (PPE) is also used when collective measures not sufficient. PPE is defined as the clothing and equipment worn by personnel to prevent and mitigate occupational disease or injury (OSHA, 2006). In general, PPE in the nuclear industry is intended to protect against external, internal radiation, physical, and chemical occupational hazards. Individual PPE is represented by variety of devices such as respirators, face shields, safety glasses, safety shoes, vests, goggles, gloves, and earplugs.

The used PPE was evaluated recently in the subsample of of French uranium enrichment workers employed at Eurodif plant (1978–2008) (Guseva Canu *et al*, 2013a) (Table 4).

Table 4. Personal protective equipment at the French uranium enrichment plant Eurodif[†]

	PPE					
Hazard	**Work clothes (vests)**	**Masks and respirators**	**Gloves**	**Goggles**	**Earmuff**	**Earplugs**
Uranium	+	+	+			
Chemical emissions	+	+	+	+		
Metal dusts		+				
Asbestos	+	+				
Noise					+	+
Heat	+					

[†]Adapted from (Guseva Canu *et al*, 2013a).
PPE, personal protective equipment.

This study found that workers were more sensibilized to protect themselves against radiological than chemical hazards (Guseva Canu *et al*, 2013a).

2.3. Monitoring of occupational uranium exposure

The main purpose of occupational radiation monitoring at nuclear fuel cycle facilities is to confirm that workers are effectively protected from IR according to the ALARA (As Low as Reasonably Achievable) principle, and to ensure that the radiation protection is in line with legal requirements.

2.3.1. Objectives of monitoring

Nuclear fuel cycle workers in contact with uranium compounds may receive radiation doses from external γ-radiation, and internal radiation by inhaling uranium dust. For external γ-radiation exposure, personal dosimeters are used to estimate the whole-body dose (at a depth of 10 mm in the body below the place of wearing the dosimeter, mSv).

For internal uranium exposure, organ absorbed doses could be estimated from uranium measurements in the body (lung counting), in bioassay measurements (urine and feces samples), and in the workplace (ambient air sampling and analysis) using radionuclide-specific biokinetic and dosimetric models.

Nuclear fuel cycle workers are monitored either on: (1) a regular basis (regular surveillance) or (2) on special occasions (special surveillance) to estimate a dosimetric impact of a suspected incident or accident. There are two types of occupational monitoring: **workplace monitoring** and **individual monitoring**.

2.3.1.1. Workplace monitoring

Workplace air uranium concentration ($Bq.m^{-3}$) measurements are usually collected from static air samplers. In general, the workplace monitoring is based on the following criteria: (1) it demonstrates that workplace meets regulatory working conditions, and (2) it provides exposure measurements for a group of workers.

In addition to the volume concentration, ambient measurements provide information on other characteristics of the aerosol, such as particle size in terms of the activity median aerodynamic diameter (AMAD, µm). This diameter and the particle density give an indication of the deposition of the particles in the respiratory system. Another important parameter for monitoring is the chemical form of uranium that indicates its type of solubility (F-fast, M-moderate or S-slow absorption from lung to blood). For example, previous workstation studies in French nuclear fuel cycle workers have shown that the average uranium concentrations in various workstations are from 0.1 to 3 $Bq.m^{-3}$ (Chazel *et al*, 2000), and the mean AMAD value is 5µm, with a range from 1.1 to 8.5 µm (Ansoborlo *et al*, 2002). Workplace data in terms of uranium physicochemical properties (solubility and isotopic composition) are used to develop directed individual bioassay programs (Table 5).

2.3.1.2. Individual monitoring

Individual exposure monitoring data are designed to refine workplace monitoring and to ensure that each worker does not exceed the maximum annual effective dose limit of 20 mSv. According to French legislation, frequency and type of individual monitoring are established by an occupational physician based on the physicochemical form of handled uranium compounds and worker's category (A and B). Category A includes workers who may receive more than 6 mSv per year under normal working conditions. In France, each radiation worker should have at least one medical examination per year.

Table 5 shows the type and frequency of current individual monitoring programs in France, based on the solubility of major industrial compounds of uranium.

Table 5. Individual uranium monitoring programs [§]

Uranium compound	Lung absorption type[†]	Preferred monitoring type	Interval between measurements (days)
Nitrate ($UO_2(NO_3)_2$	F	Urine	30
Tributylphosphate	F	Urine	30
Peroxide (UO_4)	F	Urine	30
Hexafluoride (UF_6)	F	Urine	90
Trioxide (UO_3)	F/M	Urine + feces	90
Tetrafluoride (UF_4)	M	Urine + feces	90 (urine) 180 (feces)
Octoxide (U_3O_8)	M/S	Lung + feces	180
Dioxide (UO_2)	S	Lung + feces	180

[§]Adapted from (EC, 2007; HAS, 2013a).
[†] International Commission on Radiological Protection (ICRP) classification of uranium absorption types, extracted from (Davesne & Blanchardon, 2014).
Abbreviations: F, fast; M, moderate; S, slow absorption.

As shown in Table 5, the choice of monitoring type largely depends on the uranium physicochemical properties. For example, 73% of absorption type F uranium is eliminated within 24 hours (Neuman, 1950). This justifies a shorter interval between measurements compared to the type M and S uranium compounds.

In vivo monitoring for insoluble uranium compounds (e.g., uranium oxides) includes lung counting. This exam is based on the analysis of γ-radiation emitted by ^{235}U retained in the lungs and on quantification of the corresponding activity. Because uranium is a weak γ-emitter, lung counting is less effective in the case of an old exposure, exposure to soluble uranium compounds, and low-level exposure.

In vitro monitoring is usually carried out by measuring the uranium activity in excreta, such as urine and feces.

There are three main techniques for analyzing uranium in excreta:

- **Fluorometry**. It is a rapid measurement technique used from the earliest years of the nuclear industry to determine the total mass of uranium. The amount of uranium in a sample is determined by comparison with the fluorescence method from a set of samples with known uranium concentrations. Detection limits for urinalysis are as follows: from 5 $\mu g.l^{-1}$ (corresponded to 126 $mBq.l^{-1}$ of natural uranium) to 2 $\mu g.l^{-1}$ (corresponded to 50 $mBq.l^{-1}$ of natural uranium). Fluorometry is conventionally used to measure exposures to soluble natural, depleted, and low-enriched uranium compounds.

- **Kinetic phosphorescence analysis (KPA)**. Similar to fluorometry this technique determines the total mass of uranium by measuring the luminescence of aqueous sample following laser excitation. The KPA has higher sensitivity compared to fluorometry: in the order of 0.1 $\mu g.l^{-1}$ (corresponded to 2.5 $mBq.l^{-1}$ of natural uranium).
- **Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)**. This modern technique implemented in the 2000s is based on a method of ionizing the sample with inductively coupled plasma and then using a mass spectrometer to separate ions according to their mass. Because the ICP-MS measures the number of ions, it is the most sensitive for long-lived uranium isotopes. In routine use, the ICP-MS is generally used to measure ^{238}U and ^{234}U. The technique's sensitivity is about 1.5×10^{-3} $\mu g.l^{-1}$ for ^{238}U and 2×10^{-4} $\mu g.l^{-1}$ for ^{234}U.
- **Gross α-spectrometry**. This technique involves radiochemical separation of the uranium from urine, then deposition of the uranium on a substrate. In early periods (before 1970s) only the total α-activity was measured. Later, α-spectrometry was used to discriminate between ^{234}U and ^{238}U depending upon the enrichment degree. Since the 1990s α-spectrometry has been used to measure uranium activity irrespective of the enrichment degree. Detection limits vary from a few $mBq.d^{-1}$ in the 1960s to less than 0.5 $mBq.d^{-1}$ nowadays.

In France, important work was performed by Dr. Cécile Challeton-de Vathaire and Dr. Irina Guseva Canu to review routine uranium measurement techniques used from 1960s until now in France (Challeton-de Vathaire, 2013; Guseva Canu *et al*, 2010). This information was particularly useful to estimate internal uranium doses in this PhD project (Chapter 5).

2.3.2. Biokinetic and dosimetric models

Assessment of internal radiation doses requires the use of the following: (1) biokinetic models that describe the behavior of radionuclide from its entry into the body until its elimination from the body, and (2) dosimetric models that describe the radiation-matter interactions.

The biokinetic models used in internal dosimetry are of several types: (1) models of entry (respiratory tract, gastrointestinal tract, and wounds) that describe the proportion of activity absorbed to blood, excreted in feces or locally retained, and (2) systemic models that predict

the distribution of the radionuclide in internal organs, following the blood circulation, and its elimination by natural means. Biokinetic models are specific to each radionuclide or to physicochemical forms of radionuclides (ICRP, 1989; ICRP, 1993; ICRP, 1994; ICRP, 1995; ICRP, 2002; Leggett *et al*, 2005).

Chronic inhalation exposure is by far the most important route of exposure in nuclear fuel cycle workers. Uranium-specific respiratory and systemic models are used to estimate a dose to internal organs from inhalation (Leggett, 1994). These models are based on data from patients injected with uranium intravenously, and are adjusted and validated using post-mortem measurements of uranium in tissues of occupationally and environmentally exposed subjects, and experimental data from baboons and dogs (Leggett, 1994).

The Human Alimentary Tract Model (HATM) (ICRP, 2006), which describes the paths of a radionuclide from entry into the oral cavity to emptying in feces, is not detailed in this manuscript. The wound model was developed by the United States National Council on Radiation Protection and Measurements (NCRP) (NCRP, 2006). It consists of five compartments and decribes radionuclide clearance into blood or regional lymph nodes. These two models are not described in this manuscript.

2.3.2.1. Human respiratory tract model

The HRTM was introduced by the ICRP in publication 66 (ICRP, 1994). Overall, the HRTM divides the respiratory system into extrathoracic (ET) and thoracic tissues (Figure 10).

The ET region is further divided into the anterior nasal passages, where radioactive deposits are removed by extrinsic forces (nose blowing), and the posterior nasal passages (nasopharynx, oropharynx, and larynx), from which deposits may be swallowed and transported to the gastrointestinal tract. The thoracic tissues consist of the bronchi (BB), bronchioles (bb), and alveolar interstitium (AI) (Figure 10). Uranium deposited in the thoracic airways is cleared into the gastrointestinal tract by mechanical processes (mucociliary clearance and the process of swallowing), and to the regional lymph nodes by macrophages via lymphatic vessels. Mechanical clearance from the lung is dependent on particle size because it determines the initial pattern of deposition from the extra-thoracic regions to the deeper lung regions. The ICRP defines three types of materials according to their absorbtion (solubility) type: type F (rapidly absobed), type M (moderately absorbed), and type S (slowly absorbed). In parallel to mechanical transport, a part of inhaled uranium is absorbed to blood

from extra-thoracic and thoracic regions. Absorption is assumed to occur at the same rate in all but ET_1 (anterior nose) regions.

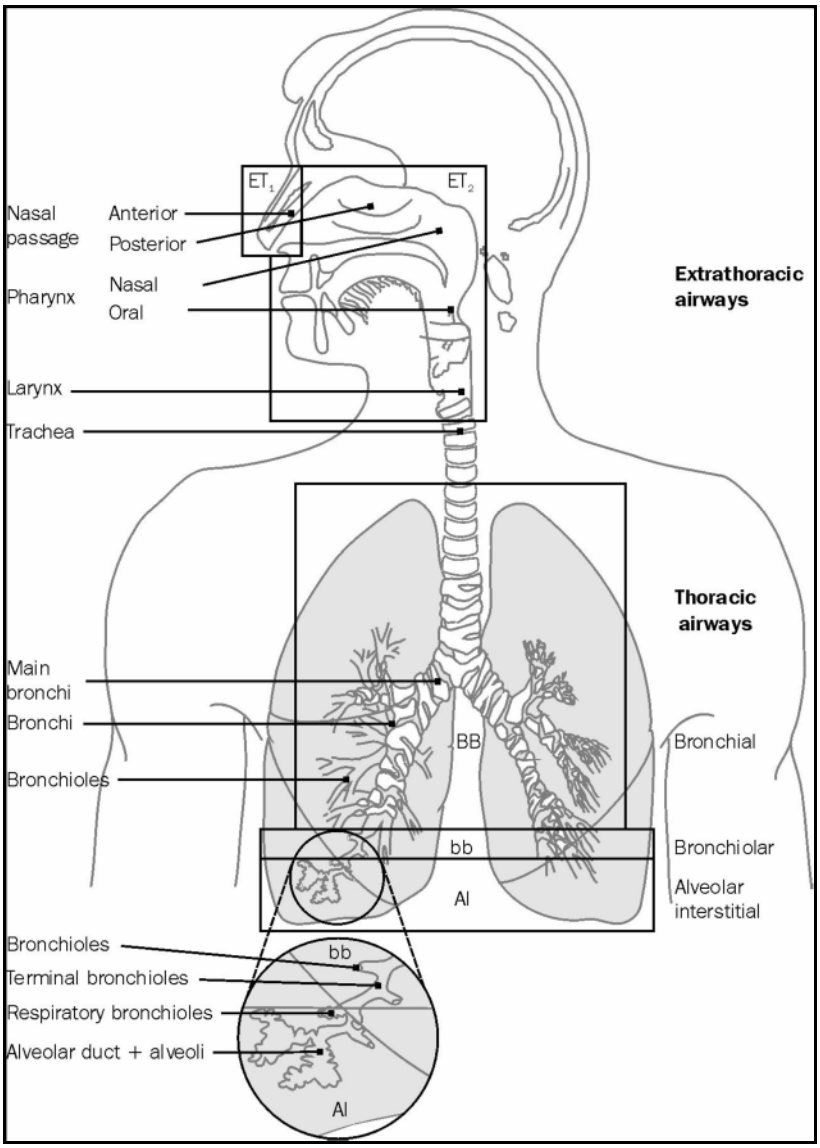

Figure 10. Human Respiratory Tract Model (HRTM)

2.3.2.2. Uranium systemic model

The uranium systemic model was introduced in the ICRP publication 69 (ICRP, 1995). It describes the uranium behavior once it reaches the blood, and includes 17 compartments (Figure 11).

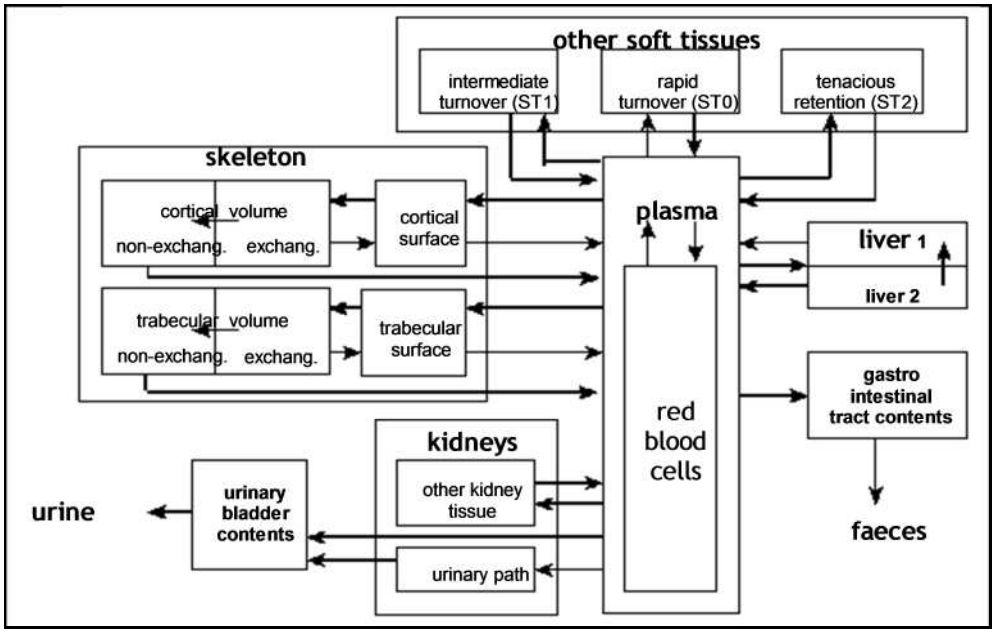

Figure 11. Uranium systemic model

The uranium systemic model has the same structure as those used for several radionuclides (Sr, Ba, Ra, Pb) because these radionuclides mimic, to some extent, calcium behavior in bones. The uranium model was further modified for the plasma and kidney compartments to address uranium rapid movements after introduction to blood. It should be noted that uranium is not a full physiological analogue of calcium, but some data suggest that uranyl-ion (UO_2^{2+}) imitates the behavior of calcium-ion (Ca^{2+}), exchanging with it at the surfaces of bone, but not participating in bone crystal formation. The uranium systemic model is the same for all uranium compounds, regardless of their initial solubility.

Uranium is constantly exchanged between the blood and other soft tissues, and different compartments within tissues (Figure 11). Skeleton and kidneys are considered the main sites of uranium deposition. Experimental animal data show that 24 hours after uranium intravenous injection, uranium will be distributed in the following tissues: skeleton (15%), kidneys (18%), other tissues (5%), and urine (63%) (Durbin, 2010).

2.3.3. Interpretation of the results of uranium monitoring

Once a bioassay result is positive—indicating an incorporation of the radioactive material—an evaluation of the radiation dose and its comparison with the regulatory limits is required. A dose estimation is usually performed by occupational physicians with the help of dosimetrists. There are two steps in the estimation process: (1) incorporated activity (*I*), which is calculated

by dividing the activity *M* measured *t* days after the intake by the retention or excretion function at time *t*, *m(t)*, prediction of the biokinetic models of the measured quantity for a unit intake, and (2) committed effective dose estimation, which is obtained by multiplying the incorporated activity *I* by the effective dose coefficient (expressed as Sv/Bq intake).
The functions of retention and excretion and effective dose coefficients are derived from biokinetic and dosimetric models. To estimate incorporated activity several parameters should be determined:

- **Radioisotopes involved**
- **Time pattern of intakes** (a worker may have one or more acute intakes or acute intakes during a period of a long chronic intake)
- **Route of intake** (inhalation, ingestion, wound, or combination of routes)
- **Physicochemical properties** (solubility, and particle size, etc.)
- **Worker's anatomophysiological characteristics** (speed of absorption into the blood and mucociliary clearance, time of radionuclide retention in different tissues, morphology, density, and radiosensitivity of tissues). These characteristics are age- and sex-dependent, and may be influenced by previous medical history or life-style habits (smoking).

In practice, the exact values of some or all of these parameters are often unknown or impossible to determine. Therefore, the ICRP recommends the use of reference values of parameters corresponding to an average of values ("standard person") reported in the literature. Some of these reference values are:

- A representative standard worker supposed to be active 8 hours a day and to have an average breathing rate of 1.2 $m^3.h^{-1}$
- Type M absorption type
- Aerosol particles follow the lognormal distribution with AMAD of 5 µm (geometric mean) and geometric standard deviation of 2.5 µm
- In a case of unknown exact date, it is supposed that an intake occurred in the middle of monitoring period.

A dose estimate is obtained by fitting a mathematical model by the maximum likelihood method. The "best estimate" of the dose is obtained by establishing the most likely contamination scenario, the error associated with each measure, and the information available

on the exposure conditions. As a result, a dose is often affected by an important uncertainty associated with different error sources. The third European intercomparison exercise on internal dose assessment showed that the choice of the model and of the exposure parameters (intake time pattern, aerosol solubility and particle size) can lead to important variability in dose estimates (Doerfel *et al*, 2000).

An assessment of effective dose is usually sufficient for monitoring occupational exposure, whereas for studying health effects in epidemiological studies an estimate of organ-specific absorbed dose is required. However, bioassay data are sometimes difficult to interpret because of the presence of detection and reporting limits. While most routine measurement are usually below limit of detection (LOD), the presence of natural uranium in food and water, and person-specific individual metabolism may cause low-level 'positive' results in the absence of an occupational intake. In addition, a worker may be exposed to a mixture of uranium compounds with different isotopic composition and solubility during the monitoring period. This makes it difficult to attribute monitoring data to one particular exposure.

2.3.3.1. Bioassay results below limit of detection

The below LOD data is common for occupational monitoring data. In general, these data are censored by the detection limits due to sensitivity of measurement techniques. Uranium analytical techniques are quite sensitive (but less sensitive than for plutonium) and for some of them the LOD could be less than the alimentary uranium excretion content. In order to discriminate alimentary and occupational intakes, the reporting limits were sometimes used by occupational physicians and laboratory technicians. The below LOD data are one of the major uncertainty sources during internal uranium dose estimations (Laurent *et al*, 2015).

2.4. Conclusions

Based on information of this chapter, we can conclude that (1) nuclear fuel cycle workers can be chronically exposed to a variety of radiological and non-radiological hazards, (2) at different stages of the nuclear fuel cycle workers can inhale various forms of uranium with respect to their physicochemical properties. To control internal uranium exposure in workers, the nuclear industry established a strong program of workplace and individual monitoring. In

case of suspected uranium uptakes, uranium doses are calculated using specific biokinetic and dosimetric models.

Chapter 3. HEALTH EFFECTS OF URANIUM EXPOSURE

This chapter reviews the biological effects of chronic uranium exposure in toxicological and epidemiological studies—with special focus on tissues and organs with known uptake of uranium or for which radiological sensitivity has been previously observed. Chapter 3.2 is based on the critical literature review performed during this PhD project.

3.1. Biological effects

All physicochemical forms of uranium pose chemical (heavy metal) and radiological (α-emitter) risks, with toxicity primarily dependent on the uranium chemical form, isotopic composition, and the route of exposure (ATSDR, 2012). It is thought, however, that some toxic effects of uranium are primarily due to its chemical toxicity (renal effects), while others are due to its radiological properties (carcinogenic effects). Animal data have also shown that genotoxic effects may depend on pre-exposure and may be aggravated with repeated exposure (Monleau *et al*, 2006).

3.1.1. Lung

The inhalation of soluble uranium compounds (UF_6, UCl_4, $UO_2(NO_3)_2$) is more toxic to systemic organs, compared to insoluble compounds, because of the rapid absorption from the lungs (ATSDR, 2012; Galle, 1997). Studies performed on rats, dogs, and monkeys that inhaled insoluble UO_2 and uranium ore dust during several years found an increased frequency of pulmonary fibrosis and neoplasia (Leach *et al*, 1973; Mitchel *et al*, 1999). In one of these studies (Mitchel *et al*, 1999), researchers administered uranium without important radon gas content, and performed dose-response analyses within three exposure groups: control, low- (lung absorbed dose 0.87 Gy), and highly-exposed (lung absorbed dose 1.64 Gy). Interestingly, lung tumor occurrence was not directly proportional to dose in exposed animals, but rather to dose rate (Mitchel *et al*, 1999). Moreover, the uranium burden was up to 60 times higher in thoracic lymph nodes than in the lungs (Mitchel *et al*, 1999), suggesting effective clearance by macrophages. In Gulf War veterans, uranium absorption from embedded fragments over 20 years was not associated with any lung function deterioration (Hines *et al*, 2013; McDiarmid *et al*, 2013).

Several researchers have studied the effects of depleted uranium (DU) at cellular level, which is known to be less radiotoxic than natural uranium (NU). These studies found that DU can be as toxic as NU because it may induce apoptosis of alveolar macrophages (Orona & Tasat, 2012), as well as secretion of tumoral biomarkers TNF-α (tumor necrosis factor α) and interleukin-6 (IL-6) (Gazin *et al*, 2004; Zhou *et al*, 1999). Expression of these biomarkers was also correlated with lung fibrosis (Zhou *et al*, 1999).

3.1.2. Bone

Bone is a major site of uranium deposition and may contain up to 75% of the total uranium burden (Leggett, 1994; Wrenn *et al*, 1985); however, the accumulation during chronic exposure is non-monotonous (Paquet *et al*, 2006). Osteoblasts appear to be the main target cell because uranium impacts bone metabolism, including bone resorption (Kurttio *et al*, 2005), formation and mineralization (Milgram *et al*, 2008a; Milgram *et al*, 2008b). A recent French study showed that chronic uranium ingestion of drinking water in rats (uranium concentration 40 $mg.l^{-1}$) led to underexpression of genes involved in bone metabolism and decreased femoral cortical bone area (Wade-Gueye *et al*, 2012).

3.1.3. Hematopoietic and immune system

Although bone accumulation of uranium may hypothetically impact erythropoiesis, a decrease in red blood cell count was shown to occur because of kidney and spleen failure (Berradi *et al*, 2008). Similarly, number of immune cell populations of intestine (neutrophils, macrophages) did not decrease after nine months of drinking water ingestion by rats (uranium concentration from 0.2 to 120 $mg.l^{-1}$) (Dublineau *et al*, 2014). At the same time, an overexpression of some inflammatory cytokines was observed (Dublineau *et al*, 2014). In Gulf War veterans with embedded shrapnel, the DU intake did not modify the lymphocyte response levels (McDiarmid *et al*, 2013).

3.1.4. Kidney

Degeneration and necrosis of the proximal tubular epithelium and glomeruli are the main toxic effects after acute exposure (Diamond *et al*, 1989; Voegtlin & Hodge, 1949). In contrast to acute exposure, chronic exposure does not clearly induce histological changes in the range

of 120-600 $mg.l^{-1}$ (Dublineau *et al*, 2014; Poisson *et al*, 2014). In fact, tissue alterations of the proximal tubules and glomeruli were observable for doses exceeding 400 $mg.kg^{-1}$ (Gilman *et al*, 1998a; Gilman *et al*, 1998b; Zhu *et al*, 2009). Dose-response analyses in rats (dose range 0.27-40 $mg.kg^{-1}$) showed that uranium did not impair either the histological kidney function or kidney biomarkers (Kidney Injury Molecule-1 (KIM-1), β2-microglobulin, and retinol binding protein) (Poisson *et al*, 2014). These analyses also found an increase in the level of the glutathione antioxidant system (Poisson *et al*, 2014). Recent human data of Gulf War veterans showed that kidney function was not impaired, regardless of the increase in kidney injury markers and low molecular weight proteins (McDiarmid *et al*, 2013).

3.1.5. Liver

Uranium biokinetics makes it less likely to be accumulated in the liver, compared to plutonium and thorium (Durbin, 2010). The most recent in vivo data show that DU may impair expression of the enzymes such as CYP3A that participate in xenobiotic metabolism (Dublineau *et al*, 2014; Gueguen *et al*, 2012). To the best of our knowledge, no studies have shown an occurrence of liver pathologies after chronic uranium exposure.

3.1.6. Brain

Current research suggests that the brain is among the most sensitive organs after uranium exposure. In fact, uranium may bypass the brain barrier by following olfactory nerves from the nose directly to the brain (Tournier *et al*, 2009). Numerous animal data have recently been published showing that uranium may alter behavior through changes in acetylcholine levels (Abou-Donia *et al*, 2002), in the serotonin and serotoninergic turnover ratio in the frontal cortex, dopamine levels and dopaminergic turnover in the stratum of the brain (Bussy *et al*, 2006). It seems that disruption in the neurotransmitter system might depend on the level of brain development, duration of exposure, and on the uranium enrichment level (Abou-Donia *et al*, 2002; Bensoussan *et al*, 2009; Bussy *et al*, 2006; Lestaevel *et al*, 2005a; Lestaevel *et al*, 2005b; Lestaevel *et al*, 2009).

3.1.7. Cardiovascular system

Studies of circulatory diseases have concentrated among populations living in northern European countries (Finland, Sweden) that may consume water from private drilled wells that contains high uranium concentrations (up to 1500 µg.l^{-1}). A Finnish study showed that uranium exposure was associated with increased systolic and diastolic blood pressure (Kurttio *et al*, 2006). Two other surveillance studies (Pinney *et al*, 2003; Wagner *et al*, 2010)—performed in residents living near the Fernald Feed Materials Production Center in the USA—showed that blood pressure was higher in the group living near the uranium site, but the distance from the plant did not impact the study conclusions (Pinney *et al*, 2003). The increase in blood pressure may be due to uranium accumulation in kidneys, where uranium can alter the renin-angiotensin system.

3.2. Critical literature review of epidemiological studies of health effects related to internal uranium exposure[5]

It is known that uranium toxicity depends on its physicochemical properties, including isotopic composition and solubility (Leggett *et al*, 2012). Enriched uranium (3% enriched for civil use or 90% enriched for military use) is mostly radiotoxic because ^{235}U and ^{234}U are more radioactive than ^{238}U. Chemical toxicity, on the other hand, is the main concern for NU and DU. In addition, insoluble forms of uranium always represent a higher radiotoxic potential because of their longer retention in the human lung.

Nuclear fuel cycle workers handle uranium compounds with various physicochemical properties, making it a population of interest for adverse health effects of uranium exposure. In addition, the uranium exposure among this group may occur at measurable levels, as opposed to the general population (IAEA, 2004).

An extensive review of literature published between 1980–2006 summarized the epidemiological studies of cancer risk in nuclear fuel cycle workers (Canu *et al*, 2008). This review found limited evidence of increased mortality from respiratory (larynx, lung) and lymphohematopoietic cancers, and listed low statistical power, inadequate internal dose

[5]The work presented here is based on our published article (Zhivin *et al*, 2014) and a presentation at the 11th International Conference on the Health Effects of Incorporated Radionuclides (HEIR 2013).

assessment, and non-consideration of potential confounders as limitations of the reviewed studies.

To update the aforementioned review, we analyzed epidemiological studies of cancer and non-cancer diseases of civil and military workers published between 1980–2013 with specific focus on uranium physicochemical properties (solubility, isotopic composition) (Zhivin *et al*, 2014). While there was an overlap between the two reviews, we excluded studies where uranium was not the major source of exposure, for example: US Rocketdyne workers (exposure to 14 different radionuclides including isotopes of U, Pu, Sr, Th, Po, Am, and Cs) (Boice Jr *et al*, 2006), US Savannah River Site workers (exposure to a wide variety of internal emitters including U, Pu, tritium, and fission products) (Cragle *et al*, 1988), and French workers of the Commissariat à l'énergie atomiques et aux énergies alternatives (CEA) (mixture of internal and external exposure) (Baysson *et al*, 2000).

We do not present studies of military workers (veterans of wars in the Persian Gulf and in the Balkans which took place in the 1990s), because these studies were uninformative in respect to internal uranium exposure (Zhivin *et al*, 2014), mainly because studies did not assess uranium exposure. After publication of our review article (Zhivin *et al*, 2014), only one relevant publication appeared (Kreuzer *et al*, 2015b) and was included in the description below.

3.2.1. Objectives

We aimed to answer the following questions:

(i) Is there an elevated rate of mortality or incidence of the defined outcomes of interest among different groups of nuclear fuel cycle workers?

(ii) Do epidemiological studies demonstrate a dose-response relationship between internal uranium exposure and any of the defined outcomes of interest?

(iii) To what extent do the physicochemical properties of the uranium to which these populations were exposed explain any of the reported associations?

3.2.2. Materials and Methods

3.2.2.1. Literature search and data considered

We searched two major biomedical databases (Pubmed and Scopus) for English-language original articles using the following key words and their combinations: mortality, morbidity, incidence, cancer, lymphatic, lymphoid, leukemia, hematopoietic, lymphohematopoietic, multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's disease, kidney, circulatory, cardiovascular, cerebrovascular, ischemic, disease, uranium, workers, processing. Further literature searches were restricted to articles published in the period 1980–2013. The bibliographies of each of the retrieved articles were subsequently scanned as a means of identifying additional studies.

3.2.2.2. Data considered in our review

The uranium production cycle typically includes seven steps between uranium mining and fuel reprocessing (Chapter 2.2, Figure 7). Exposure to external ionizing radiation and radon decay products (RDP) is possible at every step of this cycle. Some of these steps include far more significant exposure to RDP (uranium mining), plutonium and other transuranium elements (fuel reprocessing), or external γ-radiation exposure (reactor operation), compared to other steps of the fuel cycle. We were specifically interested in potential health effects associated with internal radiation exposure to uranium, and, thus, did not consider studies of uranium miners, reactor operators, or workers where uranium was not the major source of exposure. We, however, included a study of Canadian Port Hope workers by Zablotska et al. (2013), because the authors managed to distinguish uranium and radium workers in some of their analyses. We have also included a portion of a study by Boice *et al*. (2007) concerning US Colorado uranium millers, though that study analyzed the health effects of uranium exposure among both uranium mill workers and nearby residents. Where several studies had been performed on only one population, we included the study with the longest follow-up period; the only exception to this rule were the articles carried out on US uranium processing workers (Checkoway *et al*, 1988; Loomis & Wolf, 1996; Richardson & Wing, 2006), because each study provided specific data on outcomes of interest not covered by the other studies. General mortality and incidence experience were analyzed using the Standardized Mortality Ratio (SMR), Standardized Incidence Ratio (SIR), together with their confidence intervals (CI). Associations between uranium exposure and health outcomes of interest were assessed

using analyses of dose-response (within cohort) provided in the reviewed articles. We considered internal uranium doses, cumulative scores derived from job-exposure matrix (JEM) and indirect substitutes (external doses expressed in Sv or Gy), long-lived radionuclides (LLR) dose or RDP dose expressed as a working level month (WLM). We selected the analyses of dose-response relationship in the form of ERR (excess relative risk), HR (hazard ratio), OR (odds ratio), and RR (rate ratio or relative risk). Finally, studies were reviewed to ascertain whether they addressed quantification of the impact of the physicochemical properties of uranium on the risk of defined health outcomes. The impact of the physicochemical properties of uranium on the risk of health effects in uranium-exposed populations was assessed using information provided on the type of work performed (uranium milling, conversion, enrichment, or fuel fabrication), and using results of risk calculations and dose-response analyses.

Table 6. Description of reviewed articles

Reference*	Country	Work type[a]	Uranium	Solubility	Study design, max period of follow-up (years)	No. Of workers	No. of all deaths/cancer cases
[1] Boice et al. 2007†	USA	1	NU	S/IS*	CM, 25	450	186/48
[2] Boice et al. 2008	USA	1	NU	S/IS*	CM, 26	718	220/56
[3] Kreuzer et al. 2015b	Germany	1	NU	S/IS*	CM, 62	4054	1539/437
[4] Pinkerton et al. 2004	USA	1	NU	S/IS*	CM, 58	1485	810/184
[5] Zablotska et al. 2013b‡	Canada	1	NU	S/IS*	CM/CI, 49	2472	1097/266
[6] Canu et al. 2010	France	2/3	NU/EU/DU/RPU	S/IS	CM, 37	2709	411/193
[7] Canu et al. 2011	France	2/3	NU/EU/DU/RPU	S/IS	CM, 38	2897	460/214
[8] Dupree et al. 1987	USA	2	NU	S/IS*	CM, 36	995	429/74
[9] Dupree et al. 1995	USA	2/4	NU	S/IS*	NCCM, 46	1574	787/787
[10] Guseva Canu et al. 2012	France	2/3	NU/EU/DU/RPU	S/IS	CM, 38	2897	NA/NA
[11] Chan et al. 2010	USA	3	NU/EU/DU	S*	CM, 51	6759	1638/461
[12] McGeoghegan and Binks 2000a	UK	3	NU	S/IS*	CM, 49	3244	585/178
[13] Polednak and Frome 1981	USA	3	NU	S/IS*	CM, 34	18869	5394/886
[14] Yiin et al. 2009	USA	3	NU/EU/DU	S*	NCCM, 53	588	98/98
[15] Checkoway et al. 1988	USA	4	NU/EU/DU/RPU*	S/IS*	CM, 32	6781	862/196
[16] Dupree-Ellis et al. 2000	USA	4/2	NU	S/IS*	CM, 51	2514	1013/283
[17] Loomis and Wolf 1996	USA	4	NU/EU/DU/RPU*	S/IS*	CM, 43	8116	1861/503
[18] McGeoghegan and Binks 2000b	UK	4	NU/EU/DU/RPU*	S/IS*	CM, 49	13960	3476/971
[19] Richardson and Wing 2006	USA	4	NU/EU/DU/RPU*	S/IS*	CM, 43	3864	880/NA
[20] Silver et al. 2013	USA	4/2	NU/EU/DU/RPU*	S/IS*	CM, 53	6409	2767/858

*Studies were classified by work type in alphabetical order.

Work type: 1-uranium milling and refining, 2-uranium conversion, 3-uranium enrichment, 4-fuel fabrication.

[a] Major work type

† Only the occupational portion of the article was included.

‡ All absolute numbers were presented for all radium and uranium workers combined.

CI, cohort incidence study; CM, cohort mortality study; DU, depleted uranium; EU, enriched uranium; IS, insoluble; NA, not available; NCCM, nested case-control mortality study; NU, natural uranium; RPU, reprocessed uranium; S, soluble; *, supposed.

3.2.3. Results

We identified 20 relevant articles considering nuclear fuel cycle workers; (Boice Jr *et al*, 2007; Boice Jr *et al*, 2008; Canu *et al*, 2010; Canu *et al*, 2011; Chan *et al*, 2010; Checkoway *et al*, 1988; Dupree-Ellis *et al*, 2000; Dupree *et al*, 1987; Dupree *et al*, 1995; Guseva Canu *et al*, 2012; Kreuzer *et al*, 2015b; Loomis & Wolf, 1996; McGeoghegan & Binks, 2000a; McGeoghegan & Binks, 2000b; Pinkerton *et al*, 2004; Polednak & Frome, 1981; Richardson & Wing, 2006; Silver *et al*, 2013; Yiin *et al*, 2009; Zablotska *et al*, 2013b), and reviewed them in detail (Table 6). All articles presented mortality studies (the study by Zablotska *et al*. (2013) considered both mortality and incidence). The average follow-up period over all studies was 43.6 years. Due to a lack of detailed information, we assumed that most of the workers would have been exposed to both soluble and insoluble forms of uranium, except for those working in uranium enrichment, for which we considered exposure to soluble uranium compounds to be more plausible (Table 6).

3.2.3.1. Mortality risk in comparison with the general population

Figure 12 shows plotted SMR for cancer and circulatory disease outcomes. Nuclear fuel cycle workers employed in milling and conversion, enrichment, and fuel fabrication presented an excess in mortality from lung cancer compared to the general population (Boice Jr *et al*, 2007; Dupree-Ellis *et al*, 2000; Polednak & Frome, 1981; Silver *et al*, 2013; Zablotska *et al*, 2013b). This excess is statistically significant for two of those populations of fuel fabrication workers at the US Y-12 Oak Ridge and Fernald uranium processing facilities who were exposed predominantly to insoluble uranium compounds (Loomis & Wolf, 1996; Silver *et al*, 2013). Three articles of milling (exposure to more soluble uranium) and fuel fabrication (exposure to insoluble uranium) workers were found to have a non-significant increase in kidney cancer mortality compared to the general population (Boice Jr *et al*, 2008; Dupree-Ellis *et al*, 2000; Loomis & Wolf, 1996). Most of the articles concerning nuclear fuel cycle workers observed decreased mortality from all circulatory diseases (CSD), ischemic heart (IHD), and cerebrovascular diseases (CVD) in comparison with the general population (Figure 12).

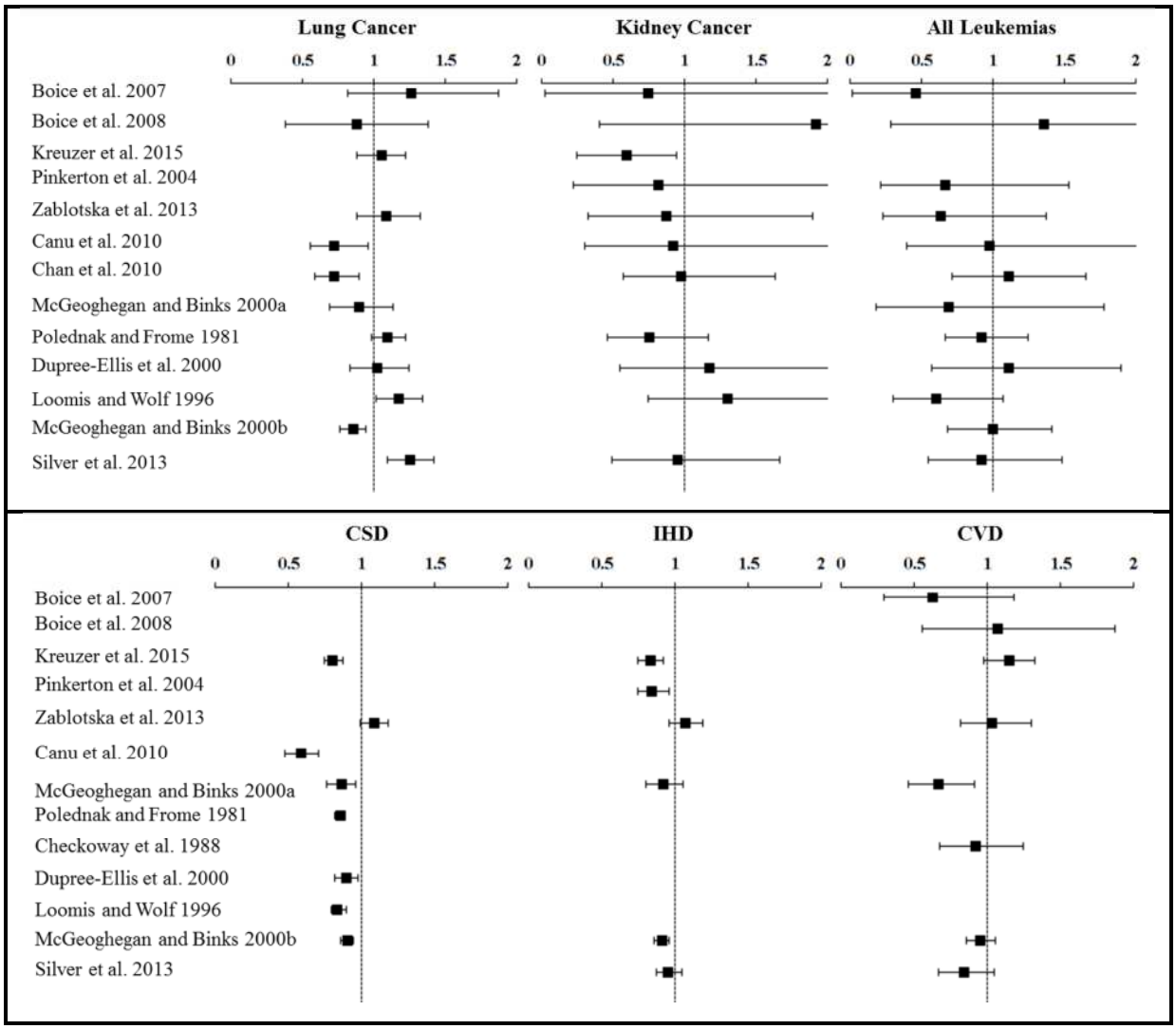

Figure 12. Standardized mortality ratios (SMR) and associated 95% confidence intervals for lung, kidney cancers, all leukemias, all circulatory diseases (CSD), ischemic heart diseases (IHD), and cerebrovascular diseases (CVD).

There was no pattern of increased mortality from any type of lymphohematopoietic cancer: non-Hodgkin's lymphoma (NHL), Hodgkin's disease, and multiple myeloma (MM) (Figure 13).

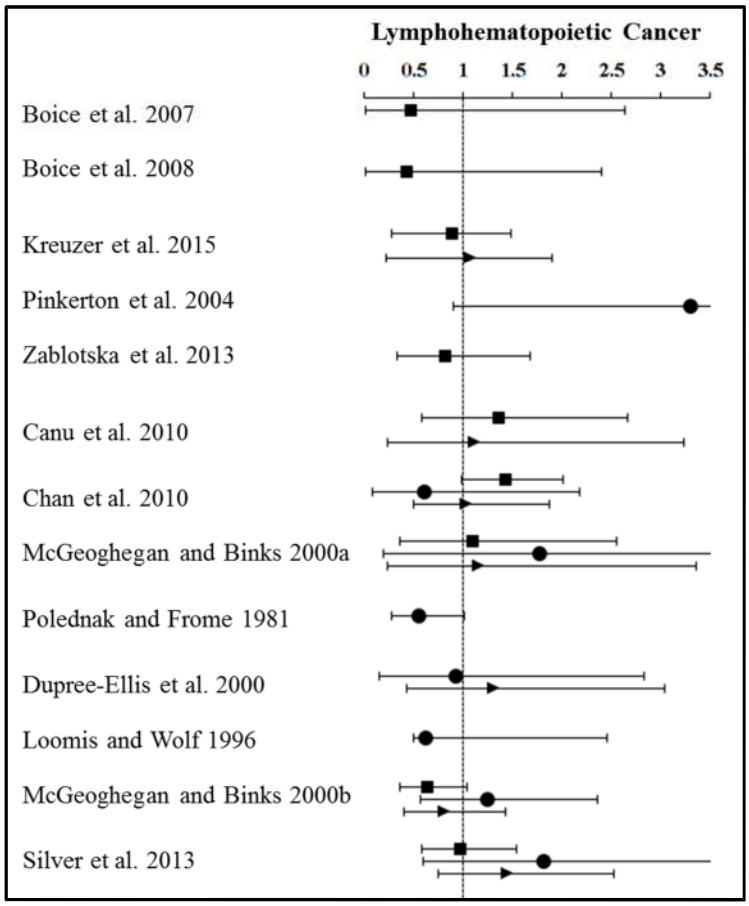

Figure 13. Standardized mortality ratios (SMR) and associated 95% confidence intervals for lymphohematopoietic cancer other than leukemia ■ Non-Hodgkin's lymphoma, ● Hodgkin's disease, ► Multiple myeloma.

3.2.3.2. Dose-response relationships

Of the 20 reviewed articles, only 9 studies performed any analysis of dose-response (Table 7). The most informative seven studies assessed internal uranium exposure (internal uranium dose, uranium intake, or cumulative score in JEM); others used a proxy of uranium exposure such as RDP, LLR, and external γ-radiation dose.

Table 7. Dose-response relationships in reviewed studies

Reference	Exposure indication	Dose-response analysis	Lung cancer, n	LHP cancer, n	Kidney cancer, n	CSD, n
[3] Kreuzer et al. 2015	U exposure ($kBqh.m^{-3}$), Rn exposure (WLM), Ext dose (Sv)	ERR/100 $kBq.m^{-3}$*	-0.61 (-1.42 to 0.19), 152	LHP: -0.65 (-2.78 to 1.47), 23	7.38 (-11.2 to 26.0), 12	CSD: -0.23 (-0.71 to 0.25), 717 IHD: -0.09 (-0.84 to 0.65), 341 CVD: -0.17 (-1.14 to 0.80), 171
[5] Zablotska et al. 2013	Rn exposure (WLM), Ext dose (Sv)	ERR/100 WLM	0.39 (<-1.22 to 4.52), 78	NHL: -0.16 (<-0.34 to 10.19), 7	0.16 (<-0.39 to 49.51), 6	CSD: 0.10 (-0.05 to 0.32), 514 IHD: 0.16 (-0.05 to 0.50), 346 CVD: -0.10 (<-0.34 to 0.38), 71
[6] Canu et al. 2011; [10] Guseva Canu et al. 2012	Cum U exposure score (JEM)	HR/1 step of score	RPU IS, 1.14 (1.00 to 1.31), 53	LHP: RPU IS,1.16 (0.96 to 1.40), 23	NA	CSD: RPU IS, 1.17 (1.07 to 1.27), 111 IHD: RPU IS, 1.17 (1.03 to 1.33), 48 CVD: RPU IS, 1.16 (1.00 to 1.35), 31
[11] Chan et al. 2010	U intake (µg/year)	SRR (cat)	0.51 (0.30 to 0.88), 146	LHP: 1.35 (0.53 to 3.41), 68 NHL: 5.74 (0.72 to 45.48), 32	NA	NA
[14] Yiin et al. 2009	Int U dose (µGy)	OR/10 µGy	NA	MM: 1.04 (1.00 to 1.09), 98	NA	NA
[15] Checkoway et al. 1988	Int U dose (rem)	RR (cat)	1.12 (0.47 to 2.65), 89	NA	NA	NA
[16] Dupree-Ellis et al. 2000	Ext dose (Sv)	ERR/Sv	NA	NA	10.5 (0.6 to 57.4), 14	NA
[19] Richardson and Wing 2006	Int dose (mSv)	RR (cat)	1.40 (0.65 to 3.01), 111	NA	NA	NA
[20] Silver et al. 2013	Int U dose (µGy)	ERR/100 µGy	0.0021 (-0.00062 to 0.0064), 297	Non-CLL: -0.061 (NA to 0.25), 35 HL: 0.33 (-0.065 to 1.6), 6 MM: 0.20 (-0.069 to 2.2), 19	0.033 (-0.021 to 0.50), 18	NA

*ERR estimation is based on Poisson regression in all presented articles.

CLL, chronic lymphocytic leukemia; CSD, circulatory diseases; CVD, cerebrovascular diseases; ERR, excess relative risk; H, Hodgkin's disease; HR, hazard ratio; IHD, ischemic heart diseases; IS, insoluble; JEM, job-exposure matrix; LHP, lymphohematopoietic cancer; MM, multiple myeloma; NA, not available; NHL, Non-Hodgkin's lymphoma; RPU, reprocessed uranium compounds; RR, rate ratio or relative risk; SRR, standardized rate ratio; WLM, working level month.

Some articles reported borderline significant or significant increases of mortality due to lung cancer (n=1), MM (n=1), kidney cancer (n=1), CSD and IHD (n=1). A study among US Paducah uranium enrichment workers reported a reverse dose-response relationship between mortality due to lung, lymphohematopoietic cancers, NHL, and quartiles of internal uranium intake (Chan *et al*, 2010). Most of the articles acknowledged the limitations of their results due to the small numbers of cases and related limited statistical power.

3.2.3.3. Impact of the physicochemical properties of uranium on mortality risk

In spite of the fact that the type of work might be considered to serve as a reasonable proxy for the physicochemical properties of uranium, we did not find any evidence of differences in uranium-processing workers, with the exception of increased mortality from lung cancer among fuel-fabrication workers who had been exposed to more of the slowly soluble uranium compounds than the general population (Loomis & Wolf, 1996; Silver *et al*, 2013). Two articles of uranium-enrichment workers exposed to soluble uranium reported a positive association between NHL (Chan *et al*, 2010), and MM (Yiin *et al*, 2009) in analyses of dose-response relationships, but these studies were limited by low statistical power. The physicochemical properties of uranium, its isotopic composition and solubility, were not usually reported clearly in the articles we identified (Table 6). Only two articles reported on the impact of both isotopic composition and solubility on the risk of CSD mortality (Canu *et al*, 2011; Guseva Canu *et al*, 2012). The latter articles reported an increased risk for decreasing solubility and for a shift from NU to reprocessed uranium.

3.2.4. Discussion

We reviewed the literature to investigate whether the physicochemical properties of uranium influence the risk of health outcomes in nuclear fuel cycle workers. Our results show the following: (a) These workers exhibit lower mortality rate compared to the general population; (b) mortality due to lung cancer and lymphohematopoietic cancer might be higher in some groups of nuclear fuel cycle workers (uranium enrichment and fuel fabrication workers) in comparison with general population and in analyses of the dose-response relationship; and (c) because of the very limited number of studies addressing this issue, the impact of the physicochemical properties of uranium on the risk of any of the defined health outcomes cannot be determined based on current studies.

3.2.4.1. Pronounced healthy worker effect

Reduced mortality compared with the reference population, observed in reviewed studies, is a common finding in occupational studies and known as healthy worker effect (HWE) (Checkoway *et al*, 2004). The HWE occurs through: (1) selection of healthy and physically active workers by the employer at time of hire, and (2) a tendancy when diseased employees leave the active workforce ("healthy worker survivor effect"). In the nuclear industry, regular medical monitoring preserves workers' health.

Many strategies have been developed so far (Checkoway & Eisen, 1998) to limit influence of HWE. The most promising analytical strategies include internal comparisons with low- or unexposed group selected as reference, and developing new prospective studies with repeated exposure measurements.

3.2.4.2. Exposure metrics in the analyses of the dose-response relationship

Exposure or dose indicators chosen by the authors of the reviewed articles may well have impacted results of the dose-response analyses (Table 7). RDP and external radiation exposure—often used as uranium exposure proxies—may only partially reflect internal uranium exposure because of differences in the RDP absorption, biokinetics, half-life periods and very low γ-radiation potential. RDP exposure is of great importance among those workers that processed radium ore (Zablotska *et al*, 2013b). Also, radon exposure primarily impacts the respiratory tract; very little is being deposited in systemic organs and it is eliminated exclusively by the lungs (Marsh *et al*, 2012). External γ-radiation is a uniform, highly penetrating radiation with low-LET and cannot reflect α-radiation exposure, which is characterized by a high-LET, and is deposited at very short distance (about 50 μm) and limited to a few target-organs or tissues. Radiotoxicity and chemical toxicity of uranium could be analyzed separately if internal uranium dose or uranium intake are used. Because NU and DU have a very long half-period and low specific activity, uranium intake (usually expressed in mass, μg) should be used in risk assessments of populations exposed to these types of uranium (Chan *et al*, 2010). It should be noted that activity (Bq) can be easily converted into intake (μg) if the isotopic composition is precisely known; however, that precise isotopic composition was rarely available in the reviewed studies. Some recent articles assessed internal uranium exposure in the framework of a JEM (Canu *et al*, 2011; Guseva Canu *et al*, 2012). While JEMs are very useful and a widespread method of exposure assessment in occupational epidemiology, they are rarely used in radiation epidemiology. JEMs allow

assigning both the frequency and amount of uranium exposure in a semi-quantitative way to each given job type (Guseva Canu *et al*, 2008). Although JEM estimates has lower sensitivity and specificity compared to individually estimated internal uranium dose estimates (Guseva Canu *et al*, 2010), JEMs allow estimation of cumulative exposure scores to uranium, and thus make it possible to perform analyses of dose-response by specific type of uranium.

3.2.4.3. Influence of the physicochemical properties

While the uranium absorbed dose is considered as a benchmark to be used in analyses of the dose-response relationship, the physicochemical properties of uranium (isotopic composition and solubility) impact on biokinetics and are thus essential parameters in estimating the absorbed dose. There is a wealth of toxicological information available on the health effects associated with exposure to uranium compounds (ATSDR, 2012). These data demonstrate that the physicochemical properties of uranium may play an important role in the toxicity of uranium compounds (ATSDR, 2012). Our review showed that epidemiological data are much more scarce and that only a handful of studies have assessed the direct impact of physicochemical properties on risk (Canu *et al*, 2011; Guseva Canu *et al*, 2012). In addition to isotopic composition and solubility, other physicochemical properties of uranium are important when considering its potential toxicity, including particle size, specific surface area, shape, and surface charge (zero potential), which are beyond the scope of the present review. All but particle size description are usually ignored in epidemiological studies, since they demand specialized sampling and analysis. Data on particle size are particularly important for modeling particle deposition and clearance in the respiratory tract, for their further intake in the target organs, and for estimation of the resulting organ-specific absorbed doses. It was shown that large particles (more than 5 μm) are usually deposited in the upper (extra-thoracic) airways, from where they are removed into the gastrointestinal tract by mucociliary clearance. Moderate size particles (about 5 μm) may enter the deeper lung, from where they are slowly removed to thoracic lymph nodes by alveolar macrophages. Very small particles (less than 1 μm) may even enter directly into the circulatory system (Snipes *et al*, 1989) and thereby cause damage to the endothelium. Slowly soluble enriched uranium compounds thus have a higher potential to deliver a larger dose to the lungs or to the lymphatic tissue, especially if the particle size is about 5 μm in diameter, as found at most industrial sites (Ansoborlo *et al*, 2002).

3.2.4.4. Reported associations and physicochemical properties

Since the lung is the primary target organ following inhalation of insoluble uranium compounds, an association between uranium exposure and lung cancer is the most plausible of the health outcomes that we reviewed. It was confirmed in two articles of fuel fabrication workers (Loomis & Wolf, 1996; Silver *et al*, 2013) and in a study of French uranium processing workers (Canu *et al*, 2011). Although insoluble uranium compounds might be transported to thoracic lymph nodes by macrophages, no increases were found in NHL or Hodgkin's disease among fuel fabrication workers in analyses of dose-response relationships. In contrast, increases in mortality from NHL (Chan *et al*, 2010) and MM (Yiin *et al*, 2009) were observed among uranium enrichment workers exposed to rapidly soluble uranium compounds (UF_6, UO_2F_2). It should be emphasized, however, that their results were borderline significant and that the risk decreased with increased uranium exposure (Chan *et al*, 2010). The kidney is considered the organ most involved in excretion of uranium, yet only one significant association was seen for kidney cancer with a crude proxy of uranium exposure—external γ-radiation exposure (Dupree-Ellis *et al*, 2000). Very little information was available on CSD. A possible explanation might be that CSD were considered as a deterministic outcome of exposure to acute high-dose and high dose-rate external ionizing radiation (threshold of 0.5 Gy (Stewart *et al*, 2012), and have been suggested quite recently as stochastic effects at lower doses (Little *et al*, 2012a). While carrying out this review, we identified significant findings for other outcomes, such as gastrointestinal cancer (Silver *et al*, 2013). Gastrointestinal cancer may be of interest for future studies of some groups of nuclear fuel cycle workers exposed to large particles of insoluble uranium, which are cleared via the gastrointestinal tract. Many studies also observed an increase in mortality from pleural cancer, but a recent review showed that these results were likely confounded by asbestos exposure during the early years of the nuclear industry (Metz-Flamant *et al*, 2013).

In summary, the current literature does not allow a definitive conclusion in relation to the physicochemical properties of uranium. Based on the available data, a preliminary conclusion could be made that nuclear fuel cycle workers (specifically, fuel fabrication workers exposed to insoluble uranium compounds) may be at risk for lung cancer mortality, while the evidence is inconclusive for lymphohematopoietic, kidney cancers, and especially CSD.

3.3. Conclusions

Based on the information in this chapter, it appears that epidemiological studies are the main sources of our knowledge of long-term health effects following chronic inhalation of uranium compounds. Based on our systematic literature review the most plausible health effect of uranium exposure is lung cancer; however, the effect may depend on the physicochemical form involved. Statistical power is one of the limitations due to limited size of national cohorts

Estimation of internal dose may be subject of important uncertainties ingrown in biokinetic and dosimetric models. Data collection on uranium physicochemical properties via JEMs may partly improve internal dose estimation. Finally, future studies of nuclear fuel cycle workers by sub-groups of specific stage of the cycle (e.g., uranium enrichment and fuel fabrication) are considered the most promising to shed light on the possible associations, given that such sub-groups present the advantage of a more homogenous exposure than the whole population of the nuclear cycle workers.

Chapter 4. MORTALITY STUDY OF THE FRENCH COHORT OF URANIUM ENRICHMENT WORKERS

This chapter focuses on mortality analysis due to cancer and non-cancer diseases in French uranium enrichment workers. Because uranium may produce different health effects depending on its physicochemical properties, uranium enrichment workers are the population of interest due to the unique exposure to rapidly soluble uranium compounds (Chapter 3).

My role in this study was to develop the research question, define inclusion and exclusion criteria for the population under study, perform statistical analyses, and interpret the obtained results. This work was presented at the 2014 Conference on Radiation and Health, and was accepted for publication as the original article in *Occupational and Environmental Medicine*.

4.1. Introduction

The first French nuclear reactor, Zoé, started its operation at the Fontenay-aux-Roses nuclear site in 1948. Following pressure from President Charles de Gaulle, Félix Gaillard, a member of the French Government, introduced a five-year strategy for the development of independent atomic energy. This plan aimed to find a solution for the energy deficit and for the production of atomic weapons. The plan included the construction of three new graphite-gas reactors. This type of reactor uses natural uranium fuel, graphite as a neutron moderator, and carbon dioxide to transport heat to the turbines. In the 1970s, pressurized water reactors using EU started appearing.

However, enriched uranium is needed for full civil and military applications. Given the intention to participate in the nuclear arms race, French authorities decided to build the Tricastin nuclear site to produce 90% enriched uranium. Construction activities started in 1958, with full industrial activity beginning in 1964. The Tricastin nuclear site is in south-eastern France (Figure 14), on the outskirts of the Pierrelatte city.

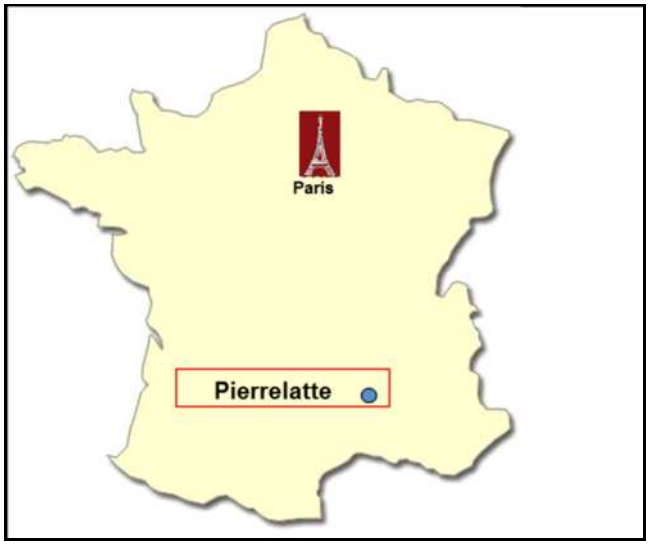

Figure 14. Geographical position of the Tricastin nuclear site

In 1992 France voted for a unilateral moratorium on nuclear testing, leading in 1996 to a decision to cease the nuclear weapons production. This process was accompanied by dismantling of all facilities that enriched uranium by more than 5% at the Tricastin nuclear site.

4.1.1. Uranium enrichment plants

The Tricastin nuclear site is the only French nuclear site where uranium undergoes enrichment at three plants operated by AREVA NC, CEA, and Eurodif. Although some experimental work was performed on laser enrichment (SILVA—*Séparation Isotopique par Laser de la Vapeur Atomique*) in the 1970s and 1980s, the main industrial enrichment technology during 1964 to 2008 was gaseous diffusion. Due to the economic profitability of centrifugation over gaseous diffusion, the AREVA NC company switched to this technology in 2011 by opening the Georges Besse II centrifuge enrichment plant.

Table 8 shows detailed characteristics of the three uranium enrichment plants that used gaseous diffusion technology.

Table 8. History of uranium enrichment by gaseous diffusion technology in France

Facility	Operation years	Enrichment %	Cohort inclusion
CEA pilot facility	1960–1964	NA	yes
CEA/AREVA NC[*¶]			
low-grade enrichment	1964–1982	2	yes
moderate-grade enrichment	1965–1984	7	yes
high-grade enrichment	1966–1996	25	yes
very high-grade enrichment	1967–1996	90	yes
Eurodif[§]	1977–2011	3-5	yes

[*] AREVA NC was operated by CEA until 1975.
[¶] Before 2006, AREVA NC was formerly known as COGEMA (Compagnie générale des matières nucléaires).
[§] Eurodif was operated under an agreement between Germany, France, the Netherlands, and the UK.
CEA, Commissariat à l'énergie atomique; Eurodif, European gaseous diffusion uranium enrichment consortium; NA, not known.

4.2. Materials and Methods

4.2.1. Cohort construction and follow-up

A roster of 5,070 nuclear fuel cycle workers involved in enrichment activities was identified from the French TRACY U (*TRAvailleurs du CYcle du combustible potentiellement exposés à l'Uranium*) cohort of 12,739 workers (Samson *et al*, 2014). Inclusion criteria for selection of workers into the French cohort of uranium enrichment workers were defined as follows:

- Employment at the AREVA NC, CEA, and Eurodif uranium enrichment plants
- Worked at least six months between 1964 and 2008
- Alive on 1st January 1968

In addition, we excluded workers with temporary contracts (n=132) due to unverifiable payroll records information, and previous uranium miners (n=31) due to their significant exposure to radon gas and RDP. The final dataset used in the statistical analyses included 4,688 eligible uranium enrichment workers (Figure 15).

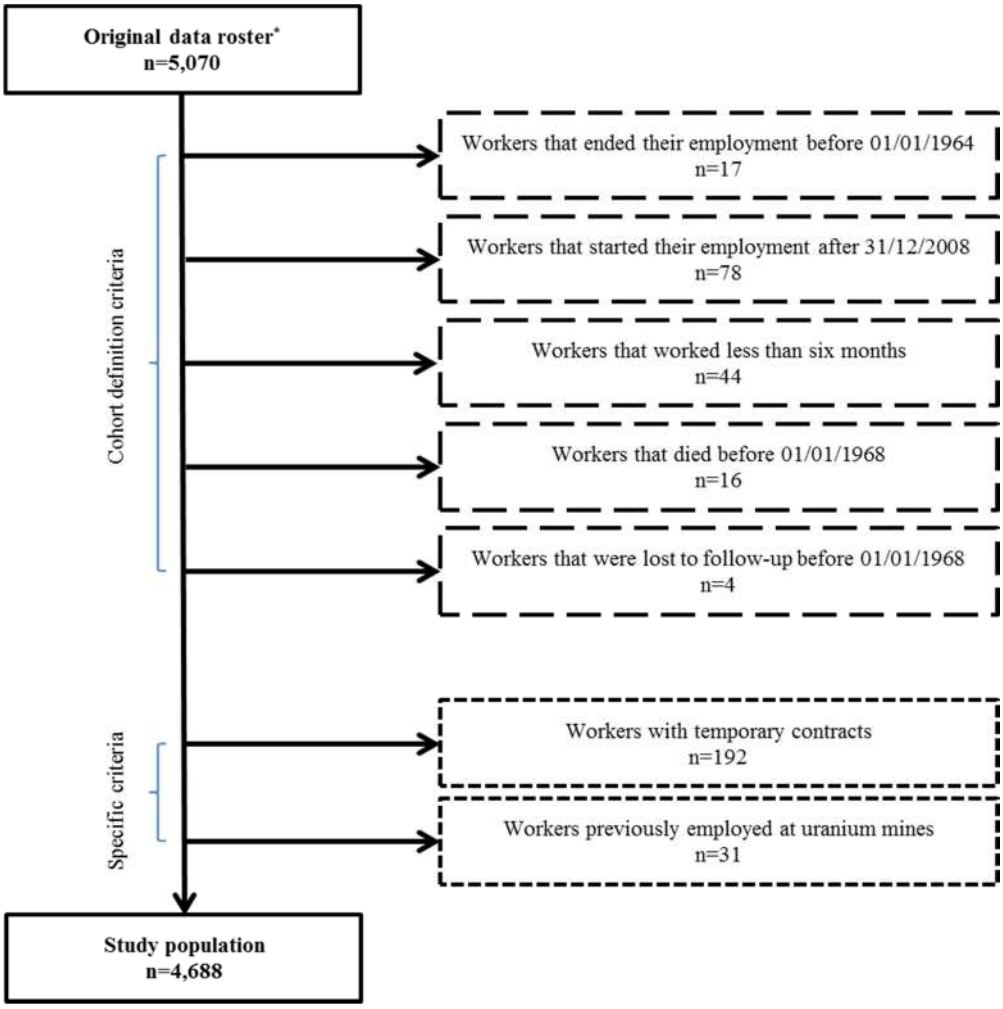

Figure 15. Construction scheme of the French cohort of uranium enrichment workers
***All identified uranium enrichment workers employed at AREVA NC, CEA, and Eurodif plants.**

Each worker contributed person-years at risk from either the date of first employment at the uranium enrichment plant plus six months or 1st January 1968 (whichever occurred later), up to the date of death, last date known to be alive or 31st December 2008 (whichever occurred earlier). Follow-up in our study began on 1st January 1968 because data on individual causes of deaths are not available prior to 1968 in France.

This study has been approved by the French Data Protection Authority (CNIL) (declaration No. DR-2012-611).

4.2.2. Occupational exposure assessment

Figure 16 shows sources of exposure data for the French cohort of uranium enrichment workers.

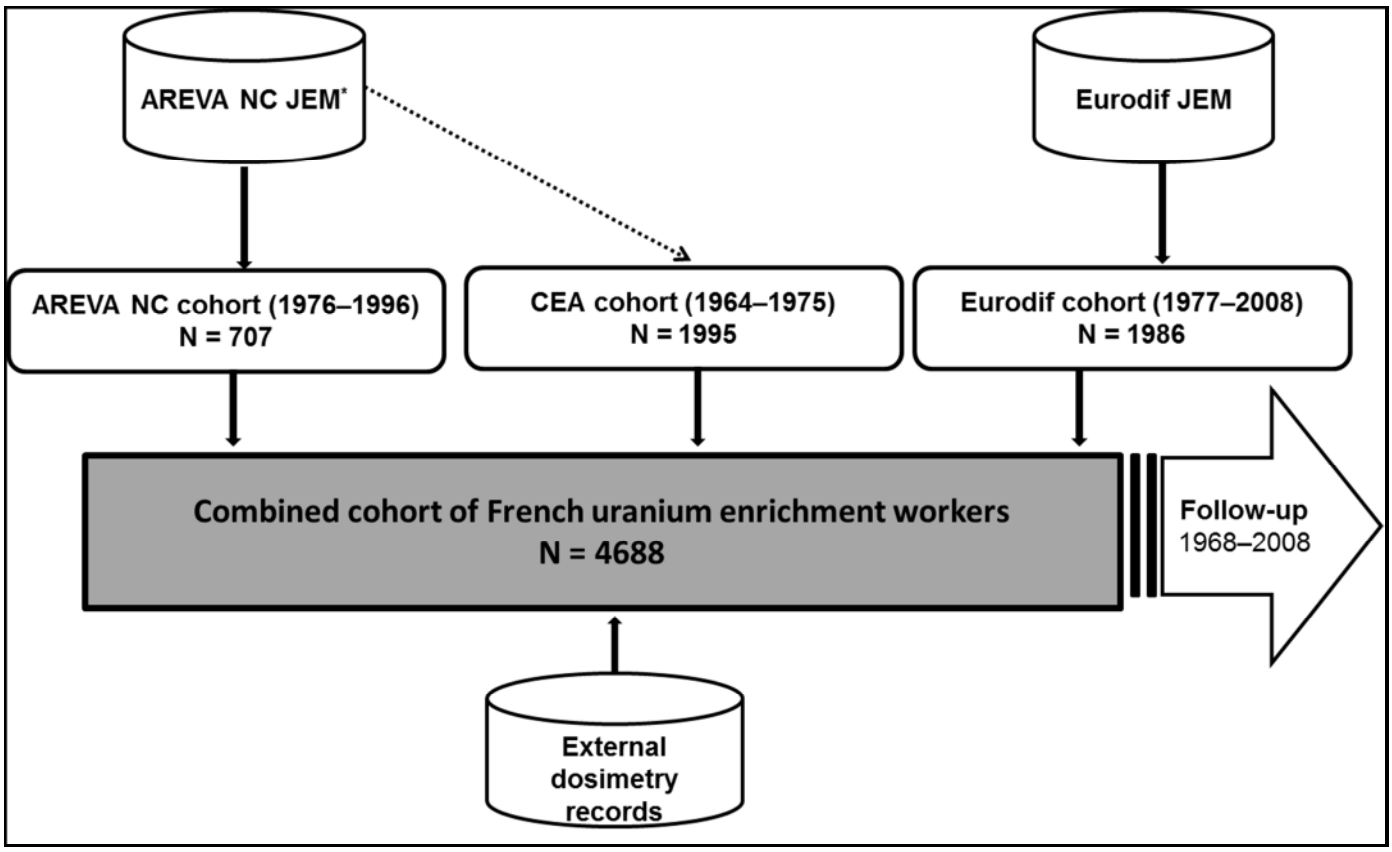

Figure 16. Sources of exposure data for the French cohort of uranium enrichment workers

*The AREVA NC JEM was extrapolated to the CEA plant because of the identical nature of the work.

JEM, job-exposure matrix.

4.2.2.1. Radiation exposure assessment

The main exposures of interest in our study were internal radiation exposure from inhalation of rapidly soluble uranium compounds and external γ-radiation exposure. In this study, we did not consider ingestion of uranium in drinking water and food.

Internal uranium exposure

Information on annual exposure to uranium was reconstructed using two plant-specific JEM for AREVA NC and Eurodif plants (Guseva Canu *et al*, 2013b; Guseva Canu *et al*, 2008). The two JEMs were constructed using the same strategy, and the AREVA NC plant JEM was validated against individual uranium bioassay data with 64% sensitivity and 80% specificity (Guseva Canu *et al*, 2010).

These JEMs assign frequency (four-level scale: 0-never, i.e. never used; 1-rarely, i.e. a few days per year; 2-occasional, i.e. a few days per month or a few weeks per year; 3-regular continuous or intermittent, i.e. a few days per week, a few months per year, or every day of the year), quantity (four level scale: 0-none, 1-low, 2-moderate, 3-significant), and exposure duration of the annual (1964–2008) uranium exposure. Exposure levels were assigned at each job and for the different time periods during which exposure was constant. The Eurodif JEM had additional information on current occupational exposure limits, which served to validate intensity and frequency of exposure. Job categories were plant-specific and thus allowed a greater level of precision compared to the International Standard Classification of Occupations (ISCO) of the International Labour Organization (ILO)[6].

A multiplicative product of frequency, intensity, and duration of employment (years) allowed deriving an individual annual exposure score used for statistical analyses, using the following formula:

$$E_A = \sum_{j=1}^{N} \sum_{pj} F_{Apj} * Q_{Apj} * D_{pj}$$

E_A, individual annual exposure score; F_{Apj} and Q_{Apj}, frequency and quantity of exposure for hazard at a job *p* during calendar period *j*; D_{pj}, duration of employment at a job *p* during calendar period *j*.

[6] Eigth version of the International Standard Classification of Occupations (ISCO) includes 10 major groups: 1-managers, 2-professionals, 3-technicians and associate professionals, 4-clerical support workers, 5-service and sales workers, 6-skilled agricultural, forestry and fishery workers, 7-craft and related trades workers, 8-plant and machine operators, and assemblers, 9-elementary occupations, and 0-armed forced occupations.

The use of PPE was not incorporated into this study because information about PPE use was only available for a subsample of the Eurodif workers (Guseva Canu *et al*, 2013a).

Exposure to rapidly soluble uranium compounds (UF_6 and its hydrolysis product UO_2F_2) was defined as exposure to type F uranium compounds according to the ICRP (ICRP, 1994). For the Eurodif subcohort, it was possible to further distinguish between isotopic forms of uranium (enriched uranium (EU) and DU). Exposure scores were cumulated for any worker who was consequently employed at several uranium enrichment plants.

External γ-radiation exposure

External γ-radiation exposure was monitored individually on either a monthly (workers susceptible to receiving between 6 and 20 mSv annually) or quarterly (those susceptible to receiving between 1 and 6 mSv annually) basis, and reported as annual whole-body dose in mGy. External dosimetry records were extracted from the plant monitoring files and the electronic SISERI system (French national database of occupational external exposure to ionizing radiation) (Feuardent *et al*, 2013).

4.2.2.2. Other occupational hazard assessment

Information on other occupational hazards, such as TCE, heat, and noise, was also considered because of their possible influence on cancerous (IARC, 2014) and circulatory diseases (Gan *et al*, 2011). These were selected due to their high prevalence and availability of monitoring data from the industrial hygiene services at uranium enrichment plants (Chan *et al*, 2010; Guseva Canu *et al*, 2013b). Established lung carcinogens (asbestos and chromium) were not considered because of their low prevalence and absence of the association with mortality in preliminary analyses (data not shown). Similar to internal uranium exposure, exposure scores to TCE, heat, and noise were estimated using JEMs. Noise was classified as a binary time-dependent variable (never exposed vs. ever exposed to sound pressure of ≥80 dB(A)). Annual exposure to noise was available for the Eurodif subcohort.

4.2.3. Mortality ascertainment

Individual vital status and causes of death were identified from the French national mortality registries: *Répertoire National d'Identification des Personnes Physiques* (RNIPP) maintained by the *Institut National de la Statistique et des Études Économiques* (INSEE), and *Centre*

d'épidémiologie sur les Causes Médicales de Décès (CépiDC) maintained by the *Institut National de la Santé et de la Recherche Médicale* (INSERM). This deterministic linkage for the period from 1968 to 2008 was performed based on name, gender, date, and place of birth. Anonymized records of all deaths and their causes exist since 1968 in France. We chose to consider 31st December 2008 as the end of follow-up in this study because of lower reliability of more recent national mortality registries.

Causes of death were coded according to the 8th revision of the International Classification of Diseases (ICD-8) from 1968 to 1977, the 9th revision (ICD-9) from 1978–1999, and the 10th revision (ICD-10) for the period 2000–2008 (Table 9).

Table 9. Coding of deaths in the French cohort of uranium enrichment workers according to the International Classification of Diseases (ICD)

Cause of death	ICD-8	ICD-9	ICD-10
All causes	0-E999	1-E999	A00-Y89
All cancers	140-207, 275.5	140-208, 273.3	C00-C97
All cancers, except leukemia	140-203, 275.5	140-203, 273.3	C00-C90, C96-C97
Solid cancers	140-199	140-199, excl 176.5	C00-C80, C97
Smoking-related cancers	140-151, 155, 157, 160-162, 180, 188, 189, 205	140-151, 155, 157, 160-162, 180, 188, 189, 205	C00-C16, C22, C25, C30-C34, C53, C64-C68, C92
Oral cavity and pharynx	140-149	140-149	C00-C14, C46.2
Larynx	161	161	C32
Lung	162	162	C33-C34
Pleura	163.0	163	C38.4, C45.0
Kidney	189	189	C64-C66, C68
Urinary bladder	188	188	C67
Esophagus	150	150	C15
Stomach	151	151	C16
Pancreas	157	157	C25
Liver	155	155.0-155.1	C22
Biliary system	156	156	C23-C24
Colon	153	153	C18
Rectum	154	154	C19-C21
Malignant melanoma	172	172	C43
Breast, females	174	174-175	C50
Prostate, males	185	185	C61
Malignant and benign tumors of brain and CNS	191-192, 225, 238.1-238.5	191-192, 225, 237.5, 237.6, 239.6	C70-C72, D32-D33, D42-D43
Malignant tumors of brain and CNS	191-192	191-192	C70-C72
All lymphomematopoietic	200-207, 275.5	200-208, 273.3	C46.3, C81-C96
All leukemia	204-207	204-208	C91.0-C91.3, C91.5, C91.7, C91.9, C92-C95
Non-Hodgkin's lymphoma	200, 202, 275.5	200, 202, 273.3	C46.3, C82-C85, C88.0-C88.3 C91.4, C96
Multiple myeloma	203	203	C88.2, C88.7, C88.9, C90
Circulatory diseases	390-458	390-459	I00-I99
Ischemic heart diseases	410-414	410-414	I20-I25
Cerebrovascular diseases	430-438	430-438	I60-I69
Hypertension	400-404	401-405	I10-I15
Respiratory diseases	460-519	460-519	J00-J99
Chronic obstructive lung disease	490-492, 518	490-492, 494, 496	J40-J44, J47

Cause of death	ICD-8	ICD-9	ICD-10
Digestive diseases	520-577	520-579	K00-K93
External causes	E800-E999	E800-E999	V01-Y89
Unknown causes	795-796	798.1, 798.2, 798.9, 799.9	R96-R99

CNS, central nervous system; ICD, International Classification of Diseases.

4.2.4. Statistical methods

We calculated SMR for selected health outcomes using the French general population as a reference. This procedure is known as indirect standardization; the SMR is the ratio of the number of observed deaths to the number that would be expected if the study population had the same mortality rates as the French general population:

$$SMR = \frac{Observed}{Expected}$$

Expected numbers of deaths for each cause were calculated using French sex-, age-, and calendar-specific mortality rates grouped in five-year intervals from 1968 to 2008:

$$Expected = \sum R_i \, n_i$$

R_i, sex- and age-, and calendar-specific mortality rate of the general French population; n_i, number of person-years in sex-, age-, and calendar-specific stratum of the study population.

We performed within-cohort analyses via Poisson regression on grouped data for all solid (n=406), lung (n=100), lymphohematopoietic (n=28) cancers, CSD (n=281), IHD (n=95), and CVD (n=71) diseases. In these analyses, person-years were cross-classified by sex, age (15-19, 20-24…80-84, 85 and over), calendar period (1968-1972, 1973-1977…1998-2003, 2004-2008), socio-professional status at hire (managerial/professional, clerical, skilled technical, unskilled), subcohort (AREVA NC, CEA, and Eurodif), and five-year lagged cumulative exposures to soluble uranium, external γ-radiation, TCE, heat, and noise. Time-dependent exposure levels were categorized (unexposed, low-, medium-, and highly-exposed) using quartiles of each cumulative exposure score weighted by person-years. Cut-points for external γ-radiation were 0-, 0.01-, 0.13-, 0.9-, 10- and more mGy so as to obtain a balanced number of deaths in each dose category. Log-linear risk models were used to obtain RR and corresponding 95% CI:

$$\exp(x_1\beta_1 * exposure)$$

where β_1, mortality regression coefficient per unit change of exposure.

In addition, linear ERR models were used to estimate ERR per 100 mGy and 95% CI associated to external γ-radiation dose:

$$\exp(\sum x_n\beta_n)(1 + x_1\beta_1 * dose)$$

β_1, mortality regression coefficient per 100 mGy (ERR); x_n, potential confounding factors; β_n, is the regression coefficient associated with confounding factor.

All models were stratified on sex, attained age, calendar period, socio-economic status at hire, and subcohort. We assessed confounding by TCE for cancer outcomes, and heat and noise for circulatory diseases, but it produced unstable risk estimates. We examined the impact of the isotopic forms of soluble uranium compounds (EU and DU) within the Eurodif subcohort for solid cancers, lung cancer, and CSD.

Correlations between uranium compounds, external γ-radiation dose, and other occupational hazards were examined by Pearson's partial correlation coefficients controlling for the individual component effect.

The DATAB and AMFIT modules of the EPICURE statistical software were used, respectively, to build the person-time table, and to obtain regression coefficients and 95% maximum likelihood-based CI (Preston *et al*, 1993). Correlations were calculated using SAS 9.2 software.

4.3. Results

4.3.1. Cohort description

The cohort includes 4,688 workers; male workers constituted more than 90% of the study population (Table 10). The median duration of follow-up was 30.2 years, and, as a whole, the cohort cumulated 136,161 person-years. Causes of death were ascertained for 99% of decedents (between 1968 and 2008). Only one percent of the workers (n=37) were lost to follow-up. At the end of follow-up, 21% (n=1,010) of the cohort had died, and 25% (n=1,164) of the workers were still employed in the French nuclear industry. Among 1,010 deaths, the cause was cancer for 42% (n=429), CSD for 28% (n=281), and non-malignant respiratory diseases for 5% (n=49).

Almost 30% (n=1312) of the workers had been employed at more than two nuclear facilities.

Table 10. Main characteristics of the French cohort of uranium enrichment workers

	n (%)
Total number of workers	4,688 (100)
Males	4251 (91)
Cumulated person-years	136,161
Work at more than two nuclear facilities	1,312 (28)
Still employed at 31/12/2008[*]	1,164 (25)
Subcohort[†]	
AREVA NC	707 (15)
CEA	1,995 (43)
Eurodif	1,986 (42)
Socio-professional status at hire	
Managerial/professional	275 (6)
Clerical	798 (17)
Skilled technical	1,862 (40)
Unskilled	1,753 (37)
Follow-up status on 31/12/2008	
Alive	3,641 (78)
Deceased	1,010 (21)
Lost to follow-up[a]	37 (1)
Age (years)	**Median (range)**
At start of follow-up	32.7 (19.1-65.5)
At end of follow-up	66.6 (22.7-95.9)
At death	67.6 (22.7-95.3)
Duration of follow-up (years)	30.2 (0.1-40.9)
Duration of employment (years)	9.2 (0.5-34.0)

[*]In the French nuclear industry

[†]"Uranium enrichment subcohort" defined by the longest duration of employment in these plants

[a]Not identified in national mortality registries

Figure 17 shows the number of workers monitored for external γ-radiation and potentially exposed to rapidly soluble uranium compounds. Two major peaks in number of workers were observed in the 1960s (beginning of nuclear era in France), and in the end of 1970s (civil enrichment development). An important decrease in external dose is seen in 1964; however workers employed 1964 onwards were included into the cohort (Figure 17).

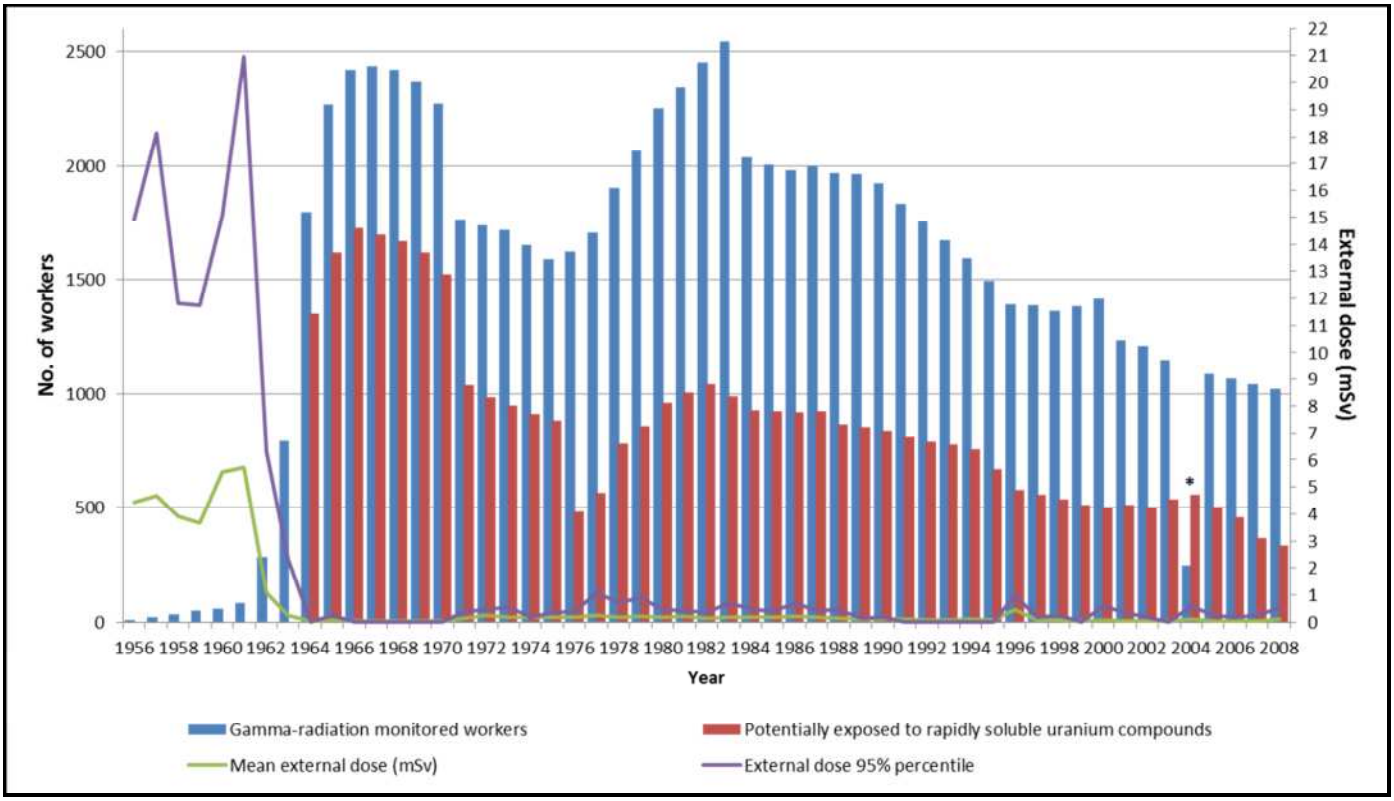

Figure 17. Number of workers monitored for external γ-radiation dose and potentially exposed to rapidly soluble uranium compounds, by external dose (mGy) in the French cohort of uranium enrichment workers

*γ-radiation dose archives for 2004 are being processed by the IRSN (information not currently available).

Figure 18 shows annual person-time distribution across the three plants included in the cohort of French uranium enrichment workers.

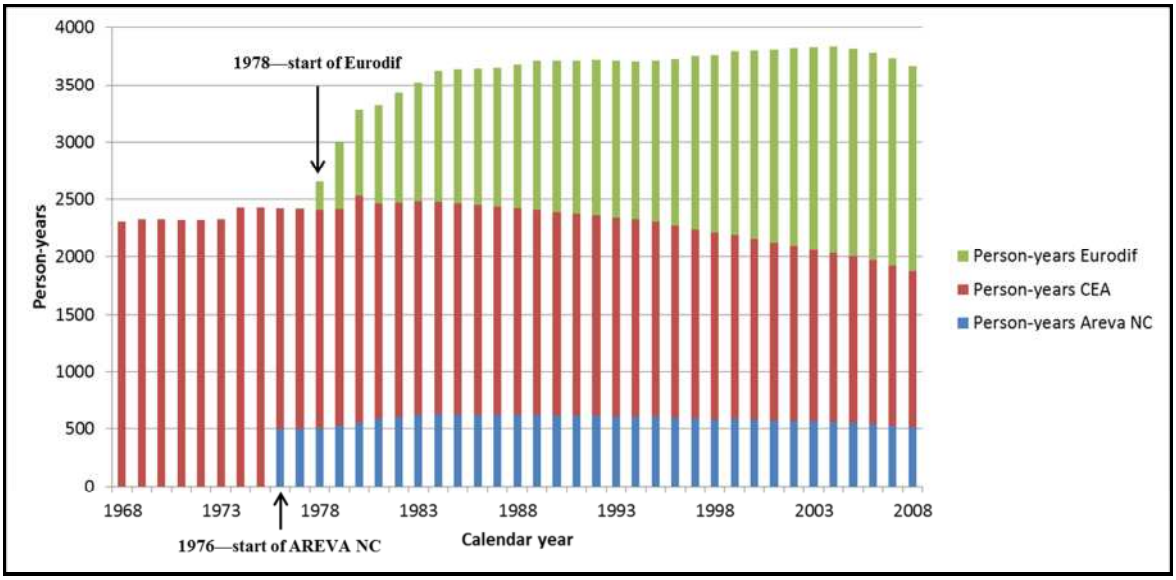

Figure 18. Annual person-year distribution in the French cohort of uranium enrichment workers

Table 11 lists exposure characteristics of the French cohort of uranium enrichment workers. Seventy percent (n=3295) of workers were potentially exposed to soluble uranium compounds and 90% (n=4253) were monitored for external γ-radiation. Median external γ-radiation among exposed monitored workers was 0.8 mGy (minimum=0.1, maximum=230.2) (Table 11). Distributions of cumulative exposure scores are presented in Figure 19.

Table 11. Exposure characteristics in the French cohort of uranium enrichment workers

	n (%)
Ever exposed to rapidly soluble uranium compounds	3,295 (70)
Ever exposed to insoluble uranium compounds	246 (5)
Ever exposed to noise ≥80 dB(A)*	3,077 (66)
Monitored for external gamma-radiation	4,253 (91)
Cumulative exposure score	**Median (range)**
Rapidly soluble uranium compounds	46.6 (0-284.6)
TCE	27.4 (0-224.3)
Heat	57.7 (0-250.2)
Cumulative external γ-radiation dose (mSv)	
In exposed, n=2019	0.8 (0.1-230.2)

*Noise exposure was assessed as binary variable (ever vs. never exposed)
dB(A), A-weighted decibel to account for the relative loudness perceived by the human ear; TCE, trichloroethylene.

More than 60% of the workers were exposed to several occupational hazards, but only 34% (n=1,616) of the workers were exposed to both rapidly soluble uranium compounds and external γ-radiation (Table 12). Exposures to natural soluble uranium compounds and external γ-radiation were not correlated (Pearson's correlation coefficient=0.1). Within the Eurodif subcohort, exposures to EU and DU were moderately correlated (Pearson's correlation coefficient=0.7) (data not shown).

Table 12. Number (percentage) of workers potentially exposed to rapidly soluble uranium compounds, trichloroethylene, heat, noise, and external γ-radiation

		TCE		**Heat**		**Noise**		**External γ-radiation**	
		E-	**E+**	**E-**	**E+**	**E-**	**E+**	**E-**	**E+**
U	**E-**	1269 (27%)	116 (2%)	772 (16%)	613 (13%)	688 (14%)	697 (15%)	982 (21%)	403 (9%)
	E+	172 (4%)	3131 (67%)	13 (1%)	3290 (70%)	923 (20%)	2380 (51%)	1687 (36%)	1616 (34%)
	r		0.8		0.7		/		0.1

E+, ever exposed; E-, never exposed; r, Pearson's correlation coefficient; TCE, trichloroethylene; U, rapidly soluble uranium compounds.

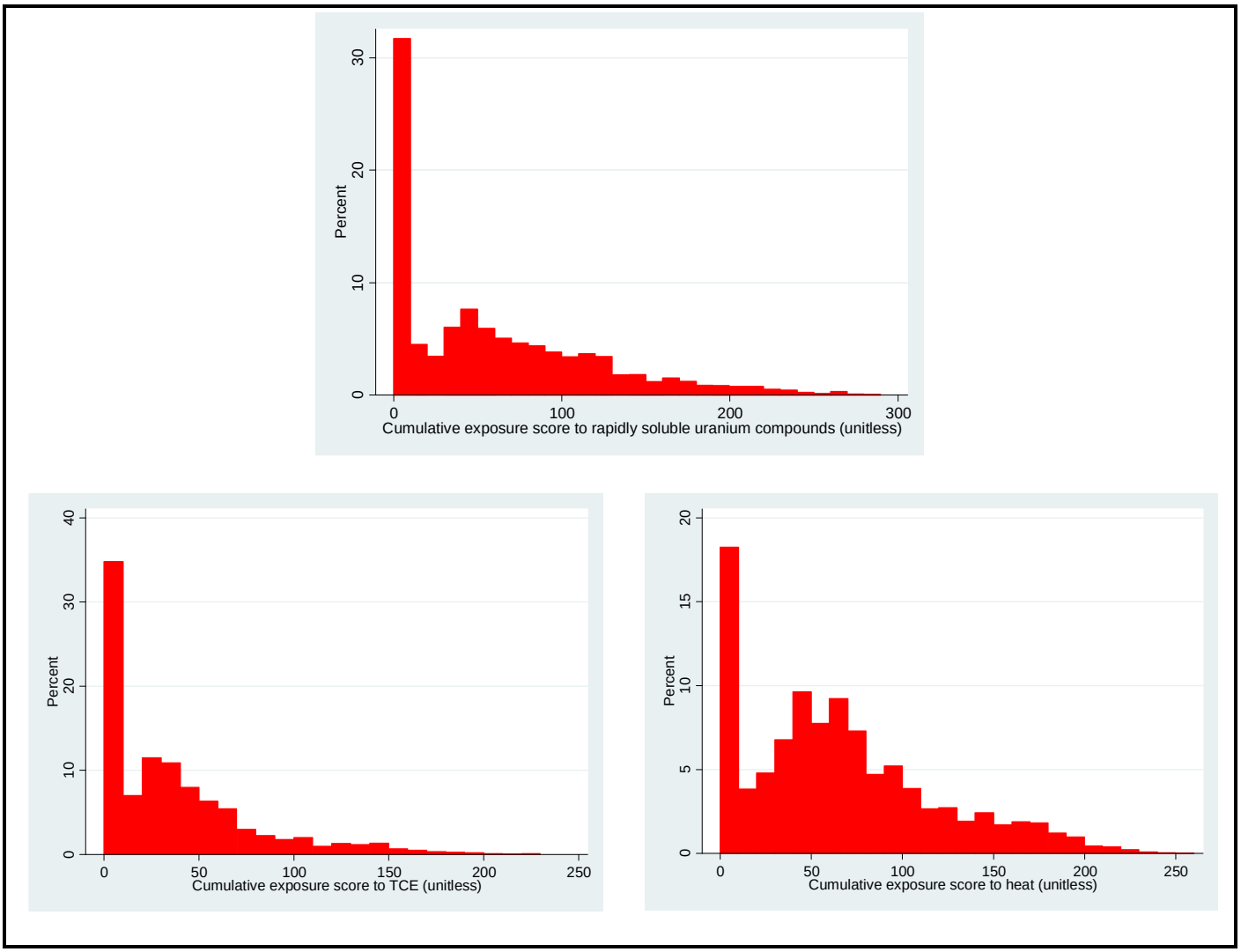

Figure 19. Distributions of cumulative exposure scores to rapidly soluble uranium compounds, TCE, and heat

4.3.2. Comparison of the cohort mortality with that from the general population

Mortality rates for all causes of death (SMR=0.69, 95% CI 0.65 to 0.74) and all-cancers (SMR=0.79, 95% CI 0.72 to 0.87) were substantially below expectation based on national rates (Table 13). An excess in mortality was observed for pleural cancer (SMR=2.32, 95% CI 1.06 to 4.41; based on nine deaths). Somewhat smaller relative excesses in mortality were also observed for kidney cancer, pancreatic cancer, biliary system cancers, malignant neoplasms of central nervous system, malignant melanoma, and breast cancer in females. Notable deficits were observed for smoking-related cancers, including lung cancer, non-malignant respiratory diseases, CSD, digestive diseases and deaths due to external causes (Table 13).

Table 13. Observed and expected number of deaths, and standardized mortality ratios (SMR) in the French cohort of uranium enrichment workers

Cause of death[‡]	Observed	Expected	SMR	95% CI	P-value[*]
All causes	1010	1452.5	0.69	0.65 to 0.74	<0.001
All cancers	429	542.1	0.79	0.72 to 0.87	<0.001
All cancers, except leukemia	418	527.6	0.79	0.72 to 0.87	<0.001
Solid cancers	406	507.4	0.80	0.72 to 0.88	<0.001
Smoking-related cancers	242	330.6	0.73	0.64 to 0.83	<0.001
Oral cavity and pharynx	17	34.8	0.48	0.28 to 0.78	<0.001
Larynx	8	18.5	0.43	0.19 to 0.85	0.01
Lung	100	135.6	0.74	0.60 to 0.90	0.02
Pleura	9	3.9	2.3	1.06 to 4.4	0.04
Kidney	13	11.6	1.1	0.60 to 1.9	0.75
Urinary bladder	12	17.4	0.69	0.36 to 1.2	0.23
Esophagus	19	28.8	0.66	0.40 to 1.03	0.07
Stomach	12	20.5	0.59	0.30 to 1.02	0.06
Pancreas	30	23.1	1.30	0.87 to 1.8	0.19
Liver	17	22.3	0.76	0.44 to 1.2	0.30
Biliary system	5	3.2	1.5	0.50 to 3.6	0.45
Colon	28	33.6	0.83	0.55 to 1.2	0.38
Rectum	11	13.6	0.81	0.40 to 1.4	0.59
Malignant melanoma	8	4.1	1.9	0.83 to 3.8	0.12
Breast, females	8	5.5	1.5	0.63 to 2.9	0.37
Prostate, males	30	34.7	0.86	0.58 to 1.2	0.48
Malignant and benign tumors of brain and CNS	21	16.1	1.3	0.80 to 1.9	0.28
Malignant tumors of brain and CNS	17	10.5	1.6	0.94 to 2.6	0.08
All lymphomematopoietic	28	35.0	0.80	0.53 to 1.1	0.27
All leukemia[†]	11	14.8	0.74	0.37 to 1.3	0.40
Non-Hodgkin's lymphoma	12	12.7	0.95	0.49 to 1.6	0.99
Multiple myeloma	5	5.9	0.84	0.27 to 1.9	0.92

Cause of death[‡]	Observed	Expected	SMR	95% CI	P-value[*]
Circulatory diseases	281	353.7	0.79	0.70 to 0.89	<0.001
Ischemic heart diseases	95	132.1	0.72	0.58 to 0.88	<0.001
Cerebrovascular diseases	71	76.3	0.93	0.73 to 1.2	0.59
Hypertension	5	12.0	0.41	0.13 to 0.97	0.04
Respiratory diseases	49	76.9	0.64	0.47 to 0.84	0.01
Chronic obstructive lung disease	18	27.3	0.66	0.39 to 1.04	0.08
Digestive diseases	25	96.8	0.26	0.17 to 0.38	<0.001
External causes	77	145.7	0.53	0.42 to 0.66	<0.001
Unknown causes	11	35.0	0.31	0.16 to 0.56	<0.001

[‡]For causes of death with at least five cases.
[*]Two-tailed p-value.
[†]Includes one case of chronic lymphocytic leukemia (CLL).
CI, confidence intervals; CNS, central nervous system; ICD, International Classification of Diseases; SMR, standardized mortality ratio.

4.3.3. Within-cohort exposure-response analyses

Exposure to rapidly soluble uranium compounds was not significantly associated with any cause of mortality, and a monotonic decreasing trend from medium- to highly-exposed was observed for lung and lymphohematopoietic cancers (Table 14). A highly imprecise ($p_{linear\ trend}$=0.5) positive trend across exposure to rapidly soluble uranium compounds (RR=0.85, 95% CI 0.56 to 1.27, low- vs. never-exposed; RR=0.98, 95% CI 0.71 to 1.35, moderate- vs. never-exposed; RR=1.16, 95% CI 0.85 to 1.59, highly- vs. never exposed) was observed for CSD (Table 14).

Table 14. Summary of results of the relationship between exposure to natural soluble uranium compounds lagged by five years, and selected causes of death in the French cohort of uranium enrichment workers

		Rapidly soluble uranium compound exposure categories			
Outcome		**Unexposed**	**Low**	**Medium**	**High**
	Person-years	40,024	21,432	33,861	40,844
	Cases	118	67	112	109
Solid cancers	RR (95%CI)	ref.	1.1 (0.83 to 1.5)	1.02 (0.78 to 1.3)	1.03 (0.79 to 1.3)
	Cases	30	20	27	23
Lung cancer	RR (95%CI)	ref.	1.2 (0.64 to 2.05)	0.92 (0.54 to 1.6)	0.74 (0.42 to 1.3)
	Cases	7	5	9	7
Lymphohematopoietic cancers	RR (95%CI)	ref.	1.7 (0.48 to 5.5)	1.41 (0.52 to 3.9)	1.08 (0.37 to 3.3)
	Cases	87	35	74	85
Circulatory diseases	RR (95%CI)	ref.	0.85 (0.56 to 1.3)	0.98 (0.71 to 1.3)	1.2 (0.85 to 1.6)
	Cases	32	16	21	26
Ischemic heart diseases	RR (95%CI)	ref.	1.1 (0.58 to 2.01)	0.71 (0.39 to 1.2)	0.91 (0.53 to 1.5)
	Cases	23	6	22	20
Cerebrovascular diseases	RR (95%CI)	ref.	0.55 (0.19 to 1.3)	1.2 (0.66 to 2.3)	1.07 (0.6 to 1.9)

All models were stratified by sex, attained age, calendar period, socio-economic status at hire, and subcohort.
CI, confidence intervals; RR, relative risk.

A positive non-significant association was found between external γ-radiation dose and mortality due to CSD (ERR/100 mGy=0.38, 95%CI <0 to 2.3) and IHD (ERR/100 mGy=0.91, 95% CI <0 to 5.1) (Table 15). Additional adjustments for non-radiological occupational hazards (TCE, heat, and noise) did not substantially change RR, ERR, or improve the model fit (data not shown).

Table 15. Summary of results of the relationship between exposure to external γ-radiation lagged by five years, and selected causes of death in the French cohort of uranium enrichment workers

		External γ-radiation dose exposure categories					
Outcome		**Unexposed**	**0.01-0.12 mGy**	**0.13-0.8 mGy**	**0.9-10 mGy**	**>10 mGy**	**ERR/100 mGy (95%CI)**
Solid cancers	Cases	270	4	77	33	22	0.16 (<0[†] to 0.75)
	RR (95%CI)	ref.	1.8 (0.55 to 4.3)	1.3 (0.98 to 1.6)	0.87 (0.59 to 1.2)	0.96 (0.59 to 1.5)	
Lung cancer	Cases	75	0	17	4	4	-0.43 (<0[†] to 0.41)
	RR (95%CI)	ref.	NE	0.97 (0.10 to 1.6)	0.35 (0.11 to 0.85)	0.65 (0.19 to 1.6)	
Lymphohematopoietic cancers	Cases	13	0	7	8	0	-0.42 (<0[†] to 1.5)
	RR (95%CI)	ref.	NE	2.3 (0.84 to 5.7)	4.2 (1.6 to 10.4)	NE	
Circulatory diseases	Cases	185	2	41	36	17	0.38 (<0[†] to 2.3)
	RR (95%CI)	ref.	1.7 (0.28 to 5.5)	1.02 (0.71 to 1.4)	1.5 (0.99 to 2.09)	1.3 (0.76 to 2.1)	
Ischemic heart diseases	Cases	64	0	11	13	7	0.91 (<0[†] to 5.1)
	RR (95%CI)	ref.	NE	0.8 (0.39 to 1.5)	1.6 (0.81 to 2.8)	1.5 (0.62 to 3.2)	
Cerebrovascular diseases	Cases	50	2	11	6	2	-0.36 (<0[†] to 1.6)
	RR (95%CI)	ref.	6.4 (0.97 to 24.3)	0.99 (0.48 to 1.7)	0.9 (0.33 to 1.9)	0.59 (0.10 to 1.9)	

All models were stratified by sex, attained age, calendar period, socio-economic status at hire, and subcohort.
[†]Lower confidence interval bound could not be estimated as it is on the boundary of the parameter space (-1/max dose).
CI, confidence intervals; ERR, excess relative risk; NE, not estimated; RR, relative risk.

Cause-specific RRs associated with exposures to EU and DU were of comparable magnitude, albeit unstable because of the very small number of cases in the Eurodif subcohort where exposure data on EU and DU was available (Table 16). A positive imprecise trend for CSD was observed across DU but not EU exposure categories (Table 16).

Table 16. Summary of results of the relationship between exposure to rapidly soluble uranium compound exposure lagged by five years, and selected causes of death in the Eurodif subcohort of the French cohort of uranium enrichment workers (n=1,986)

			Rapidly soluble uranium compound exposure categories			
Outcome			**Unexposed**	**Low**	**Medium**	**High**
		Cases	37	8	19	21
	Enriched uranium	RR (95%CI)	ref.	0.59 (0.25 to 1.2)	1.3 (0.69 to 2.2)	0.82 (0.47 to 1.4)
		Cases	38	3	19	25
Solid cancers	Depleted uranium	RR (95%CI)	ref.	0.30 (0.10 to 0.84)	1.4 (0.77 to 2.4)	1.07 (0.63 to 1.8)
		Cases	10	1	7	5
	Enriched uranium	RR (95%CI)	ref.	0.25 (0.10 to 1.3)	1.8 (0.64 to 4.6)	0.69 (0.21 to 1.9)
		Cases	10	0	4	9
Lung cancer	Depleted uranium	RR (95%CI)	ref.	NE	1.2 (0.33 to 3.7)	1.5 (0.6 to 3.9)
		Cases	19	7	8	11
	Enriched uranium	RR (95%CI)	ref.	0.91 (0.29 to 2.9)	0.96 (0.32 to 2.9)	0.84 (0.28 to 2.8)
		Cases	23	3	7	12
Circulatory diseases	Depleted uranium	RR (95%CI)	ref.	0.37 (0.10 to 1.2)	0.64 (0.23 to 1.7)	0.84 (0.32 to 2.3)

All models are stratified by sex, attained age, calendar period, and socio-economic status at hire.
CI, confidence intervals; NE, not estimated; RR, relative risk.

Associations of mortality with non-radiological hazards (TCE, heat, and noise) are presented in Appendix 2. Decreasing trends across exposure categories were observed for lung, lymphohematopoietic cancers, and TCE exposure (Table A2). IHD, albeit not CSD or CVD, were positively associated with heat and noise exposures (Table A2).

4.4. Discussion

In our study, we analyzed mortality in a national cohort of French uranium enrichment workers exposed to soluble uranium compounds, external γ-radiation, and other non-radiological occupational hazards. Overall, this workforce exhibits a strong healthy worker effect, with the exception of a significantly elevated mortality risk for pleural cancer. We did not find an association between exposure to soluble uranium compounds and external γ-radiation, and cause-specific mortality. A positive non-significant linear trend for CSD was observed across NU and DU exposure categories.

4.4.1. Study strengths and limitations

4.4.1.1. Unique exposure scenario

The most important strength of our study is exposure reconstruction of both radiological and non-radiological (chemical and physical) occupational hazards and distinguishing isotopic forms of rapidly soluble uranium compounds (NU, EU, and DU). Due to production characteristics, uranium enrichment workers are exclusively exposed to the products of the UF_6 hydrolysis (hydrofluoric acid and UO_2F_2). Knowledge gained from several accidental exposures of UF_6 has shown that 73% of the uranium was excreted during the first 24 hours (Beau & Chalabreysse, 1989).

Together with ionizing radiation, uranium enrichment workers are known to be exposed to numerous non-radiological hazards (Guseva Canu *et al*, 2013b; Yiin *et al*, 2005; Zhivin *et al*, 2013). While these chemical and physical hazards are present in nuclear fuel cycle activities, they are rarely considered in epidemiological studies. Also, partly due to historical and regulatory reasons, employers and employees in the French nuclear industry might have been more concerned with radiation protection than with protection against non-radiological hazards (Guseva Canu *et al*, 2013a). While the exposure data were collected on more than 20 hazards, we only considered the three most prevalent non-radiological risk factors for cancer or circulatory diseases (TCE, heat, and noise) because of the multicollinearity issue. For example, TCE, as a chlorinated solvent, is a known carcinogen of group 1 according to the International Agency for Research on Cancer (IARC) (IARC, 2014). Some non-radiological exposures were non-significantly associated with mortality (Appendix 1), as observed in our previous study (Zhivin *et al*, 2013). Adjustment for non-radiological hazards produced non-convergent models, and they were not adjusted for.

4.4.1.2. Statistical power and data on confounders

In our study, we included all French uranium workers who enriched uranium by gaseous diffusion. Uranium enrichment in France started in the beginning of the 1960s, which is late compared to the US where the first uranium enrichment facilities were opened during the Manhattan Project in the 1940s. Table 17 presents estimated statistical power of our study for solid cancer, lung and LHP cancer, and CSD.

Table 17. Statistical power estimation for the French cohort of uranium enrichment workers

	Solid cancer	Lung cancer	LHP cancer	Circulatory diseases
Proportion of diseased in unexposed	0.08	0.02	0.0001	0.06
RR for 50% statistical power*	1.2	1.5	4.8	1.3
RR for 85% statistical power*	1.4	1.8	6.8	1.4

* Estimated in WINPEPI software (Abramson, 2011).
LHP, lymphohematopoietic; RR, relative risk.

For solid cancer and circulatory diseases, the statistical power is 85% to detect RR of 1.4 (Table 17). However, for less frequent causes of death, such as LHP cancer, the statistical power to detect small increases in risk is very limited (Table 17). Nevertheless, the statistical power will be improved by continuing the follow-up, but also by conducting combined analyses with similar cohorts of nuclear fuel cycle workers.

Our findings should be regarded in a view of multiple comparisons, because we performed a large number of tests. However, we sought to minimize this problem by choosing *a priori* outcomes and exposures (for within-cohort exposure-response analyses) based on biological evidence and the literature review presented in Chapter 3.

As in other occupational cohorts based on payroll records, our study lacks information on many life-style variables (smoking, physical activity, cholesterol levels, etc.). Stratification on socio-economic status at hire was used to partly address this issue, because blue-collar workers are known to smoke more and to pay less attention to their health. Also, in short-term perspective, a nested case-control study could be planned. For example, recent nested case-control studies of French uranium miners showed that the estimated dose-risk relationship for lung cancer and CSD persisted after adjustment for smoking and other potential confounders (Drubay *et al*, 2015; Leuraud *et al*, 2011).

4.4.1.3. Use of job-exposure matrix

Most medical files, radiological bioassay monitoring, and industrial hygiene data are hard-copy and not adapted for an immediate use in large-scale epidemiological studies. Thus, the

absence of individual absorbed uranium radiation dose estimates is a major limitation of our study. Even though the use of a JEM can cause non-differential misclassification of exposure, it was shown to be a good proxy of internal uranium dose (Guseva Canu *et al*, 2010). The JEM exposure score used in this study was calculated individually as a product of the frequency, intensity, and duration of the exposure, allowing for quantitative exposure-response analyses in the absence of internal uranium doses. Moreover, JEM distinguishes EU and DU, which is not always possible during internal dose estimations.

Important limitations of the JEM in our study are non-characterization of acute exposure, and non-consideration of the usage of PPE. Due to its construction characteristics, acute exposure cannot be incorporated into exposure score because it is impossible to predict levels of exposure during the accidents. Nevertheless, recent dose estimations of French (see Chapter 5) and US (Anderson *et al*, 2015) data showed that a majority of the total dose is due to chronic intake. Adherence to anti-uranium PPE is high in French uranium enrichment workers (Guseva Canu *et al*, 2013a), and the uranium exposure score could be adjusted by multiplying with the reduction coefficient of product-specific PPE (Guseva Canu, 2015). This will be done, as soon as information on the use of PPE is available for the total cohort.

4.4.2. Comparison with the general population

Nuclear workers are subject to selection at time of hiring on the basis of initial health status, and regular surveillance by occupational health services, which leads to selection of healthy workers. Decreased mortality in comparison with the general population—or HWE—is common in occupational studies. As in other occupational cohorts (Checkoway *et al*, 2004), a HWE was evident in our study for many causes of death (e.g., cancerous and circulatory diseases) influenced by the selection processes. An excess risk typically becomes apparent when workers are exposed to an occupational hazard associated with a high risk of disease. Although it was possible to find a significant association in the SMR analysis due to the large number of statistical tests performed, the significant result for pleural cancer might be linked with previous exposure to asbestos. The magnitude of latency for pleural mesothelioma is 40-50 years after first asbestos exposure, depending on the occupation and the intensity of exposure (Bianchi *et al*, 1997). This increased pleural cancer mortality (mostly represented by pleural mesothelioma) is a common finding in studies of nuclear workers exposed to low-level radiation, and a critical role of unmeasured confounding by asbestos has been emphasized (Metz-Flamant *et al*, 2011). The excess for pleural cancer, albeit based on nine

cases, may be a true finding due to the fact that many French nuclear workers might have started their career at naval shipyards where exposure to asbestos and external γ-radiation was quite significant. Nine workers—who died from pleural cancer in our study—had a higher mean γ-radiation dose (13.3 mGy) compared to the cohort average (2.81 mGy), and started their employment in uranium enrichment at the age of 37.6 years, on average. Similar mortality risks from pleural mesothelioma were found in other cohorts of French nuclear workers and were attributed in part to past asbestos exposure (personal communication, E. Samson and K. Leuraud). Thus, the increased mortality due to pleural cancer may be attributed to exposures received before the work in uranium enrichment. Continued monitoring of mortality due to pleural cancer is necessary in this study; however, detailed exposure-response analyses are not feasible at this stage due to the limited number of cases.

4.4.3. Within-cohort exposure-response analyses

An absence of significant associations between exposure to soluble uranium compounds and cause-specific mortality is noticeable. In fact, decreasing trends of uranium exposure for lung and lymphohematopoietic cancer was already observed in US uranium enrichment workers (Chan *et al*, 2010; Figgs, 2013). Thus, the acute toxic effects of hydrofluoric acid (skin damages and lung edema) may prevail over the long-term health effects of UF_6.

A recent study of US Paducah gaseous diffusion plant workers found an imprecise increase in mortality due to lymphohematopoietic cancer (Chan *et al*, 2010), which may be explained by the re-enrichment of reprocessed uranium at this plant. This type of uranium may have been contaminated with other transuranic elements, such as neptunium and plutonium (Chan *et al*, 2010), having a shorter half-life. In addition, as recently suggested by one case of accidental exposure to UF_6, its biokinetics may be sometimes modified and lead to prolonged material retention in lungs and lymphatic nodes (Avtandilashvili *et al*, 2015). In our study, an additional analysis excluding 246 workers with potential exposure to insoluble uranium compounds did not produce different risk estimates for lymphohematopoietic cancer (Appendix 1, Table A1).

The only suggestive non-significant trend across exposure categories of exposure to soluble uranium compounds was noted for CSD. A recent review of toxic effects of chronic uranium ingestion in animals has reported heterogeneous tissue sensitivity to uranium (Dublineau *et al*, 2014). It seems that toxic effects of uranium exposure are not directly correlated with the amount of uranium accumulated in the organs, based on animal studies where animals were

contaminated through water ingestion (Dublineau *et al*, 2014). While the studies reviewed by Dublineau *et al*. (2014) did focus on cancer or CSD, there are numerous mechanistic theories of the relationship between CSD and low-dose radiation, such as induction of atherosclerosis, microvascular damage to heart, kidney and lung, and direct damage to the heart (AGIR, 2010). Because of the lack of statistical significance of our observations and of the lack of radiobiological studies on the effect of chronic uranium inhalation on the circulatory system, our findings should be considered very cautiously. In our study, a positive but non-significant association was also observed between CSD and external γ-radiation, which was comparable with other studies of French nuclear workers (Metz-Flamant *et al*, 2013).

Differences in magnitude of mortality risks associated with exposures to NU, EU, and DU were indistinguishable in our study. NU, EU and DU share the same chemical toxicity, but the radiological toxicity of these three types of isotope mixtures varies, from lowest for DU, intermediate for NU, to highest for EU. Although EU, having strong α-emission potential, is more likely to produce double-strand breaks in DNA, a recent study showed that DU produces the same kind of DNA damage in bronchoalveolar cells of rats (Monleau *et al*, 2006). It should be noted, however, that an analysis stratified by isotopic form of soluble uranium compounds was only possible within the Eurodif subcohort. This subcohort is the youngest of the three subcohorts included into this study, with only 9% of workers having died at the end of follow-up. In time, it will therefore be necessary to include more workers exposed to EU and DU to allow for more powerful analyses.

At this stage, the most appropriate risk estimates of rapidly soluble uranium compounds are those obtained in the analysis of the total cohort of French uranium enrichment workers presented in this chapter.

4.5. Conclusions

In summary, the first mortality analysis of the cohort of French uranium enrichment workers has not shown conclusive associations between exposure to soluble uranium compounds and cause-specific mortality, except for suggestive evidence for CSD. The findings obtained in this study should be revisited after continuing follow-up of this cohort, carrying out further analyses using individual-level internal uranium doses, and ultimately combining the data with those of similar cohorts of nuclear fuel cycle workers to increase statistical power.

Studies of uranium enrichment represent an excellent opportunity for studying the effects of homogenous exposure to rapidly soluble uranium compounds. Our project was included in the

framework of the European Commission-funded collaborative project CURE on the biological and health effects of occupational uranium exposure, integrating epidemiology, biology/toxicology, and dosimetry. A harmonized approach was developed during this project to estimate internal doses in the European cohorts of uranium workers in France, the UK, and Belgium (Laurent *et al*, 2015). It was concluded that the use of the JEM that describes the solubility and isotopic composition of uranium compounds will improve the accuracy of internal dosimetry (Laurent *et al*, 2015).
Because monitoring data are not completely computerized, internal doses will be estimated once the computerization is finished.

The French cohort of uranium enrichment workers is a very unique European cohort, because other European countries enriched uranium via centrifugation. In the USA, substantial efforts have been made by the National Institute of Occupational Safety and Health (NIOSH) to establish a cohort of 30,000 US uranium enrichment workers, and to estimate individual organ-specific uranium doses (Anderson & Apostoaei, 2015; Anderson *et al*, 2015). Because France and the USA use gaseous diffusion as their main enrichment technology, it may be possible to establish a combined cohort of French and US uranium enrichment workers.

Chapter 5. CASE-CONTROL STUDY OF CIRCULATORY DISEASES OF FRENCH AREVA NC PIERRELATTE URANIUM PROCESSING WORKERS

This chapter focuses on the analysis of a relationship between CSD mortality and internal uranium dose. It is based on a nested case-control study of French AREVA NC Pierrelatte uranium processing workers.

The methodology of the nested case-control study and collection of the data were developed previously to my PhD thesis. My role in this study was to validate the collected data, collaborate with internal dosimetrists to develop an internal dosimetry protocol, analyze the data, and interpret the final results.

5.1. Introduction

5.1.1. Etiology of circulatory disease and risk factors

CSD is a multifactorial disease that may be caused by an array of different life-style and constitutional risk factors.

The Framingham study, set up in the 1950s in the USA, was the first study that collected data on suspected personal CSD risk factors. These risk factors (male gender, obesity, smoking, high blood pressure, high total serum cholesterol, and diabetes mellitus) were later shown to be predictors of increased risk of CSD and were denoted as classic CSD risk factors (Kannel *et al*, 1971; Kannel *et al*, 1961; Kannel *et al*, 1976). In the later 1960s additional attention was focused on the importance of separating lipid fractions into high-density (HDL) and low-density (LDL) lipoproteins (Fredrickson *et al*, 1967; Gofman & Lindgren, 1950) as risk predictors. LDL ("bad cholesterol") can be deposited in atherosclerotic plaques, HDL ("good cholesterol") has the ability to recover cholesterol from plaques and to transport it to the liver for further secretion into the bile.

Chronic kidney disease was also suggested as a CSD risk factor because of the close relationship between kidney function and blood pressure (BP) regulation. The *juxtaglomerular apparatus*, situated in the afferent arterioles of the kidney, secrete renin in

response to decreasing perfusion pressure of the blood. Renin activates liver protein angiotensin, leading to hypertension due to increasing blood volume.
Other CSD risk factors may also include alcohol consumption, diet, absence of physical activity, and psychosocial factors. Together with advances in medical treatment, knowledge of CSD risk factors has led to decreased mortality trends from CSD in developed countries (Puska, 2010; WHO, 2003).

More recent large-scale international nested case-control studies largely confirmed the importance of classical CSD risk factors for CSD subtypes: IHD, ischemic and intracerebral hemorrhagic stroke (O'Donnell *et al*, 2010; Yusuf *et al*, 2004); however, they found that the relationship with alcohol was J-shaped for ischemic stroke, and that total cholesterol was associated with a reduced mortality risk of intracerebral hemorrhagic stroke (O'Donnell *et al*, 2010).

5.1.2. Radiation exposure and circulatory diseases

IR is also one of the suspected causes of CSD (AGIR, 2010; Little *et al*, 2012a). While the carcinogenic effects of IR have been studied for many decades (NRC, 2006; UNSCEAR, 2006), evidence about associations with CSD started appearing very recently. Strong evidence from the studies of *ankylosing spondylitis* and breast cancer patients exposed to high doses (>5 Gy) exists regarding the relationship between IR and CSD (Darby *et al*, 2010; Darby *et al*, 1987; Darby *et al*, 2013). At low doses, the first significant associations started to appear in the 1990s in the Japanese cohort of A-bomb survivors(Kodama *et al*, 1996; Shimizu *et al*, 1992; Wong *et al*, 1993)—a finding that was confirmed in further cohort follow-ups (Ozasa *et al*, 2012; Preston *et al*, 2003; Shimizu *et al*, 2010; Takahashi *et al*, 2012; Yamada *et al*, 2004). More recently, several studies of tuberculosis patients who had undergone repeated fluoroscopic procedures suggested an increased CSD risk (Little *et al*, 2015; Zablotska *et al*, 2014).

It should be emphasized that nuclear fuel cycle workers are exposed to external γ-radiation at much lower doses, compared to radiotherapy patients and A-bomb survivors. A significantly increased risk of mortality due to CSD was found in a Russian cohort of Chernobyl liquidators (Ivanov *et al*, 2006), UK BNFL workers (McGeoghegan *et al*, 2008), Mayak Production Association workers (Azizova *et al*, 2015a; Azizova *et al*, 2015b; Azizova *et al*,

2014), and the Siberian Group of Chemical Enterprises workers (Karpov *et al*, 2012). A recent meta-analysis that included a majority of the aforementioned studies concluded that mortality risk may range from 4.2% to 5.6% per Sv of whole-body γ-external radiation (Little *et al*, 2012a). This study also stressed an issue of uncontrolled confounding by life-style factors (Little *et al*, 2012b).

5.1.2.1. Possible pathophysiological mechanisms

High radiation doses (>10 Gy) may induce circulatory disease through two mechanisms: (1) microvascular (drop in capillary density leading to myocardial fibrosis and subsequent ischemic heart disease), and (2) macrovascular (induction of atherosclerosis in the arteries) (Little *et al*, 2008). During a pathological examination, one may see direct damages to heart structures (pericarditis, atherosclerosis, valvular changes, pericardial and myocardial fibrosis) (Little *et al*, 2008). At the cellular level, pathologists may observe massive cell killing and pro-inflammatory effects (Schultz-Hector & Trott, 2007). Inflammation is a major component of atherosclerosis, and molecular studies have found increased levels of pro-inflammatory cytokine interleukin-6 (IL-6), C-reactive protein, and cell adhesion molecules such as intercellular cell adhesion molecule 1, vascular cell adhesion molecule 1, and endothelial leukocyte adhesion molecule 1 (Little *et al*, 2010).

Some indirect causal mechanisms were recently suggested between radiation and CSD. For example, external γ-radiation exposure may also be a cause of hypertension due to degenerative and occlusive changes in kidney arterioles (Adams *et al*, 2012; Sasaki *et al*, 2002; Sera *et al*, 2013; Wachholz & Casarett, 1970), and may provoke CSD through an increase in total cholesterol levels (Wong *et al*, 1999a).

Cautious interpretation of low-dose epidemiological studies is often emphasized in view of unknown mechanisms. Some authors have developed theoretical models based on monocyte cell killing in the intima after fractionated low-dose IR exposure (Little *et al*, 2009), but these models should be proven in view of biological studies showing the enhancement of atherosclerotic lesions stability and inhibition of pro-inflammatory reactions following low-dose IR (Le Gallic *et al*, 2015). It was concluded that further developments of molecular epidemiology may help us understand the mechanisms involved in CSD development at low radiation doses (Kreuzer *et al*, 2015a).

5.1.3. Research lacunas

It is often impossible to consider CSD risk factors in large cohort studies because these data are not available. In the studies of nuclear fuel cycle workers, this is also coupled with the absence of individual and accurately estimated internal uranium doses (Zhivin *et al*, 2014). To the best of our knowledge, only studies of A-bomb survivors (Shimizu *et al*, 2010; Takahashi *et al*, 2012) and Mayak workers (Azizova *et al*, 2015a; Azizova *et al*, 2015b; Azizova *et al*, 2014) collected information on life-style variables, and considered confounding by some risk factors (high BP, obesity, diabetes, smoking, and alcohol consumption) on the relationship between IR dose and CSD mortality. Only one recent study of French uranium miners allowed adjusting by total cholesterol (Drubay *et al*, 2015).

The potential association between CSD and internal α-radiation is not well known. An increased risk was observed in Mayak plutonium workers (Azizova *et al*, 2015a; Azizova *et al*, 2015b; Azizova *et al*, 2014), French AREVA NC Pierrelatte uranium processing workers (Guseva Canu *et al*, 2012), and French uranium miners (Nusinovici *et al*, 2010). A recent nested case-control of French uranium miners observed similar, albeit non-significant, association, and noted an absence of confounding by individually measured CSD risk factors (Drubay, 2015; Drubay *et al*, 2015).

5.1.4. Objectives of the study

Previous investigation has shown an increased mortality risk due to CSD in the AREVA NC cohort of uranium processing workers (Guseva Canu *et al*, 2012). That analysis was based on exposure scores to six physicochemical forms of uranium and did not have data on life-style risk factors, with except of smoking data for a subset of the cohort. A decision was made to set up a nested case-control study, collect individual monitoring data and information on classical CSD risk factors in order to estimate internal uranium dose and to adjust the dose-response analyses.

In the frame of my PhD thesis, research was organized around two main objectives:

1) **Objective 1**: to coordinate activities of the epidemiology-dosimetry committee on the developing methodology of internal dose estimations to support epidemiological studies using individual monitoring data and a JEM-defining solubility (chemical

form) of uranium compounds. During this task, I participated in check of the case-control database, extraction and validation of individual monitoring data, and in dose estimations for a number of workers.

2) **Objective 2**: to perform dose-response analyses between the internal uranium dose and CSD mortality in a nested case-control study of AREVA NC uranium processing workers, adjusting for potential life-style confounders and external γ-radiation exposure. During this task, I reviewed the existing literature, defined the study's analytical strategy and analyzed the data. This task took place partially during my two-month internship at the University of California San Francisco (UCSF) under the supervision of Drs. Lydia B. Zablotska[7] and Dominique Laurier.

5.2. Materials and Methods

5.2.1. Cohort of AREVA NC Pierrelatte uranium processing workers

The cohort of AREVA NC Pierrelatte uranium processing workers was set up in 2005 as a pilot study of French nuclear workers with potential for internal uranium exposure (Guseva Canu *et al*, 2008). The processing plant was built in 1960 and enriched uranium until 1996. Uranium chemical transformations and associated logistic operations were also carried out. The cohort included 2,709 male workers employed at the plant for at least six months between 1960 and 2005 (Canu *et al*, 2010). Workers with employment history at uranium mines were excluded due to their specific exposure to RDP. In 2010, the cohort was enlarged to include female workers, and follow-up was extended until December 31st 2006 (date when mortality registries were assumed the most complete at that time). The final cohort totaled 2,897 workers (Canu *et al*, 2011). Vital status and causes of death were extracted from the RNIPP and the CépiDC. The causes of death were coded according to the ICD-10. Table 18 shows the basic characteristics of the AREVA NC Pierrelatte worker cohort.

[7] Dr. Lydia B. Zablotska is the lead investigator of the Canadian (Eldorado) cohort study of uranium processing workers and Canadian fluoroscopy patients, and of the National Cancer Institute (NCI)-funded Chernobyl case-control studies of leukemia and thyroid cancer.

Table 18. Description of the AREVA NC Pierrelatte cohort

	n (%)
Number of workers	2,897 (100)
Number of female workers	188 (6.5)
Number of person-years	79,892 (100)
Total number of deaths	460 (15.9)
Cancer	214 (46.5)
Circulatory diseases	111 (24.1)
Ischemic heart diseases	48 (10.4)
Cerebrovascular diseases	31 (6.7)
Socio-economic status at hire	
Managerial/professional	269 (9.3)
Clerical	246 (8.5)
Skilled technical	1596 (55.1)
Unskilled	786 (8.5)
Age (years)	**Median (min-max)**
At the beginning of follow-up	30.7 (18.6-57.9)
At the end of follow-up	63.0 (21.6-92.7)
Follow-up duration (years)	27.9 (1.7-38.9)

5.2.1.1. Internal uranium exposure assessment through job-exposure matrix

Because historical internal monitoring data were not available in computerized form, the calculation of the internal uranium doses was not previously feasible in this cohort. A plant-specific JEM was developed to assess the cumulative exposure to uranium. Uranium compounds were classified according to their isotopic composition by distinguishing reprocessed uranium compounds from the natural uranium compounds, and by their lung solubility (Table 19).

Table 19. Classification of uranium compounds by the AREVA NC Pierrelatte job-exposure matrix

Characteristic	**Uranium compound**
Solubility[*]	
Type F	UF_6, UF_4, $UO_2(NO_3)_2$
Type M	$(U_2O_7)(NH_4)_2$
Type S	UO_2
Isotopic composition[†]	
Natural	^{234}U, ^{235}U, ^{238}U
Reprocessed	^{232}U, ^{233}U, ^{234}U, ^{235}U, ^{236}U, ^{237}U, ^{238}U, ^{237}Np, ^{231}Am, $^{231\text{-}241}Pu$

[*] The solubility of uranium compounds was determined in terms of lung absorption types (F-fast, M-moderate, S-slow) according to the Human Respiratory Tract Model (HRTM) described in the International Commission on Radiological Protection (ICRP) publication 66 (ICRP, 1994).
[†] The isotopic composition and relative abundance is rarely known precisely.

This JEM provided six types of exposure scores: to natural (type F, M, and S) and reprocessed (type F, M, and S) uranium compounds. Similarly to Chapter 4, the individual cumulative

exposure score was calculated as the product of frequency, intensity of exposure, and duration of employment for each of the jobs in the worker's career at the AREVA NC Pierrelatte plant.

5.2.2. Case-control study of circulatory disease mortality nested in the AREVA NC Pierrelatte cohort

Previous analysis of the AREVA NC Pierrelatte cohort suggested that exposure to uranium, especially slowly soluble reprocessed uranium, may increase the risk of mortality from CSD (Guseva Canu *et al*, 2012). That study used a retrospective estimate of cumulative exposure to six types of uranium compounds and did not have data on the known classical CSD risk factors. Thus, it was decided to set a nested case-control study of CSD nested in the AREVA NC Pierrelatte cohort. This task was performed in 2010 during the postdoctoral fellowship of Dr. Jérôme-Philippe Garsi, supervised by Dr. Irina Guseva Canu (Garsi *et al*, 2014).

5.2.2.1. Selection of cases

In accordance with the existing literature (Little *et al*, 2012a), CSD was defined as ICD-10 grouping "I00-I99", IHD as "I20-I25", and CVD as "I60-I69". A total of 111 all CSD cases were included, comprising 48 cases of IHD, 31 cases of CVD, and 32 cases from other CSD.

5.2.2.2. Selection of controls and matching

First, incidence density sampling was used to select all possible controls alive at the attainted age of the corresponding cases. Incidence density sampling is a technique that controls for confounding by attained age (Richardson, 2004). Controls were also individually matched to cases with the following factors to avoid potential confounding:

- gender
- birth cohort (≤1925, 1926-1935, 1936-1945, ≥1946)
- socio-professional status at hire (managerial/professional, skilled technical, unskilled).

No match was found for nine cases and they were excluded from further analyses (Garsi *et al*, 2014).

Second, random sampling was used to select up to five controls per case.

5.2.2.3. Final dataset of the nested case-control study

The final analytical database comprised 518 observations (395 unique workers) and was organized in 102 risk-sets: 102 cases of CSD (including 44 cases of IHD and 31 cases of CVD) and 416 controls. On average, there were four controls per cases: 70 cases were matched to five controls, five cases to four controls, five cases to three controls, nine cases to two controls, and 13 cases to one control. It should be noted that incidence density sampling allows reusing cases and controls in different risk-sets (Richardson, 2004). Thirty-two cases (31%) were selected as controls. Some individuals were also selected as controls several times: twice (48 controls), three times (15 controls), four times (3 controls), and five times (one control).

All information (radiation doses and life-style CSD risk factors) in each risk set was truncated at the attained age of the index case.

5.2.2.4. Radiation dose assessment

External γ-radiation dose

External γ-radiation was measured by individual dosimeter badges and kept in the plant monitoring files. Electronic SISERI system (Feuardent *et al*, 2013) was also used to complete exposure history. All records were extracted in the form of the whole-body dose expressed in mGy.

Internal uranium dose

Individual uranium bioassay data were extracted from the workers' medical files. The internal uranium dose for each worker was estimated based on these individual records by applying uranium biokinetic and dosimetric models, and by attributing the uranium chemical form (absorption type) according to the AREVA NC Pierrelatte JEM.

The dosimetry protocol—on the basis of the General guidelines for the estimation of committed effective doses from the incorporation monitoring data (IDEAS)(EURADOS, 2013)—was validated by the epidemiology-dosimetry committee (S. Zhivin, E. Blanchardon, E. Davesne, D. Laurier, I. Guseva Canu, and E. Samson). Dose estimation protocol was implemented in dosimetry software DOSEPI developed by the Laboratory of Internal Dose Assessment of the IRSN (Dr. Estelle Davesne). The description of this software is beyond the

scope of this PhD manuscript and will be reported elsewhere. During the calculations, internal dosimetrists were blinded to case-control status of study participants.

Most parts of the uranium concentration data were in the form of urinalysis: uranium gravimetric measurements ($\mu g.l^{-1}$) and radioactivity concentration (in $Bq.l^{-1}$). Five workers were sporadically monitored for ^{134}Cs, ^{137}Cs and ^{106}Ru (these doses were assessed by S. Zhivin under the supervision of Dr. Eric Blanchardon and summed with the low-LET portion of uranium doses). Of the 395 unique workers included into the nested case-control study, uranium dose estimations were performed for 350 workers, of whom 123 workers had only below LOD data. Forty-five workers, who did not have any uranium monitoring data, were assumed to be unexposed (zero dose was attributed to them) after detailed verifications of their medical and administrative files.

- **Bioassay data normalization**

All samples collected over periods of less than 24h were normalized to 24h value. Normalization to the amount of creatinine was preferred in our study. Urine sample were measured in $mBq.g^{-1}$ creatinine or in $mBq.l^{-1}$; a creatinine value was normalized assuming 24h creatinine excretion of 1.7 $g.d^{-1}$ for males and 1 $g.d^{-1}$ for females (ICRP, 2002). Urine samples measured in $mBq.l^{-1}$ without creatinine were normalized assuming a 24h urine volume of 1.6 $l.day^{-1}$ for males and 1.2 $l.day^{-1}$ for females (ICRP, 2002). Fecal samples measured in $mBq.g^{-1}$ ashes were normalized assuming that the sample was representative of a 24h excretion. If the ash weight was not given, the fecal measurement was not used in the study. All gravimetric measurements were converted to radiation activity, assuming exposure to natural uranium compounds (specific activity=2.53×10^4 $Bq.g^{-1}$).

- **Route of intake**

Unless otherwise confirmed, it was assumed that exposure occurred through dust inhalation. Wound contamination occurred during 33 accidents.

- **Time pattern of intake**

A worker exposure history was divided into periods of chronic exposure with the help of the AREVA NC Pierrelatte JEM (Canu *et al*, 2011). Each period was assumed correspond to constant chronic intake of specified uranium physicochemical forms. Additional effort was

made to extract information on accidental exposure—corresponding to potential acute intakes—from the Pierrelatte facility incident registry.

The whole period of chronic exposure started on the date of first bioassay measurement minus six months and ended at the date of last bioassay measurement. If the date of employment was in between the date of first measurement minus six months and date of first measurement, the date of employment was taken as the date of start of chronic intake. If a worker did not have bioassay data over 18 months, chronic exposure was interrupted during this interval and started six months before the next available bioassay. The underlying idea is that the worker was not exposed if no bioassay was sampled and that an 18-month period without monitoring cannot be explained by missing samples.

When there was evidence to assume an acute intake, the date of the incident was the one found in the incident registry. All following bioassay data (until the second measurement below LOD or another incident) were attributed to this acute intake.

- **Considered radionuclide**

^{234}U was considered as the main radionuclide because: (1) precise isotopic composition at the AREVA NC Pierrelatte was not known, (2) in natural uranium, 50% of the activity comes from ^{234}U and this proportion increases with enrichment. It should be emphasized, however, that estimation based on ^{234}U may have resulted in slightly higher dose estimates than that based on ^{235}U and ^{238}U.

- **Uranium physicochemical properties**

Because absorption type (F, M, and S) is one of the major sources of dose uncertainty (Etherington *et al*, 2006; Laurent *et al*, 2015), we used the JEM to extract information on solubility profiles of uranium at each period of the worker's career (Canu *et al*, 2011).

The following scenarios were used in our study: (1) exposure to one particular absorption type (exposure to types F, M or S in JEM), (2) combined exposure (exposure to type F and M, and S), (3) exposure to the specific uranium type (according to the chemical form specified in the incident registry). In the absence of information, a mixture of types F, M, and S was used. A default AMAD value of 5 µm was assumed (Ansoborlo *et al*, 2002; ICRP, 1994).

In case of wound contamination, "weak" category was used for soluble uranium compounds, and "particles" category was used for insoluble compounds, as decribed by the NCRP model (NCRP, 2006).

- **Alimentary uranium intake**

The excretion patterns of uranium coming from alimentary intakes were previously studied in a geographical region closed to Pierrelatte (Davesne *et al*, 2014). These data were used to decide whether the activity measurement was representative of alimentary or occupational intakes. For urine samples, data showed that alimentary intakes lead to an activity below the LOD of Pierrelatte workers (Davesne *et al*, 2014). Therefore, alimentary background of uranium in urine was not further considered. For fecal samples, we supposed occupational intakes if measured activity was equal or higher than 250 mBq or if the ratio of ^{234}U activity by the ^{238}U activity was greater than two. Fecal samples, which did not satisfy these criteria, were not used for the dose estimation. Finally, for both urine and above 250 mBq fecal bioassay samples, we assumed that the alimentary intake contribution was negligible to the activity measurement.

- **Dosimetry scenario**

Because of the high proportion of workers (n=123) with only below LOD bioassay data samples, for whom the above protocol can provide no dose assessment, we estimated doses using two dosimetry scenarios. Further in the text, these scenarios are referred to as **dosimetry scenario 1** and **dosimetry scenario 2**.

In dosimetry scenario 1 (main scenario for statistical analyses), workers with only below LOD measurements were assumed unexposed and dose zero was attributed to them.

In dosimetry scenario 2, doses for workers with only below LOD measurements were calculated using LOD value for the last sample of each chronic exposure period.

- **Absorbed doses**

Annual absorbed doses (in mGy) were estimated as the doses received between 1st January and 31st December of each year for five organs of interest in uranium studies: heart wall, lung, intra-thoracic lymph nodes (LN), red bone marrow (RBM), and kidney. For additional analyses, annual absorbed doses from α-radiation were weighted by an RBE of 10 or 20 as suggested in previous studies (Marsh *et al*, 2014; Rage *et al*, 2012), and expressed as mGy-Eq. Only the high-LET component of the absorbed dose was multiplied by the RBE value.

It should be noted that the HRTM describes three types of radiosensitive cells in three regions of the lung: (1) basal and secretory cells in the bronchial (BB) region, (2) secretory cells in the bronchiolar (bb) region, and (3) secretory and type II epithelial cells in the alveolar-interstitial region (AI). Each of the three regions is assigned an equal proportion of lung detriment (0.33). Therefore, total lung dose was calculated as the mean of the three region doses with a contribution from LN: lung dose=$0.33*dose_{AI} + 0.33*dose_{BB} + 0.33*dose_{bb} + 0.001*dose_{LN}$.

5.2.3. Collection of data on classical circulatory disease risk factors

Data on classical CSD risk factors were collected from the paper medical files kept at the AREVA NC Occupational Health Department. Medical examinations spanned from 1959 to 2010, and were generally annual, but some of the workers received biannual or trimestrial check-ups, depending on their exposure status (Garsi *et al*, 2014). The number of medical examinations per worker ranged from 1 to 57 (mean 25), and 12,735 blood test results were collected in total (Garsi *et al*, 2014). Data completeness varied from 98% for BP to 1% for HDL measurements, because for the latter routine measurements started only from the mid 1970s (Garsi *et al*, 2014). Smoking records were only analyzed as a binary variable ("never-smoker" vs. "ever-smoker") because they were heterogeneous and, probably, dependent on the physician practice and the evolution of French smoking public policies (1976 Veil and 1991 Évin laws).

Medical follow-up at the occupational health department is not compulsory after retirement, so no data were available post retirement. The mean time between the last medical examination and death from CSD among cases was 12 years (Garsi *et al*, 2014).

The final list of time-dependent variables was compiled based on data completeness and discussion with AREVA NC Pierrelatte Occupational Health Department physicians: smoking, weight (kg), height (m), systolic and diastolic BP (mmHg), total cholesterol ($g.l^{-1}$), and glycaemia ($g.l^{-1}$). Body mass index (BMI, kg/m^2) was calculated from weight and height variables using the standard formula:

$$BMI\ (kg/m^2) = \frac{weight\ (kg)}{height^2\ (m^2)}.$$

5.2.3.1. Risk factor categorization

For most risk factors considered, the maximum of all values recorded before the death of the case (or at attained age of the index case for controls) was retained for each worker. Further,

variables were categorized according to the literature (Go *et al*, 2014; HAS, 2013b) as follows:

- **Smoking**: 'never-smoker' vs. ' ever smoker'
- **BMI**: ≤25 kg/m^2'normal weight', 25-29 kg/m^2 'overweight', and ≥30 kg/m^2 'obese'
- **BP**: >150 mmHg of systolic BP or >90 mmHg for diastolic BP 'hypertension', otherwise 'normal'; these cutpoint values were recommended by the AREVA NC Pierrelatte physicians
- **Total cholesterol**: ≤2.4 g.l^{-1} 'normal' vs. >2.4 g.l^{-1} 'elevated'; this cutpoint value is generally used to detect elevated concentrations in persons older than 30 years
- **Glycemia**: ≤1.26 g.l^{-1} 'normal' vs. >1.26 g.l^{-1} 'elevated' g.l^{-1}; this cutpoint value is generally used to detect elevated fasting blood glucose.

5.2.4. Statistical methods

We explored the relationship between individual CSD risk factors and mortality via log-linear OR model, adjusted for total absorbed lung dose, using conditional logistic regression. This model has the following form:

$$\exp(\beta_1 * CSD\ risk\ factor)$$

where the exponention of β_1 is the estimated OR of CSD mortality-associated with the considered CSD risk factors or external γ-radiation (*CSD risk factor*).

To analyze the relationship between cumulative lung uranium dose and CSD mortality, we used the linear excess odds ratio (EOR) model using conditional logistic regression, as classically used in radiation epidemiology to analyze case-control data (Breslow & Day, 1987; Leuraud *et al*, 2011; Zablotska *et al*, 2013a; Zablotska *et al*, 2011). This model has the following form:

$$\exp(\sum x_n\beta_n)(1 + \beta_1 * dose)$$

where β_1 is the EOR per mGy of cumulative uranium lung dose (*dose*), and β_n are regression coefficients associated to potential confounding variables x_n: CSD risk factors and external γ-radiation.

In addition, we examined the linear trend between CSD mortality and categories of cumulative uranium lung dose (cut-points: <0.01, 0.01-0.9, 1-5 and >5 mGy).

The choice of lung instead of heart dose was based on the following: (1) non-converged models with heart dose because of the extremely small dose range, (2) high correlation between uranium organ doses (Pearson's correlation coefficient >0.8), and (3) potential inflammatory reactions in the lungs following uranium inhalation (organ of entry) that may lead to atherosclerosis development (Little, 2013; Little *et al*, 2008).

All statistical models were systematically adjusted for matching variables (attained age, gender, birth cohort, and socio-professional status) (Breslow & Day, 1987; Rothman *et al*, 2008). Simple regression models were fitted with cumulative uranium lung dose, adjusted for each individual CSD risk factor (smoking, BMI, BP, total cholesterol, and glycemia), and external γ-radiation dose. We also fitted multiple regression models adjusted for all CSD risk factors and external γ-radiation dose to examine joint confounding (Breslow & Day, 1987) due to the multifactorial nature of CSD.
The main analyses were performed considering no lag between CSD mortality and radiation exposure, dosimetry scenario 1, and RBE=1 for cumulative uranium lung dose. Sensitivity analyses were performed regarding dosimetry scenario 2, a lag of 5 and 10 years, and cumulative uranium lung dose weighted by a RBE=10 or RBE=20.

Regression parameters and 95% CI were estimated using the maximum likelihood method in the GMBO/PECAN module of EPICURE software (Preston *et al*, 1993). Wald-based CI were calculated if the EOR bounds were on the boundary of the parameter space (-1/maximum dose). A linear trend test was based on the means of the internal dose categories.

5.2.5. Results

5.2.5.1. Descriptive statistics

Table 20 presents basic characteristics of the cases (n=102) and controls (n=416). Cases and controls were quite similar across variables used for matching (Table 20).
Although the median employment duration was similar, some controls (minimum: 0.6 years) worked much less than cases (minimum: 12 years) (Table 20). Average age at death of cases was 69 years (range=44.1-87.8).

Table 20. Basic characteristics of the nested case-control study of circulatory diseases in AREVA NC Pierrelatte uranium processing workers

Characteristics	Cases (n=102)	Controls (n=416)
Males, n(%)	100 (98)	409 (98)
Socio-economic status at hire, n (%)		
Managerial/professional	18 (18)	67 (16)
Skilled technical	6 (6)	14 (3)
Unskilled	78 (76)	335 (81)
Birth cohort, n (%)		
≤1925	52 (51)	164 (39)
1926-1935	31 (30)	167 (40)
1936-1945	15 (15)	55 (14)
≥1946	4 (4)	30 (7)
Employment duration (yrs), median (min-max)	19.4 (12.0-37.2)	19.0 (0.6-37.8)

5.2.5.2. Internal uranium dose

The average cumulative organ doses from uranium exposure ranged from 0.01 mGy (heart wall) to 4 mGy (LN) (Table 21). The maximal doses were observed among cases for LN (89 mGy) and lungs (27 mGy). The dose distribution was highly skewed to the left (Appendix 3). All internal doses were highly correlated (Pearson's correlation coefficient >0.8) (data not shown).

Table 21. Internal uranium organ-specific radiation doses among cases and controls

	Mean		Median		IQR (25-75%)		Maximum	
Organ dose (mGy)*	Cases	Controls†	Cases	Controls†	Cases	Controls†	Cases	Controls†
Heart	0.01	0.01	0.001	0.002	0-0.01	0-0.01	0.2	0.3
Lung	1	0.7	0.01	0.01	0-1	0-0.6	27	11
LN	4	3	0.01	0.01	0-2	0-0.3	89	47
RBM	0.04	0.04	0.005	0.01	0-0.05	0-0.05	0.9	1
Kidney	0.2	0.2	0.02	0.03	0-0.2	0-0.2	4	4

* Dosimetry scenario 1 was used. Dose from other radionuclides was added to uranium dose. Relative biological effectiveness (RBE) of 1 and lag period of 0 years were assumed.
† Doses to controls censored at the attained age of index case.
IQR, interquartile range; LN, intra-thoracic lymph nodes; RBM, red bone marrow.

Because high-LET (α-radiation) contribution to the uranium dose was over 95% (data not shown), the RBE-weighted cumulative uranium lung doses were almost directly proportional to the total non-weighted doses (Table 22).

Table 22. Impact of the relative biological effectiveness (RBE) factor on cumulative uranium lung dose among cases and controls

	Mean		Median		IQR (25-75%)		Maximum	
Total lung dose (mGy-Eq)*	**Cases**	**Controls†**	**Cases**	**Controls†**	**Cases**	**Controls†**	**Cases**	**Controls†**
RBE=1	1	0.7	0.01	0.01	0-1	0-0.6	27	11
RBE=10	11	7	0.1	0.1	0-10	0-6	272	108
RBE=20	22	14	0.2	0.1	0-20	0-12	545	217

*Total lung dose is a sum of chronic and acute doses. Dosimetry scenario 1 was used. Dose from other radionuclides was added to uranium dose. Lag period of 0 years was assumed.
† Doses to controls censored at the attained age of index case.
IQR, interquartile range.

Applying a minimal lag-period of 5 years had no impact on the estimated cumulative uranium lung doses (data not shown). Applying a lag-period of 10 years led to decreasing maximum but not median lung doses: cases (median=0.01 mGy, min=0, max=21.6) and controls (median=0.005 mGy, min=0, max=9.3).

Considering the uranium doses of 123 workers estimated with dosimetry scenario 2 (see Chapter 5.2.2.4), led to increasing average doses by 50% among cases and 70% among controls (Table 23). Dosimetry scenario 2 had low impact on average cumulative doses among all workers (Table 23).

Table 23. Impact of the dosimetry scenario on cumulative uranium lung dose among cases and controls

	Mean		Median		IQR (25-75%)		Maximum	
Total lung dose (mGy)*	**Cases**	**Controls†**	**Cases**	**Controls†**	**Cases**	**Controls†**	**Cases**	**Controls†**
Workers with only below LOD bioassay data[a]								
Dosimetry scenario 1	0	0.002	0	0	0	0	0	0.1
Dosimetry scenario 2	1	1	1	1	0-3	0-2	8	9
All workers								
Dosimetry scenario 1	1	0.7	0.01	0.01	0-1	0-0.6	27	11
Dosimetry scenario 2	2	1	0.3	0.3	0-2	0-2	27	11

* Total lung dose is a sum of chronic and acute doses. Dose from other radionuclides was added to uranium dose.
[a] Based on 30 cases and 130 controls (123 unique workers).
Relative biological effectiveness (RBE) of 1 and lag of 0 years were assumed.
† Doses to controls censored at the attained age of index case.
IQR, interquartile range; LOD, level of detection.

5.2.5.3. Circulatory diseases and their risk factors

In general, positive non-significant associations were observed between CSD (Table 24), IHD (Table 25), and CVD (Table 26) mortality, and CSD risk factors. Adjustment for cumulative uranium lung dose did not reverse associations (Table 24, Table 25, Table 26). CSD mortality

was significantly associated with hypertension (Adjusted Odds Ratio (AOR)=3.89, 95% CI 2.16 to 7.02) and borderline significant with elevated glycemia (AOR=1.09, 95% CI 0.98 to 1.22) (Table 24). External γ-radiation dose was non-significantly associated with CSD mortality without (OR/mGy=1.01, 95% CI 0.99 to 1.04) and with (AOR/mGy=1.01, 95% CI 0.98 to 1.04) adjustment for uranium lung dose.

Table 24. Relationship between circulatory diseases (CSD) mortality and circulatory disease risk factors

		Cases (n=102)	Controls (n=416)		
Risk factors		**n (%)**	**n (%)**	**OR (95% CI)[†]**	**AOR (95% CI)[‡]**
Smoking	Never	37 (36)	182 (44)	ref.	ref.
	Ever	65 (64)	224 (54)	1.34 (0.84 to 2.17)	1.39 (0.86 to 2.24)
	Missing	0	10 (2)		
BMI	Normal	24 (24)	109 (27)	ref.	ref.
	Overweight	49 (48)	230 (55)	1.01 (0.58 to 1.77)	1.03 (0.58 to 1.82)
	Obese	28 (27)	72 (17)	1.65 (0.88 to 3.09)	1.65 (0.87 to 3.13)
	Missing	1 (1)	5 (1)		
BP	Normal	21 (21)	192 (46)	ref.	ref.
	Hypertension	81 (79)	224 (54)	3.91 (2.18 to 7.02)	3.89 (2.16 to 7.02)
	Missing	0	0		
Total cholesterol	Normal	90 (22)	13 (13)	ref.	ref.
	Elevated	317 (76)	88 (86)	1.62 (0.86 to 3.08)	1.52 (0.80 to 2.91)
	Missing	9 (2)	1 (1)		
Glycemia	Normal	62 (61)	279 (67)	ref.	ref.
	Elevated	39 (38)	128 (31)	1.09 (0.98 to 1.22)	1.09 (0.98 to 1.22)
	Missing	1 (1)	9 (2)		

[†] Adjusted for matching variables (attained age, gender, birth cohort, and socio-professional status).
[‡] Adjusted for matching variables, and cumulative uranium lung dose.
AOR, adjusted odds ratio; BMI, body mass index; BP, blood pressure; CI, confidence intervals; OR, odds ratio.

IHD mortality was significantly associated only with hypertension (AOR=3.46, 95% CI 1.46 to 8.21) (Table 25), but the magnitude of the association was somewhat lower compared to CSD (AOR=3.89, 95% 2.16 to 7.02) or CVD (AOR=4.47, 95% CI 1.53 to 13.03).

Table 25. Relationship between ischemic heart disease (IHD) mortality and circulatory disease risk factors

		Cases (n=44)	Controls (n=181)		
Risk factors		**n (%)**	**n (%)**	**OR (95% CI)[†]**	**AOR (95% CI)[‡]**
Smoking	Never	15 (34)	78 (43)	ref.	ref.
	Ever	29 (66)	97 (54)	1.35 (0.65 to 2.80)	1.46 (0.69 to 3.09)
	Missing	0	6 (3)		
BMI	Normal	12 (27)	54 (30)	ref.	ref.
	Overweight	19 (43)	96 (53)	0.94 (0.43 to 2.04)	1.02 (0.46 to 2.28)
	Obese	13 (30)	28 (15)	1.91 (0.77 to 4.72)	1.90 (0.76 to 4.76)
	Missing	0	3 (2)		
BP	Normal	10 (23)	84 (46)	ref.	ref.
	Hypertension	34 (77)	97 (54)	3.54 (1.50 to 8.36)	3.46 (1.46 to 8.21)
	Missing	0	0		
Total cholesterol	Normal	6 (14)	42 (23)	ref.	ref.
	Elevated	38 (86)	136 (75)	1.58 (0.61 to 4.09)	1.48 (0.56 to 3.89)
	Missing	0	3 (2)		
Glycemia	Normal	28 (64)	123 (70)	ref.	ref.
	Elevated	16 (36)	55 (29)	1.30 (0.65 to 2.58)	1.41 (0.70 to 2.85)
	Missing	0	3 (1)		

[†] Adjusted for matching variables (attained age, gender, birth cohort, socio-professional status).
[‡] Adjusted for matching variables, and cumulative uranium lung dose.
AOR, adjusted odds ratio; BMI, body mass index; BP, blood pressure; CI, confidence intervals; OR, odds ratio.

Although BMI was positively associated with CSD and IHD mortality, it was not associated with CVD mortality: either among overweight (AOR=0.80, 95% CI 0.27 to 2.34) or obese (AOR=0.87, 95% CI 0.25 to 3.11) workers (Table 26).

Table 26. Relationship between cerebrovascular disease (CVD) mortality and circulatory disease risk factors

		Cases (n=31)	Controls (n=128)		
Risk factors		**n (%)**	**n (%)**	**OR (95% CI)[†]**	**AOR (95% CI)[‡]**
Smoking	Never	13 (42)	56 (44)	ref.	ref.
	Ever	18 (58)	69 (54)	1.15 (0.52 to 2.57)	1.26 (0.55 to 2.91)
	Missing	0	3 (2)		
BMI	Normal	8 (26)	30 (23)	ref.	ref.
	Overweight	16 (52)	75 (59)	0.94 (0.33 to 2.84)	0.80 (0.27 to 2.34)
	Obese	6 (19)	21 (16)	0.98 (0.30 to 3.24)	0.87 (0.25 to 3.11)
	Missing	1 (3)	2 (2)		
BP	Normal	5 (16)	57 (45)	ref.	ref.
	Hypertension	26 (84)	71 (55)	3.83 (1.40 to 10.49)	4.47 (1.53 to 13.03)
	Missing	0	0		
Total cholesterol	Normal	3 (10)	34 (27)	ref.	ref.
	Elevated	27 (87)	93 (72)	3.03 (0.87 to 10.62)	2.75 (0.77 to 9.82)
	Missing	1 (3)	1 (1)		
Glycemia	Normal	19 (61)	86 (67)	ref.	ref.
	Elevated	11 (36)	41 (32)	1.30 (0.58 to 2.92)	1.20 (0.52 to 2.74)
	Missing	1 (3)	1 (1)		

[†] Adjusted for matching variables (attained age, gender, birth cohort, socio-professional status).
[‡] Adjusted for matching variables, and cumulative uranium lung dose.
AOR, adjusted odds ratio; BMI, body mass index; BP, blood pressure; CI, confidence intervals; OR, odds ratio.

5.2.5.4. Relationship between circulatory diseases and internal uranium dose

An increasing trend of CSD mortality was observed across cumulative internal lung dose categories (Table 27). The trend was not statistically significant ($p_{linear\ trend}$=0.4) (Table 27).

Table 27. Circulatory disease (CSD) mortality across categories of cumulative uranium lung dose

Dose category, mGy	Mean dose, mGy	No. cases	No. controls	OR (95% CI)[†]
<0.01	0.0003	47	200	ref.
0.01-0.9	0.2	29	133	0.9 (0.5 to 2)
1-5	2	21	71	1.5 (0.7 to 3)
>5	8	5	12	2.4 (0.7 to 8)

[†]Adjusted for matching variables (attained age, gender, birth cohort, and socio-professional status), CSD risk factors (smoking, BMI, BP, total cholesterol, and glycemia), and γ-radiation dose.
Relative biological effectiveness (RBE) of 1 and lag period of 0 years were assumed.
CI, confidence intervals; OR, odds ratio.

Table 28 shows results from the dose-response analysis between mortality and cumulative internal lung dose. There was a positive borderline significant association between cumulative total absorbed lung dose and mortality due to CSD (EOR/mGy=0.2, 95% CI 0.004 to 0.5), IHD (EOR/mGy=0.2, 95% CI -0.01 to 1), and CVD (EOR/mGy=0.5, 95% CI 0.04 to 2) (Table 28). There was little evidence of confounding by CSD risk factors and external γ-radiation (Table 28).

Table 28. Relationship between circulatory (CSD), ischemic (IHD), and cerebrovascular (CVD) disease mortality and cumulative uranium lung dose

	CSD	IHD	CVD
Adjustment	**EOR/mGy (95%CI)[*]**		
Unadjusted	0.2 (0.02 to 0.6)	0.3 (-0.005 to 1)	0.8 (0.1 to 3)
Smoking	0.2 (0.01 to 0.6)	0.2 (-0.01 to 1)	0.9 (-0.4[†] to 3)
BMI	0.2 (0.01 to 0.5)	0.2 (-0.01 to 1)	0.6 (-0.5[†] to 2[†])
BP	0.2 (0.01 to 0.6)	0.3 (-0.01 to 1)	0.8 (0.1 to 3)
Total cholesterol	0.2 (0.01 to 0.6)	0.2 (-0.01 to 1)	0.7 (0.1 to 2)
Glycemia	0.2 (0.02 to 0.6)	0.3 (-0.0005 to 1)	0.8 (0.1 to 3)
γ-radiation dose	0.2 (0.02 to 0.6)	0.3 (-0.01 to 1)	0.8 (0.1 to 3)
Fully adjusted[‡]	0.2 (0.004 to 0.5)	0.2 (-0.01 to 1)	0.7 (0.1 to 3)

[*]Adjusted for matching variables (attained age, gender, birth cohort, socio-professional status). Estimated by the linear excess odds ratio model.
[†]Wald-based method.
[‡]Adjusted for matching variables, CSD risk factors, and γ-radiation dose.
Relative biological effectiveness (RBE) of 1 and lag period of 0 years were assumed.
BMI, body mass index; BP, blood pressure; CI, confidence intervals; CSD, circulatory diseases; CVD, cerebrovascular diseases; EOR, excess odds ratio; IHD, ischemic heart diseases.

Figure 20 shows the dose-response analysis. As may be inferred from Figure 20, categorical OR analysis was in good agreement with the linear prediction, but it was only based on four categories.

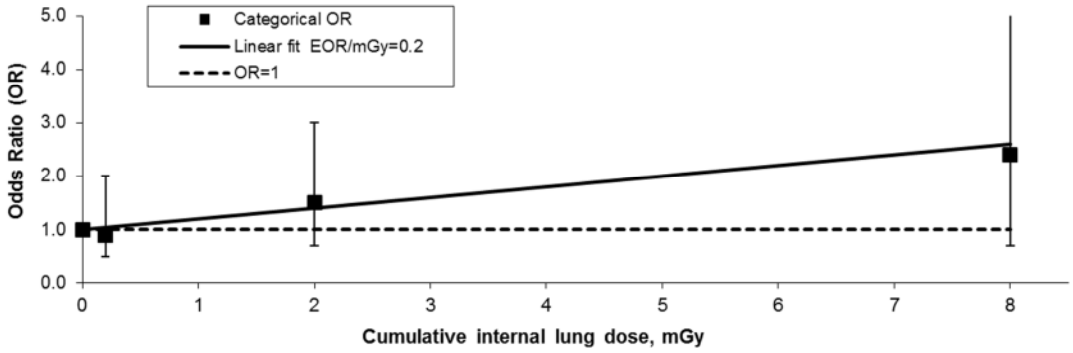

Figure 20. Circulatory disease mortality (CSD) in relation to cumulative uranium lung dose ERR/mGy=0.2 (95% CI 0.004 to 0.5), adjusted for matching variables, CSD risk factors, and external γ-radiation dose

EOR was the same when five-year lagged doses were used (data not shown). When ten-year uranium lagged doses were used, the adjusted EOR increased slightly for CVD (EOR/mGy=0.8, 95% CI 0.08 to 4), but not the adjusted EOR for CSD (EOR=0.2, 95% -0.01 to 0.6) and for IHD (EOR/mGy=0.2, 95% CI -0.02 to 1).

By multiplying the high-LET contribution of the cumulative lung dose by different RBE values, the EOR per mGy-Eq of CSD mortality was 0.02 (95% CI 0.001 to 0.1) with RBE=10 and 0.01 (95% CI 0.01 to 0.03) with RBE=20 (Table 29).

Table 29. Impact of the relative biological effectiveness (RBE) factor on on the relationship between mortality and cumulative uranium lung dose

	CSD	IHD	CVD
Adjustment	**EOR/mGy-Eq (95%CI)[*], RBE=10**		
Unadjusted	0.02 (0.002 to 0.1)	0.03 (-0.0005 to 0.1)	0.08 (0.01 to 0.3)
Smoking	0.02 (0.002 to 0.1)	0.03 (-0.0001 to 0.1)	0.08 (0.01 to 0.3)
BMI	0.02 (0.001 to 0.1)	0.03 (-0.0005 to 0.1)	0.07 (0.01 to 0.3)
BP	0.02 (-0.01[†] to 0.1)	0.03 (-0.001 to 0.1)	0.1 (0.02 to 0.4)
Total cholesterol	0.02 (0.001 to 0.05)	0.02 (-0.001 to 0.1)	0.08 (0.01 to 0.3)
Glycemia	0.02 (-0.01[†] to 0.1)	0.03 (-0.001 to 0.1)	0.08 (0.01 to 0.3)
γ-radiation dose	0.02 (0.002 to 0.1)	0.03 (-0.001 to 0.1)	0.08 (0.01 to 0.3)
Fully adjusted	0.02 (0.001 to 0.1)	0.03 (-0.03[†] to 0.1)	0.1 (0.02 to 0.4)
	EOR/mGy-Eq (95%CI)[*], RBE=20		
Unadjusted	0.01 (0.001 to 0.03)	0.01 (-0.0002 to 0.05)	0.04 (0.001 to 0.1)
Smoking	0.01 (0.001 to 0.03)	0.01 (-0.0001 to 0.1)	0.04 (0.01 to 0.1)
BMI	0.01 (0.001 to 0.03)	0.01 (-0.0003 to 0.05)	0.04 (0.004 to 0.1)
BP	0.01 (0.001 to 0.03)	0.01 (-0.0004 to 0.1)	0.05 (0.01 to 0.2)
Total cholesterol	0.01 (0.0004 to 0.03)	0.01 (-0.001 to 0.05)	0.04 (0.005 to 0.1)
Glycemia	0.01 (0.001 to 0.03)	0.01 (-0.0002 to 0.05)	0.04 (0.005 to 0.1)
γ-radiation dose	0.01 (0.001 to 0.03)	0.01 (-0.0003 to 0.05)	0.04 (0.01 to 0.1)
Fully adjusted	0.01 (0.001 to 0.03)	0.02 (-0.01[†] to 0.1)	0.05 (0.01 to 0.2)

[*]Adjusted for matching variables (attained age, gender, birth cohort, socio-professional status). Estimated by the linear excess odds ratio model. Lag of 0 years was assumed.
[†]Wald-based method.
BMI, body mass index; BP, blood pressure; CI, confidence intervals; CSD, circulatory diseases; CVD, cerebrovascular diseases; EOR, excess odds ratio; IHD, ischemic heart diseases.

Application of dosimetry scenario 2 resulted in lower EOR/mGy estimates for CSD (0.1, 95% CI -0.1 to 0.3), IHD (0.1, 95% CI -0.03 to 0.5), and CVD (0.5, 95% CI 0.04 to 2) mortality (Table 30). The EOR/mGy estimate for CSD mortality risk in dosimetry scenario 2 was 50% lower (Table 30), and non-significant, compared to dosimetry scenario 1 (Table 28).

Table 30. Impact of using dosimetry scenario 2 on the relationship between mortality and cumulative uranium lung dose

	CSD	IHD	CVD
Adjustment	**EOR/mGy (95%CI)***		
Unadjusted	0.2 (0.01 to 0.5)	0.1 (-0.02 to 0.6)	0.5 (-0.3 to 1)
Smoking	0.2 (0.004 to 0.4)	0.02 (-0.2 to 0.2)	0.2 (-0.3† to 0.8†)
BMI	0.2 (0.01 to 0.5)	0.1 (-0.03 to 0.5)	0.5 (0.05 to 2)
BP	0.2 (0.0001 to 0.5)	0.1 (-0.03 to 0.7)	0.5 (0.04 to 2)
Total cholesterol	0.2 (0.003 to 0.5)	0.1 (-0.02 to 0.6)	0.5 (0.04 to 2)
Glycemia	0.1 (0.003 to 0.4)	0.1 (-0.02 to 0.6)	0.5 (0.04 to 2)
γ-radiation dose	0.1 (-0.1† to 0.5)	0.1 (-0.02 to 0.6)	0.6 (0.1 to 2)
Fully adjusted	0.1 (-0.1 to 0.3)	0.1 (-0.03 to 0.5)	0.5 (0.04 to 2)

*Adjusted for matching variables (attained age, gender, birth cohort, socio-professional status).
Relative biological effectiveness (RBE) of 1 and lag period of 0 years were assumed.
† Wald-based method.
BMI, body mass index; BP, blood pressure; CI, confidence intervals; CSD, circulatory diseases; CVD, cerebrovascular diseases; EOR, excess odds ratio; IHD, ischemic heart diseases.

5.3. Discussion

In this study, we examined the effects of individually estimated internal uranium doses on CSD mortality in a nested case-control study of French AREVA NC Pierrelatte uranium processing workers. Our results showed a positive but imprecise association between cumulative uranium dose and mortality from CSD, IHD, and CVD adjusted for individual life-style risk factors, and external γ-radiation dose.

5.3.1. Strengths and limitations

5.3.1.1. Study design

The nested case-control study design—that uses incidence density sampling and individual matching—constitutes a pertinent approach to analyze the dose-response relationship while controlling for major confounders.

The incidence density procedure allowed sampling controls longitudinally as attained age augments (Richardson, 2004; Vandenbroucke & Pearce, 2012); thus, sampling of controls happens at the same time as a case occurs. Exposure assessment is based on data before the case arose (Tager, 2000), minimizing the possible selection bias. Because incidence density

sampling is proportional to person-time accumulated by persons at risk of disease during the follow-up, the EOR in our study closely approximates the ERR that can be estimated from the cohort. Matching on gender, birth cohort, and socio-professional status was used to control for confounding by these factors efficiently. To avoid residual confounding, statistical models were systematically adjusted for matching variables.

However, the construction of the nested case-control dataset in this study may have resulted in several drawbacks[8]:

- Drop of certain (non-informative) risk sets during analysis
- Sampling of the same individuals several times
- Loss of efficiency due to over-matching

Drop of non-informative risk sets

A drop in informative risk sets occurred because of exclusion of cases without controls, similar exposure information or missing data on confounders. For example, EOR estimates for CSD mortality risk in fully-adjusted models were based on 98 (out of 102) informative risk sets because of missing data for some variables (complete case analysis). It may have thus resulted in lower precision of risk estimates.

Sampling of the same individuals several times

Risk set sampling of controls was performed at random without replacement (Breslow & Day, 1987), allowing for individuals to participate in different risk sets. The high proportion of individuals sampled several times for different risk sets may have decreased variability. Furthemore, a particularity of occupational medical data in our study is that information is censored at the end of employment because workers did not have registered medical visits after the end of employment. Thus, the same workers participating in different risk sets may have had the same information on confounding variables reducing again variability.

Loss of efficiency due to over-matching

The loss of statistical power occurred because of matching on many potential confounders (Breslow & Day, 1980). It may have made cases and controls very similar regarding their exposure. For example, it would have been more appropriate to adjust for socio-professional

[8] Based on L.B. Zablotska's lecture "Case-control and other less commonly used observational study designs". UCSF, School of Medicine, Department of Epidemiology and Biostatistics. 2015.

status than to match on it. Over-matching also lead to a reduction in the number of controls: on average there were 4 cases per control instead of 5 controls per case as initially expected. Nine cases were excluded due to unmatched combinations.

The use of countermatching designs (Bernstein *et al*, 2004; Drubay, 2015) in future studies may help to gain efficiency and to increase precision of the risk estimates (Tager, 2000).

5.3.1.2. Statistical power

The main limitatation of our study is its limited statistical power due to the small size of the AREVA NC Pierrelatte cohort, the small number of CSD cases, and the small range of internal uranium doses. An attempt was made during the design stage to increase the statistical power by matching each case with up to five controls, but it was only achievable for 70 cases.

Statistical power estimation has been performed with POWER software (Garcia-Closas & Lubin, 1999). A test was based on a linear trend for four categories of cumulative uranium lung dose: <0.01 (25 exposed controls), 0.01-0.9 (133 exposed controls), 1-5 (71 exposed controls), and >5 mGy (12 exposed controls). The power to detect an OR of 1.5 between the lowest and the highest categories was only 20%. The power was only 65% to detect an OR of 2.4 (as observed in our study, Table 27), and only OR of at least 3 could be detected with a power of 85%.

Conversely, the observation of a significant linear EOR/mGy for CSD mortality is surprising in a context of limited statistical power and should be considered cautiously. Our results should be considered preliminary, and larger national and international studies should be undertaken for detailed risk assessment (Laurent *et al*, 2015).

5.3.1.3. Exposure assessment

Due to limitations of previous studies (Guseva Canu *et al*, 2008; Zhivin *et al*, 2014), particular attention was given to estimation of individual uranium organ-specific doses. An important part of my PhD project was to collaborate with internal dosimetrists to establish a dosimetry protocol.

Use of absorbed lung dose

As recommended by the ICRP, we estimated annual absorbed doses rather than equivalent radiation doses (ICRP, 2007). Majority of recent dose estimations within internal radiation workers followed this recommendation (Anderson *et al*, 2015; Anderson *et al*, 2012; Boice Jr *et al*, 2006; Rage *et al*, 2012). Annual organ-specific absorbed doses partitioned into low- and high-LET components will be calculated for the US DOE nuclear workers included in the one million worker study (Bouville *et al*, 2015). In our study, we did not perform analyses with different components of absorbed dose because the high-LET component largely dominated. In fact, only five workers were monitored for exposure to cesium and other fission products, primarily low-LET radiation sources. The latter dose (mean cumulative cesium lung dose=0.2 mGy) was summed with the uranium dose.

We used lung dose rather than heart dose in our analyses. The heart is not a specific retention site of uranium according to its biokinetic model. On the other hand, insoluble uranium particles deposited in the lungs, which are only partly dissolved and absorbed to the blood a long time after inhalation, will cause increased irradiation of the lungs and LN as compared to the rest of the body. It was therefore more likely that possible mechanism will be the induction of atherosclerosis because of inflammation reactions in the lungs. Athough we tried to fit statistical models with heart dose, they did not converge, probably due to their very low range (0-0.3 mGy). High correlation between internal doses was the additional factor in favor of using the lung dose in statistical analyses.

Internal dose uncertainties

Our study was a basis to assess sensitivity of the dose estimates to the different uncertainty sources in the European project CURE. It was shown that primary sources of internal dose uncertainties are: choice of uranium solubility (pulmonary absorption type), use of bioassay data below LOD, and, to a lesser extent, the choice of exposure regime (acute vs. chronic) (Giussani *et al*, 2014). That was a reason to incorporate solubility parameters into the dose estimation of our study. To account for bioassay data below LOD, internal doses were estimated, and subsequent analyses were performed using two dosimetry scenarios (Chapter 5.2.2.4). It should be noted that apart from sensitivity analyses, we did not use any specific statistical tool to account for dosimetric uncertainty; characterization and propagation of uncerties into risk estimates is planned in the future international study of nuclear fuel cycle workers study (Laurent *et al*, 2015).

5.3.1.4. Circulatory disease risk factors

An important strength of our study is data collection on classical life-style CSD risk factors (smoking, BP, BMI, total cholesterol, and glycemia). Other lipid fractions, such as HDL and LDL, were not considered due to their rare abundance in medical files (Garsi *et al*, 2014).
As expected, all of the considered risk factors, and external γ-radiation dose were positively associated with CSD mortality, albeit generally associated with large confidence intervals. Precision of statistical analyses may have been affected by measurement errors, misclassification, our choice of categorization of CSD risk factors, and small sample size.

Measurement error

BP measurements are a typical example of a measurement error. In fact, to obtain an accurate BP measurement, a physician should follow a detailed protocol: patient should remove all clothing covering the cuff placement, be comfortably seated with legs uncrossed, and back and arm supported (Pickering *et al*, 2005). To have high predictive power, it is recommended that at least two measurements are obtained with a minimum of five minutes between readings (Pickering *et al*, 2005). Such strict protocols are rarely followed in uncontrolled clinical settings. For example, performing only one BP measurement may well have increased the risk of finding elevated BP due to the stress associated with a medical visit (the so called "white-coat hypertension"). To reduce a number of stress-associated measurements we used non-classical thresholds to define hypertension: more than 150 mmHg for systolic or more 90 mmHg for diastolic BP. A similar strategy was reported elsewhere (Azizova *et al*, 2015a; Drubay *et al*, 2015).

Misclassification

Misclassification occurred because medical follow-ups were done by different physicians and spanned over more than 50 years. The frequency of medical visits in the French nuclear industry was conditioned by the exposure level. It is thus more likely that more health problems may have been reported in exposed individuals.

Smoking information was certainly affected by clinical practice in different time periods, related to the S. Veil's law in 1976 (the first official French policy against smoking that limited advertisement to written sources and a number of places to buy cigarettes, and health labelling caution on cigarette packages), and the L. Évin law in 1991 (prohibited any

advertisements or smoking in public areas). The absence of physician sensibilization before 1976 may explain the high percentage of missing data and limited information on smoking in early years.

BMI was the only available variable to define obesity in our study; however, the current literature has shown that the waist-hip ratio is the most accurate and sensitive indication of obesity (Yusuf *et al*, 2004). BMI can overestimate obesity by more than 5% compared with waist-hip ratio (Dalton *et al*, 2003), probably by not properly distinguishing muscular and overweight persons.

Choice of categorization

In the field of radiation epidemiology, only few studies attempted to account for a history of medical observations in their statistical analyses. For example, information was collected at baseline for a sub-sample of A-bomb survivors (Shimizu *et al*, 2010; Takahashi *et al*, 2012), and at pre-employment visits for Russian Mayak workers (Azizova *et al*, 2015a).

In our study, categorization was based on a maximum value of all measurements recorded before the censor date (latest information for cases and attained age of index cases for controls). However, the choice of this method probably did not account for antihypertensive and anticholesterol treatments occurred through the occupational medical monitoring. Information on such treatments was rarely present in the medical files. An epidemiological study performed in 1972 noted a small proportion of workers treated for hypertension at Pierrelatte (HCL, 1972). Due to complexities of BP longitudinal profiles, it was not possible to classify workers as definitively treated or untreated (data not shown).

Further work is planned to explore temporal relationships between BP, cholesterol and radiation exposure. In the future, the development of the national health insurance database SNIIRAM (*Système National d'Informations Inter-Régimes de l'Assurance Maladie*) should allow extracting treatment information. This database covers 96% of the general French population from 2003 onwards (Moulis *et al*, 2015). This detail complicates using the SNIIRAM in retrospective epidemiological studies.

5.3.2. Dose-response analyses

The ERR/mGy estimates adjusted for all CSD risk factors and external γ-radiation for all CSD (0.2, 95% CI 0.004 to 0.5) in our study were identical to IHD (0.2, 95% CI -0.01 to 1), but lower compared with CVD (0.7, 95% CI 0.1 to 3) (Table 27). Similar findings were observed in a cohort of Russian Mayak workers (Azizova *et al*, 2015a; Azizova *et al*, 2015b; Azizova *et al*, 2014). Nevertheless, due to limited number of cases in our study, the difference in risk estimates between CSD, IHD, and CVD observed in our study should be further investigated in larger studies.

5.3.2.1. Results based on job-exposure matrix

Previous analysis of the relationship between internal uranium exposure and CSD mortality was based on JEM exposure scores (Guseva Canu *et al*, 2012). Analysis based on JEM exposure scores within the nested case-control study confirmed an increase of CSD mortality after adjusting for CSD risk factors. The most increased AOR (per step of JEM exposure score) were observed for exposure to natural (1.07, 95% CI 1.00 to 1.14) and reprocessed (1.22, 95% CI 0.91 to 1.35) insoluble uranium compounds (J.-P.Garsi, personal communication of unpublished data).

We did not have objectives to compare results based on JEM exposure scores, and internal uranium dose. The advantage of internal uranium dose is that it is based on individual monitoring data and allows production of a single risk estimate. However, a persistence of the association between uranium exposure (based either on JEM or internal uranium dose) and CSD mortality risk is noticeable.

5.3.2.2. Comparison with previous studies

Our study was among the first studies of nuclear fuel cycle workers that incorporated CSD risk factors. The relationship between CSD mortality and radiation persisted after adjustment for risk factors, as observed in studies of Japanese A-bomb survivors (Shimizu *et al*, 2010; Takahashi *et al*, 2012), Russian Mayak workers (Azizova *et al*, 2015a; Azizova *et al*, 2015b; Azizova *et al*, 2014), and French uranium miners (Drubay *et al*, 2015).

The presentation below compares the level of uranium dose, and magnitude of risk estimates with other studies of nuclear fuel cycle workers.

Internal uranium dose

Table 31 compares the level of internal uranium doses in the recent studies of nuclear fuel cycle workers. Cumulative doses were generally lower than 1 mGy (Table 31). Dose estimates in our study were generally comparable with other studies. Similarly to our study (see Table 21), the issue of small dose range was also present in other populations (for example, 0.1-5.9 mGy in Rage et al. 2012).

Table 31. Internal uranium dose estimations in studies of nuclear fuel cycle workers

Reference	N of workers	Study design	Organ dose	Mean dose (mGy)	Outcome
French studies					
Our study	518	CC	Lung	cases=1, controls=0.7	CSD
(Guseva Canu *et al*, 2010)	30	C	Lung	4.49	NA
(Rage *et al*, 2012)	3,377	C	Lung	1	Lung cancer
US studies					
(Yiin *et al*, 2009)	588	CC	RBM	cases=0.026, controls=0.012	MM
(Anderson *et al*, 2012)	6,409	C	Lung	1.1*	Lung and other cancers
(Anderson *et al*, 2015)	29,303	C	Lung	0.04*	NA
Combined study (UK, France, Belgium)					
α-risk study‡	1,893	CC	Lung	cases=0.24, controls=0.12*†	Lung cancer

*Median.
†For French workers.
‡Preliminary results, analyses in progress (Tirmarche *et al*, 2009; Grellier *et al*, in preparation).
C, cohort study; CC, case-control study; CSD, circulatory diseases; MM, multiple myeloma; NA, not available; RBM, red bone marrow.

None of the studies presented in Table 31 analyzed CSD mortality risk. However, the ERR/Gy estimates for lung cancer were elevated and very imprecise: 503.2 (95% CI 121.5 to 1225.0) in the French uranium miners cohort based on a dose from LLR in ore dust (Rage *et al*, 2012), and 22 (95% CI -9.3 to 70) in US Fernald Feed Materials Production Center workers based on internal uranium dose (Silver *et al*, 2013). In the α-risk study the risk estimates for uranium dose (ERR/Gy=4.18, 95% CI -2.91 to 19.21) was lower than that for total uranium and plutonium dose (ERR/Gy=10.33, 95% CI 0.62 to 26.34) (Grellier *et al*, in preparation).

Risk estimates

Table 32 presents the ERR/Gy estimates in major epidemiological studies that assessed CSD mortality risk. For comparison purposes all estimates were rescaled to the ERR/Gy (Table

32). A recent meta-analysis of populations exposed to external γ-radiation (Little *et al*, 2012a) was not included in Table 32 because it only estimated ERR for CSD subtypes, namely IHD and CVD.

Table 32. Estimates of the excess relative risk per unit dose (ERR/Gy) of circulatory diseases (CSD) in major recent epidemiological studies

Study	Reference	Dose indicator	Dose to	Cases	ERR/Gy (95%CI)
Our study		Int U	Lung	102	200 (4 to 500)
Moderate to high-dose					
Japanese A-bomb survivors	(Ozasa *et al*, 2012; Shimizu *et al*, 2010)	Ext	Colon	19,054	0.11 (0.05 to 0.17)[*]
Russian Chernobyl liquidators	(Ivanov *et al*, 2006)	Ext	Whole body	32,189	0.18 (-0.03 to 0.39)[*]
Russian Mayak workers	(Azizova *et al*, 2015a)	Int Pu	Liver	3782	0.27 (0.12 to 0.48)
Russian Techa river population	(Krestinina *et al*, 2013)	Int fission products	Muscles	7595	0.13 (-0.16 to 0.46)[‡]
Canadian fluoroscopy patients	(Zablotska *et al*, 2014)	Ext	Lung	6580	0.02 (-0.025 to 0.074)
US fluoroscopy patients	(Little *et al*, 2015)	Ext	Thyroid/Lung/RBM	3221	-0.023 (-0.067 to 0.028)
Low-dose studies					
International nuclear workers	(Vrijheid *et al*, 2007)	Ext	Lung	8412	0.09 (-0.43 to 0.70)[*]
UK BNFL workers	(McGeoghegan *et al*, 2008)	Ext	Whole body	5319	0.65 (0.36 to 0.98)[*†]
UK National Registry for Radiation Workers	(Muirhead *et al*, 2009)	Ext	Whole body	12,265	0.25 (0.03 to 0.49)[*†]
French AREVA-CEA-EDF workers	(Metz-Flamant *et al*, 2013)	Ext	Whole body	1468	0.31 (-0.90 to 1.74)[*†]
French uranium miners	(Rage *et al*, 2015)	Ext	Whole body	442	-0.02 (-0.14 to 0.17)
German uranium miners	(Kreuzer *et al*, 2013)	Ext	Whole body	9039	-0.13 (-0.38 to 0.12)[*]

[*] Radiation unit is Sv.
[†] 90% CI.
CI, confidence interval; ERR, excess relative risk.

Risk estimates in our study do not seem similar to other studies, after rescaling to ERR/Gy (Table 32), and therefore less transferable to other exposed populations with different dose range. Similarly high risk estimates were observed in studies of nuclear fuel cycle workers (Rage *et al*, 2012; Silver *et al*, 2013). It should be noted that the majority of previous studies were mainly based on populations exposed to external γ-radiation with large range of doses (Table 32).

The Russian Mayak worker study, that used unweighted internal plutonium doses, estimated the ERR/Gy of 0.27 (95% CI 0.12 to 0.48). This estimate decreased and became non-significant after adjustment for external γ-radiation (Azizova *et al*, 2015a).

When we performed analyses with radiation-weighted (RBE=20) absorbed dose, the risk estimates droped but still were high (ERR/Gy-Eq=10 (95% CI 1 to 30) with wide confidence intervals and not comparable with studies of external γ-radiation (Table 29). Nevertheless, it

was noticeable that this weighted estimate in our study was identical to that of external γ-radiation (ERR/mGy=0.01, 95% CI -0.01 to 0.08).

As expected, application of dosimetry scenario 2 had a very important impact on risk estimates. It is an indication of uncertainty associated with below LOD measurements. In fact, our risk estimate of CSD mortality decreased by 50% and became non-significant (ERR/mGy=0.1, 95% CI -0.1 to 0.3), as compared with dosimetry scenario 1 (ERR/mGy=0.2, 95% CI 0.004 to 0.5). Although the treatment of below LOD data differed in our and in the Mayak study (Azizova *et al*, 2015b), both studies found an impact of these data on risk estimates. Further research is needed to understand the exact impact of uncertainty sources associated with internal dose estimation.

5.4. Conclusions

In conclusion, our study was implemented to verify previous association between CSD mortality and internal uranium exposure suggested in the cohort study of AREVA NC Pierrelatte workers (Guseva Canu *et al*, 2012). This is the first analysis of CSD mortality with relation to individually estimated internal uranium dose. The relationship between mortality and internal uranium dose was not substantionally confounded by CSD risk factors, as was observed in studies of Japanese A-bomb survivors, Russian Mayak workers, and French uranium miners. Estimated doses due to uranium were particularly low. This led to a very high estimated EOR/Gy, not coherent with those observed in previous studies. The EOR estimate was associated with wide CI, reflecting the limited statistical power, and must be interpreted with caution.

It is planned that the relationship between CSD and internal uranium exposure will be further explored in the national French cohort of nuclear fuel cycle workers, and in the combined studies of European uranium workers. Because the mechanisms of possible excess CSD risk are unknown, further investigation of temporal trends of CSD risk factors and radiation could help to confirm or not confirm the indirect mechanism of the potential effect of radiation. Molecular epidemiological studies would be helpful to understand the possible processes implicated in the early effects of low-dose radiation and CSD.

Chapter 6. GENERAL DISCUSSION, PERSPECTIVES AND CONCLUSION

The magnitude of health risks is the major question of current radiation research when exposures are of low-level and delivered in a protracted manner (HLEG, 2009). Moreover, risks associated with intakes of radionuclides are of significant societal and scientific concern because of the potential for nuclear materials releases, nuclear accidents and terrorist attacks. Nuclear fuel cycle workers constitute one of the most appropriate populations for this research because of their long-term exposure to various uranium compounds and the availability of monitoring data (Cardis & Richardson, 2000; Cardis *et al*, 2001; Laurier *et al*, 2012).

While a strong consensus exists about the lung cancer risk following the inhalation of RDP in uranium miners, little is known about the health effects of various physicochemical forms of uranium in other groups of nuclear fuel cycle workers. A recent literature review, taking into account uncertainties of internal dose estimation, suggested that two further directions of work may be undertaken: (1) studies of sub-groups of workers employed in specific stages of the nuclear fuel cycle (uranium enrichment and fuel fabrication) because of their homogenous exposure to specific uranium compounds compared to the whole population of nuclear fuel cycle workers, and (2) dose-response analyses with improved internal dose estimation based on individual monitoring data and solubility profiles extracted from JEM (Zhivin *et al*, 2014).

Aforementioned actions were implemented in this PhD project while studying mortality due to cancerous and non-cancerous diseases in the French cohort of uranium enrichment workers, and CSD mortality in the nested case-control study of AREVA NC Pierrelatte workers.

In this chapter, I discuss the limitations and advantages of the work performed, and provide perspectives for future research.

6.1. Main inputs of the performed work

6.1.1. Impact of rapidly soluble uranium compounds on mortality

The population of uranium enrichment workers is the only sub-group of workers throughtout the nuclear fuel cycle where a homogenous exposure to rapidly soluble uranium compounds occurs. Gaseous diffusion was the only industrial-level method of enriching uranium in France until 2011. This was the main reason to study mortality within the French cohort of uranium enrichment workers, and to separate it from other groups of nuclear fuel cycle workers. A unique feature of this population is its very low external γ-radiation dose (mean=2.81 mGy compared to 16.1 mGy in the combined cohort of French nuclear workers (Metz et al. 2013)) due to uranium handling in its pure form, and the successful radiation protection system.

Both radiological and non-radiological hazards are prevalent in the nuclear industry (Zhivin *et al*, 2013). Consideration of different occupational exposures was rarely achievable in studies of nuclear workers (Zhivin *et al*, 2013). Thus, we assessed exposure to both radiological (uranium and external γ-radiation) and non-radiological (TCE, heat, noise) hazards. The use of a JEM allowed us to distinguish between various isotopic compositions of uranium (NU, EU, DU) and perform dose-response analyses by specific type of uranium.

The results within this cohort revealed a very strong HWE, an indication of important selection of workers prior to employment. In fact, only individuals after military service and with good parameters of cardiovascular system health were hired in the uranium enrichment field (P. Collomb, personal communication). A statistically significant SMR for pleural cancer suggested an exposure to asbestos prior to employment in uranium enrichment.

Non-radiological hazards were associated with similar magnitude of risk estimates, as compared with uranium exposure. Models that included both radiological and non-radiological hazard terms did not converge, suggesting a correlation between various exposures. Usual multiple models cannot be used in such situations and other more complicated biostatistical tools should be applied (Billionnet *et al*, 2012).

Except for a suggestive association with CSD, mortality was not associated with exposure to uranium and external γ-radiation exposure. This may be due to very low radiation exposure in this cohort. Due to limited statistical power, the follow-up of this cohort should be continued as only 21% of the cohort deceased. A biological explanation is that rapidly soluble uranium

compounds are effectively eliminated from the human body, not delivering important radiation doses to internal organs.

A rather surprising decreasing trend with increasing uranium exposure was observed for lung and LHP cancer. It should be considered very cautiously because of the absence of information on life-style confounders. However, a similar decreasing trend based on internal uranium dose and JEM exposure score was observed in US uranium enrichment workers (Chan *et al*, 2010; Figgs, 2013).

Risk estimates associated with exposure to EU and DU were similar to those of NU. The interpretation of these risk estimates, however, is not straight-forward because a majority of the workers were exposed to a mix of uranium compounds with different isotopic compositions. Moreover, these results were obtained within the Eurodif subcohort of 1,986 workers. The statistical power of this analysis was very limited because Eurodif workers were employed after 1976, and only 9% of workers were deceased at the end of the follow-up in 2008.

Because of its unique exposure and wealth of various occupational data, analyses within the cohort of French uranium enrichment workers provide essential information on health effects associated with exposure to rapidly soluble uranium compounds. A follow-up continuation, life-style factor data collection, and reanalysis after internal dose estimation are recommended. Contacts with foreign research teams in charge of studies of uranium enrichment workers will also be of interest to verify coherence of obtained results.

6.1.2. Relationship between circulatory disease mortality and internal uranium dose

Recent studies indicate that CSD mortality might be related to low-dose chronic external γ- and internal radiation exposure (Azizova *et al*, 2015a; Little *et al*, 2012a). More research is needed in this area and collection of information on confounding factors was called for (Little *et al*, 2012b).

A cohort study of the AREVA NC Pierrelatte workers suggested an increase in CSD mortality in relation to internal uranium exposure (Guseva Canu *et al*, 2012). Analyses were based on six types of cumulative uranium exposure scores from a JEM, and did not have data on CSD risk factors. This observation led to the implementation of a nested case-control study, in

order to estimate uranium absorbed radiation doses and to collect data on individual CSD risk factors.

Internal dose estimation is prone to significant uncertainties because of sensitive biokinetic and dosimetric models. Major uncertainties were identified to be: solubility, data below LOD, and exposure regime (Giussani *et al*, 2014). Large-scale studies usually use default parameters for biokinetic and dosimetric models. Such an approach does not allow deriving the most accurate dose estimates. A marked advantage of the internal dose assessment of our study was that in addition to individual monitoring data, information about solubility of uranium compounds was extracted from a JEM. Nevertheless, the level of estimated internal cumulative uranium dose was very low with a small range (mean lung dose=1 mGy, range=0-27 mGy; mean heart dose=0.01, range=0-0.3 mGy).

Because CSD are multifactorial diseases, analyses between CSD mortality risk and radiation exposure should be adjusted for personal risk factors. Thus, collection of major classical CSD risk factors is another advantage of our study. In fact, only three previous studies of Japanase A-bomb survivors, Russian Mayak workers, and French uranium miners managed to collect such data (Azizova *et al*, 2015a; Drubay *et al*, 2015; Shimizu *et al*, 2010).

Results of our study confirmed the previously observed association. They show an association between internal uranium dose and CSD mortality that is independent of impact of classical CSD risk factors and external γ-radiation, as it was not substantionally confounded by CSD risk factors. The level of risk estimate (after rescaling to Gy, ERR/Gy=200, 95% CI 4 to 500) was very high and not comparable with previous studies of populations exposed to external γ-radiation. This high risk magnitude is probably due to the very low level of estimated doses. Such a phenomenon has also been reported (Rage *et al*, 2012; Silver *et al*, 2013), but more research is needed to verify and to explain it.

Our study suggests that uranium exposure migh have an independent effect on CSD mortality. However, risk estimates and uncertainties associated with internal dose estimations are incredibly high. If confirmed, such associations may have important practical implications for radiation protection. For the moment, however, the results should be considered suggestive in a view of wide confidence intervals suggesting limited statistical power.

The internal dosimetry protocol developed in our study will be used for internal dose assessment in the TRACY cohort of 12,000 French nuclear workers. Further analyses within this and combined European cohorts of nuclear fuel cycle workers will help to refine our results. Collaboration between epidemiologists, internal dosimetrists, and biologists will allow

us to define uncertainties associated with different scenarios of exposure, and to clarify the nature of the relationship between CSD and radiation via molecular epidemiological studies.

6.2. Perspectives

6.2.1. TRACY cohort of French nuclear fuel cycle workers

Future dose-response analyses in the TRACY cohort, one of the largest European cohorts of nuclear fuel cycle workers with improved statistical power, are foreseen to further improve our understanfing of health effects after chronic uranium inhalation.

The TRACY cohort of nuclear fuel cycle workers comprises more than 12,000 workers employed at least six months between 1958 and 2006 by AREVA and CEA companies (Samson *et al*, 2014). Exposure assessment is realized by a dual approach combining individual monitoring data and plant-specific JEM to characterize physicochemical properties of uranium compounds and other non-radiological exposures. Longitudinal data (smoking, BMI, BP, lipid profils, blood count, inflammation markers) are being collected from medical files extracted from the occupational health departments since the 1960s.

Planned research within this cohort will include: internal dose assessment and impact of uncertainty, establishment of a cohort of fuel fabrication workers, and temporal relationships between uranium exposure and risk factors.

6.2.1.1. Internal dose assessment and impact of uncertainty

The internal dosimetry protocol developed during our study and the CURE project will be used to estimate organ-specific uranium doses in the TRACY cohort. An improvement was made to reduce uncertainty by considering solubility of uranium compounds. The analyses performed in this PhD project showed that impact of monitoring data below LOD is important: risk estimate decreased by 50% and became non-significant when below LOD values were set at the LOD (see Table 30). There is already a strong collaboration between IRSN epidemiologists and dosimetrists in the area of uncertainty evaluation among uranium miners (Allodji *et al*, 2012). This research will be further strengthened during uncertainty evaluations of nuclear fuel cycle workers in the frame of two future PhD projects.

6.2.1.2. Cohort of fuel fabrication workers

Analyses of the cohort of French uranium enrichment workers did not show a significantly increased mortality risk from lung cancer. By contrast to exposure to rapidly soluble uranium compounds during uranium enrichment, fuel fabrication workers are exposed to insoluble uranium compounds (UO_2). Insoluble uranium is more likely to remain in the lungs (ATSDR, 2012; ICRP, 1994). Thus, the main outcome of interest in this population is lung cancer, due to the possible protracted irradiation of the lung tissue. Lung cancer mortality will be analyzed in the combined cohort of French and Belgian fuel fabrication workers.

6.2.1.3. Temporal relationships between circulatory disease risk factors and uranium exposure

Our study established an association between CSD mortality risk and internal uranium dose. The current view is that low-dose radiation may act through inducing atherosclerosis (Kreuzer *et al*, 2015a; Little *et al*, 2008; Little *et al*, 2010). Recent studies suggested that radiation may damage kidney function (Adams *et al*, 2012; Sera *et al*, 2013), induce hypertension (Sasaki *et al*, 2002), and disrupt lipid metabolism (Wong *et al*, 1999b). Radiation exposure may also interact with anti-atherosclerotic drugs, reducing their efficiency (Hoving *et al*, 2010; Hoving *et al*, 2011). The wealth of longitudinal data collected during the medical follow-up of French nuclear fuel cycle workers will be essential to confirm or refute these hypotheses. Analyses of the temporal relationships between internal uranium dose, BP, and total cholesterol are planned in the near future.

6.2.2. Molecular epidemiologic studies

It is clear that classical epidemiological studies alone will not be strong enough to establish associations between exposure to very low-dose radiation and chronic diseases. Molecular epidemiological studies are on the rise in the radiation field because they could possibly explain pathological processes embedded in the development of chronic diseases (Kreuzer *et al*, 2015a; Pernot *et al*, 2014; Pernot *et al*, 2012). Nuclear fuel cycle workers are among the most promising populations because of job stability, individual monitoring data, and the possibility of collecting biological samples in a prospective manner (Kreuzer *et al*, 2015a; Pernot *et al*, 2012). Protocols of pilot studies among French and Czech nuclear workers are now in a preparation (Laurent *et al*, 2015).

6.3. Conclusion

Because of the omnipresence of uranium, more data are needed to assess potential health effects associated with this exposure. Nuclear fuel cycle workers are the gold-standard population for studying chronic low-dose uranium exposure. The interpretation of results from previous studies of this population was hindered by limitations of exposure assessment, non-consideration of uranium physicochemical properties, limited statistical power, and non-consideration of confounding factors.

In this PhD work, we attempted to handle some of the limitations by establishing the cohort of French uranium enrichment workers to study health effects of rapidly soluble uranium compounds, and by studying CSD mortality in relationship with accurately assessed internal uranium dose in the nested case-control study of AREVA NC Pierrelatte workers. Exposure to rapidly soluble uranium compounds was not significantly associated with any cause of mortality. The relationship between CSD mortality and internal uranium dose was not confounded by CSD risk factors and external γ-radiation, but was surprisingly high in magnitude and associated with large uncertainties.

Low-level uranium exposure and the small number of workers were the key explanations of the limited statistical power of our work. Future analyses of the larger French cohort TRACY and development of international combined studies of nuclear fuel cycle workers, accompanied with molecular epidemiological studies, will help to refine possible associations between chronic uranium exposure and risk of health effects.

BIBLIOGRAPHY

Abou-Donia MB, Dechkovskaia AM, Goldstein LB, Shah DU, Bullman SL, Khan WA (2002) Uranyl acetate-induced sensorimotor deficit and increased nitric oxide generation in the central nervous system in rats. *Pharmacol Biochem Behav* **72**(4)**:** 881-90

Abramson JH (2011) WINPEPI updated: Computer programs for epidemiologists, and their teaching potential. *Epidemiol Perspect Innov* **8**(1):1

Adams MJ, Grant EJ, Kodama K, Shimizu Y, Kasagi F, Suyama A, Sakata R, Akahoshi M (2012) Radiation dose associated with renal failure mortality: a potential pathway to partially explain increased cardiovascular disease mortality observed after whole-body irradiation. *Radiat Res* **177**(2)**:** 220-8

AGIR (2010) *Advisory Group on Ionising Radiation. Circulatory Disease Risk, Report of the Independent Advisory Group on Ionising Radiation*. Health Protection Agency: London

Allodji RS, Leuraud K, Thiebaut AC, Henry S, Laurier D, Benichou J (2012) Impact of measurement error in radon exposure on the estimated excess relative risk of lung cancer death in a simulated study based on the French Uranium Miners' Cohort. *Radiat Environ Biophys* **51**(2)**:** 151-63

Alpen EL (1998) *Radiation Biophysics*, 2nd edition. Elsevier: Netherlands

Anderson JL, Apostoaei AI (2015) Method for analyzing left-censored bioassay data in large cohort studies. *J Expo Sci Environ Epidemiol* **13**(10)**:** 36

Anderson JL, Apostoaei AI, Yiin JH, Fleming DA, Tseng CY, Chen PH (2015) Internal Exposure to Uranium in a Pooled Cohort of Gaseous Diffusion Plant Workers. *Radiat Prot Dosimetry* **24**, doi: 10.1093/rpd/ncv357

Anderson JL, Daniels RD, Fleming DA, Tseng CY (2012) Exposure assessment for a cohort of workers at a former uranium processing facility. *J Expo Sci Environ Epidemiol* **22**(4)**:** 324-330

Ansoborlo E, Chazel V, Hengé-Napoli MH, Pihet P, Rannou A, Bailey MR, Stradling N (2002) Determination of the physical and chemical properties, biokinetics, and dose coefficients of uranium compounds handled during nuclear fuel fabrication in France. *Health Phys* **82**(3)**:** 279-289

ATSDR (2012) *Agency for Toxic Substances and Disease Registry. Toxicological Profile of Uranium*. CDC: Atlanta

Avtandilashvili M, Puncher M, McComish SL, Tolmachev SY (2015) US Transuranium and Uranium Registries case study on accidental exposure to uranium hexafluoride. *J Radiol Prot* **35**(1)**:** 129-151

Azizova TV, Grigorieva ES, Hunter N, Pikulina MV, Moseeva MB (2015a) Risk of mortality from circulatory diseases in Mayak workers cohort following occupational radiation exposure. *J Radiol Prot* **35**(3)**:** 517-538

Azizova TV, Grigoryeva ES, Haylock RG, Pikulina MV, Moseeva MB (2015b) Ischaemic heart disease incidence and mortality in an extended cohort of Mayak workers first employed in 1948-1982. *Br J Radiol* **27**, doi: 10.1259/bjr.20150169

Azizova TV, Haylock RG, Moseeva MB, Bannikova MV, Grigoryeva ES (2014) Cerebrovascular diseases incidence and mortality in an extended Mayak Worker Cohort 1948-1982. *Radiat Res* **182**(5)**:** 529-44

Baysson H, Laurier D, Tirmarche M, Valenty M, Giraud JM (2000) Epidemiological response to a suspected excess of cancer among a group of workers exposed to multiple radiological and chemical hazards. *Occup Environ Med* **57**(3)**:** 188-194

Beau PG, Chalabreysse J (1989) Knowledge gained from bioassay data on some metabolic and toxicological features of uranium hexafluoride and its degradation products. *Radiat Prot Dosimetry* **26**(1-4)**:** 107-112

Bensoussan H, Grancolas L, Dhieux-Lestaevel B, Delissen O, Vacher CM, Dublineau I, Voisin P, Gourmelon P, Taouis M, Lestaevel P (2009) Heavy metal uranium affects the brain cholinergic system in rat following sub-chronic and chronic exposure. *Toxicology* **261**(1-2)**:** 59-67

Bernstein JL, Langholz B, Haile RW, Bernstein L, Thomas DC, Stovall M, Malone KE, Lynch CF, Olsen JH, Anton-Culver H, Shore RE, Boice JD, Jr., Berkowitz GS, Gatti RA, Teitelbaum SL, Smith SA, Rosenstein BS, Borresen-Dale AL, Concannon P, Thompson WD (2004) Study design: evaluating gene-environment interactions in the etiology of breast cancer - the WECARE study. *Breast Cancer Res* **6**(3)**:** 9

Berradi H, Bertho JM, Dudoignon N, Mazur A, Grandcolas L, Baudelin C, Grison S, Voisin P, Gourmelon P, Dublineau I (2008) Renal anemia induced by chronic ingestion of depleted uranium in rats. *Toxicol Sci* **103**(2)**:** 397-408

Bianchi C, Giarelli L, Grandi G, Brollo A, Ramani L, Zuch C (1997) Latency periods in asbestos-related mesothelioma of the pleura. *Eur J Cancer Prev* **6**(2)**:** 162-166

Billionnet C, Sherrill D, Annesi-Maesano I (2012) Estimating the health effects of exposure to multi-pollutant mixture. *Ann Epidemiol* **22**(2)**:** 126-41

Boice JD, Jr. (2014) The importance of radiation worker studies. *J Radiol Prot* 34(3):E7-12.

Boice Jr JD, Cohen SS, Mumma MT, Chadda B, Blot WJ (2007) Mortality among residents of Uravan, Colorado who lived near a uranium mill, 1936-84. *J Radiol Prot* **27**(3)**:** 299-319

Boice Jr JD, Cohen SS, Mumma MT, Chadda B, Blot WJ (2008) A cohort study of uranium millers and miners of Grants, New Mexico, 1979-2005. *J Radiol Prot* **28**(3)**:** 303-325

Boice Jr JD, Leggett RW, Ellis ED, Wallace PW, Mumma M, Cohen SS, Brill AB, Chadda B, Boecker BB, Yoder RC, Eckerman KF (2006) A comprehensive dose reconstruction methodology for former Rocketdyne/Atomics International radiation workers. *Health Phys* **90**(5)**:** 409-430

Bosch de Basea M, Pearce MS, Kesminiene A, Bernier MO, Dabin J, Engels H, Hauptmann M, Krille L, Meulepas JM, Struelens L, Baatout S, Kaijser M, Maccia C, Jahnen A, Thierry-Chef I, Blettner M, Johansen C, Kjaerheim K, Nordenskjold A, Olerud H, Salotti JA, Andersen TV, Vrijheid M, Cardis E (2015) EPI-CT: design, challenges and epidemiological methods of an international study on cancer risk after paediatric and young adult CT. *J Radiol Prot* **35**(3)**:** 611-628

Bouville A, Toohey RE, Boice JD, Jr., Beck HL, Dauer LT, Eckerman KF, Hagemeyer D, Leggett RW, Mumma MT, Napier B, Pryor KH, Rosenstein M, Schauer DA, Sherbini S, Stram DO, Thompson JL, Till JE, Yoder C, Zeitlin C (2015) Dose reconstruction for the million worker study: status and guidelines. *Health Phys* **108**(2)**:** 206-20

Breslow NE, Day NE (1980) *Statistical Methods in Cancer Research. Volume I - The Analysis of Case-Control Studies*. International Agency for Research on Cancer (IARC): Lyon

Breslow NE, Day NE (1987) *Statistical Methods in Cancer Research. Volume II - The Design and Analysis of Cohort Studies.* International Agency for Research on Cancer (IARC): Lyon

Bussy C, Lestaevel P, Dhieux B, Amourette C, Paquet F, Gourmelon P, Houpert P (2006) Chronic ingestion of uranyl nitrate perturbs acetylcholinesterase activity and monoamine metabolism in male rat brain. *Neurotoxicology* **27**(2)**:** 245-52

Canu IG, Cardis E, Metz-Flamant C, Caër-Lorho S, Auriol B, Wild P, Laurier D, Tirmarche M (2010) French cohort of the uranium processing workers: Mortality pattern after 30-year follow-up. *Int Arch Occup Environ Health* **83**(3)**:** 301-308

Canu IG, Ellis ED, Tirmarche M (2008) Cancer risk in nuclear workers occupationally exposed to uranium-emphasis on internal exposure. *Health Phys* **94**(1)**:** 1-17

Canu IG, Jacob S, Cardis E, Wild P, Caër S, Auriol B, Garsi JP, Tirmarche M, Laurier D (2011) Uranium carcinogenicity in humans might depend on the physical and chemical nature of uranium and its isotopic composition: Results from pilot epidemiological study of French nuclear workers. *Cancer Causes Control* **22**(11)**:** 1563-1573

Cardis E, Richardson D (2000) Invited editorial: health effects of radiation exposure at uranium processing facilities. *J Radiol Prot* **20**(2)**:** 95-7

Cardis E, Richardson D, Kesminiene A (2001) Radiation risk estimates in the beginning of the 21st century. *Health Phys* **80**(4)**:** 349-61

Challeton-de Vathaire C (2013) *Etude cas-témoin de mortalité par cancers du poumon et par leucémies chez les travailleurs du nucléaire exposés au plutonium et/ou à l'uranium : procédures d'estimation dosimétrique pour la cohorte française (projet européen alpha-risk, WP3).* Rapport PRP-HOM/SDI-2013-08. IRSN: Fontenay-aux-Roses

Chan C, Hughes TS, Muldoon S, Aldrich T, Rice C, Hornung R, Brion G, Tollerud DJ (2010) Mortality patterns among Paducah Gaseous Diffusion Plant Workers. *J Occup Environ Med* **52**(7)**:** 725-732

Chazel V, Houpert P, Ansoborlo E, Henge-Napoli MH, Paquet F (2000) Variation of solubility, biokinetics and dose coefficient of industrial uranium oxides according to specific surface area. *Radiat Prot Dosimetry* **88**(3)**:** 223-231

Checkoway H, Eisen EA (1998) Developments in occupational cohort studies. *Epidemiol Rev* **20**(1)**:** 100-111

Checkoway H, Pearce N, Crawford-Brown DJ, Cragle DL (1988) Radiation doses and cause-specific mortality among workers at a nuclear materials fabrication plant. *Am J Epidemiol* **127**(2)**:** 255-266

Checkoway H, Pearce N, Kriebel D (2004) *Research Methods in Occupational Epidemiology*. Oxford University Press: Oxford

Cragle DL, McLain RW, Qualters JR, Hickey JLS, Wilkinson GS, Tankersley WG, Lushbaugh CC (1988) Mortality among workers at a nuclear fuels production facility. *Am J Ind Med* **14**(4)**:** 379-401

Dalton M, Cameron AJ, Zimmet PZ, Shaw JE, Jolley D, Dunstan DW, Welborn TA (2003) Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. *J Intern Med* **254**(6)**:** 555-63

Darby SC, Cutter DJ, Boerma M, Constine LS, Fajardo LF, Kodama K, Mabuchi K, Marks LB, Mettler FA, Pierce LJ, Trott KR, Yeh ET, Shore RE (2010) Radiation-related heart disease: current knowledge and future prospects. *Int J Radiat Oncol Biol Phys* **76**(3)**:** 656-65

Darby SC, Doll R, Gill SK, Smith PG (1987) Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. *Br J Cancer* **55**(2)**:** 179-90

Darby SC, Ewertz M, Hall P (2013) Ischemic heart disease after breast cancer radiotherapy. *N Engl J Med* **368**(26)**:** 2527

Davesne E, Blanchardon E (2014) Physico-chemical characteristics of uranium compounds: a review. *Int J Radiat Biol* **90**(11)**:** 975-88

Davesne E, Blanchin N, Chojnacki E, Touri L, Ruffin M, Blanchardon E, Franck D (2014) Collective dosimetry to distinguish occupational exposure to natural uranium from alimentary uranium background in bioassay measurements. *Int J Radiat Biol* **90**(11)**:** 1048-54

Diamond GL, Morrow PE, Panner BJ, Gelein RM, Baggs RB (1989) Reversible uranyl fluoride nephrotoxicity in the Long Evans rat. *Fundam Appl Toxicol* **13**(1)**:** 65-78

Doerfel H, Andrasi A, Bayley MR, Birchall A, Castellani CM, Hurtgen C, Jarvis N, Johansson L, Le Guen B, Tarroni G (2000) Third European intercomparison exercise on internal dose assessment.

Drubay D (2015) *[Analyse de la relation dose-réponse pour les risques de mortalité par cancer et par maladie d'appareil circulatoire chez les mineurs d'uranium], PhD dissertation.* Université Paris-Sud: Villejuif

Drubay D, Caer-Lorho S, Laroche P, Laurier D, Rage E (2015) Mortality from Circulatory System Diseases among French Uranium Miners: A Nested Case-Control Study. *Radiat Res* **183**(5)**:** 550-62

Dublineau I, Souidi M, Gueguen Y, Lestaevel P, Bertho JM, Manens L, Delissen O, Grison S, Paulard A, Monin A, Kern Y, Rouas C, Loyen J, Gourmelon P, Aigueperse J (2014) Unexpected lack of deleterious effects of uranium on physiological systems following a chronic oral intake in adult rat. *Biomed Res Int* **181989**(10)**:** 12

Dupree-Ellis E, Watkins J, Ingle JN, Phillips J (2000) External radiation exposure and mortality in a cohort of uranium processing workers. *Am J Epidemiol* **152**(1)**:** 91-95

Dupree EA, Cragle DL, McLain RW, Crawford-Brown DJ, Teta MJ (1987) Mortality among workers at a uranium processing facility, the Linde Air Products Company Ceramics Plant, 1943-1949. *Scand J Work Environ Health* **13**(2)**:** 100-107

Dupree EA, Watkins JP, Ingle JN, Wallace PW, West CM, Tankersley WG (1995) Uranium dust exposure and lung cancer risk in four uranium processing operations. *Epidemiology* **6**(4)**:** 370-375

Durante M (2014) New challenges in high-energy particle radiobiology. *Br J Radiol* **87**(1035)**:** 20130626

Durbin PW (2010) Actinides in animals and man. In *The chemistry of the actinide and transactinide elements*, Morss LR, Edelstein N, Fuger J, Katz JJ (eds), Chapter 31, pp 3339-3374. Springer: Netherlands

EC (2004) *European Commission Parliament and Council of the European Union. DIRECTIVE 2004/37/EC of 29 April 2004 on the protection of workers from the risk related to exposure to carcinogens or mutagens at work (sixth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC).* EC: Brussels

EC (2007) *European Commission Nuclear science and technology, Optimisation of monitoring for internal exposure (OMINEX).* EC: Brussels

EC (2013) *European Commission Radiation Protection No. 168. EU scientific seminar 2010 "Issues with internal emitters":* EC: Luxembourg

Etherington G, Birchall A, Puncher M, Molokanov A, Blanchardon E (2006) Uncertainties in doses from intakes of radionuclides assessed from monitoring measurements. *Radiat Prot Dosimetry* **121**(1)**:** 40-51

EURADOS (2013) *European Radiation Dosimetry Group, IDEAS guidelines for the estimation of committed doses from incorporation monitoring data*. EURADOS: Braunschweig

Feuardent J, Scanff P, Crescini D, Rannou A (2013) Occupational external exposure to ionising radiation in France (2005-2011). *Radiat Prot Dosimetry* **157**(4)**:** 610-8

Figgs LW (2013) Lung cancer mortality among uranium gaseous diffusion plant workers: a cohort study 1952-2004. *Int J Occup Environ Med* **4**(3)**:** 128-40

Fredrickson DS, Levy RI, Lees RS (1967) Fat transport in lipoproteins--an integrated approach to mechanisms and disorders. *N Engl J Med* **276**(1)**:** 34-42

Galle P (1997) *Toxiques nucléaires*. Masson: Paris

Gan WQ, Davies HW, Demers PA (2011) Exposure to occupational noise and cardiovascular disease in the United States: the National Health and Nutrition Examination Survey 1999-2004. *Occup Environ Med* **68**(3)**:** 183-90

Garcia-Closas M, Lubin JH (1999) Power and sample size calculations in case-control studies of gene-environment interactions: comments on different approaches. *Am J Epidemiol* **149**(8)**:** 689-92

Garsi JP, Samson E, Chablais L, Zhivin S, Niogret C, Laurier D, Guseva Canu I (2014) Half-century archives of occupational medical data on French nuclear workers: a dusty warehouse or gold mine for epidemiological research? *Arh Hig Rada Toksikol* **65**(4)**:** 407-16

Gazin V, Kerdine S, Grillon G, Pallardy M, Raoul H (2004) Uranium induces TNF alpha secretion and MAPK activation in a rat alveolar macrophage cell line. *Toxicol Appl Pharmacol* **194**(1)**:** 49-59

Gilman AP, Moss MA, Villeneuve DC, Secours VE, Yagminas AP, Tracy BL, Quinn JM, Long G, Valli VE (1998a) Uranyl nitrate: 91-day exposure and recovery studies in the male New Zealand white rabbit. *Toxicol Sci* **41**(1)**:** 138-51

Gilman AP, Villeneuve DC, Secours VE, Yagminas AP, Tracy BL, Quinn JM, Valli VE, Moss MA (1998b) Uranyl nitrate: 91-day toxicity studies in the New Zealand white rabbit. *Toxicol Sci* **41**(1)**:** 129-37

Giussani A, Ancelet S, Atkinson W, Bethel G, Bingham D, Blanchardon E, Bull R, Cockerill R, Davesne E, Fensske N, Grellier J, Hall J, Haylock R, Horngardt S, Kotik L, Laurent O, Laurier D, Marsh J, Nosske D, Puncher M, Rage E, Riddell T, Samaga D, Tomasek L (2014) *Task 5.8. "CURE project", Final report of the uncertainties working group (UWG).* BfS: Neuherberg

Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB (2014) Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation* **129**(3)**:** e28-e292

Gofman JW, Lindgren F (1950) The role of lipids and lipoproteins in atherosclerosis. *Science* **111**(2877)**:** 166-71

Grant EJ, Ozasa K, Ban N, de Gonzalez AB, Cologne J, Cullings HM, Doi K, Furukawa K, Imaoka T, Kodama K, Nakamura N, Niwa O, Preston DL, Rajaraman P, Sadakane A, Saigusa S, Sakata R, Sobue T, Sugiyama H, Ullrich R, Wakeford R, Yasumura S, Milder CM, Shore RE (2015) A report from the 2013 international symposium: the evaluation of the effects of low-dose radiation exposure in the life span study of atomic bomb survivors and other similar studies. *Health Phys* **108**(5)**:** 551-6

Gueguen Y, Rouas C, Leblond FA (2012) [Kidney injury biomarkers]. *Nephrol Ther* **8**(3)**:** 146-55

Guseva Canu I (2015) *[Regard pluridisciplinaire sur la notion de dose et sa determination en biologie, toxicologie et épidémiologie], Rapport de la habilitation à diriger des recherches (HDR).* Université Paris-Est: Créteil

Guseva Canu I, Faust S, Canioni P, Collomb P, Samson E, Laurier D (2013a) Attitude towards personal protective equipment in the French nuclear fuel industry. *Arh Hig Rada Toksikol* **64**(2)**:** 285-293

Guseva Canu I, Faust S, Knieczak E, Carles M, Samson E, Laurier D (2013b) Estimating historic exposures at the European Gaseous Diffusion plants. *Int J Hyg Environ Health* **216**(4)**:** 499-507

Guseva Canu I, Garsi JP, Caër-Lorho S, Jacob S, Collomb P, Acker A, Laurier D (2012) Does uranium induce circulatory diseases? First results from a French cohort of uranium workers. *Occup Environ Med* **69:** 404-409

Guseva Canu I, Laurier D, Caër-Lorho S, Samson E, Timarche M, Auriol B, Bérard P, Collomb P, Quesne B, Blanchardon E (2010) Characterisation of protracted low-level exposure to uranium in the workplace: A comparison of two approaches. *Int J Hyg Environ Health* **213**(4)**:** 270-277

Guseva Canu I, Molina G, Goldberg M, Collomb P, David JC, Perez P, Paquet F, Tirmarche M (2008) Development of a job exposure matrix for the epidemiological follow-up of workers in the French nuclear industry. Results of a pilot study. *Rev Epidemiol Sante Publique* **56**(1)**:** 21-29

Guseva Canu I, Paquet F, Goldberg M, Auriol B, Bérard P, Collomb P, David JC, Molina G, Perez P, Tirmarche M (2009) Comparative assessing for radiological, chemical, and physical exposures at the French uranium conversion plant: Is uranium the only stressor? *Int J Hyg Environ Health* **212**(4)**:** 398-413

Harrison J, Day P (2008) Radiation doses and risks from internal emitters. *J Radiol Prot* **28**(2)**:** 137-59

HAS (2013a) *Haute Autorité de Santé, Recommandation de bonne pratique, Surveillance médico-professionnelle de l'exposition interne aux radionucléides en installations nucléaires de base*. HAS: Paris

HAS (2013b) *Haute autorité de santé, Recommandation de bonne pratique. Stratégie médicamenteuse du contrôle glycémique du diabète de type 2*. HAS: Paris

HCL (1972) Hospices Civils de Lyon Premiers résultats de l'enquête du Professeur Froment. HCL: Lyon

Hines SE, Gucer P, Kligerman S, Breyer R, Centeno J, Gaitens J, Oliver M, Engelhardt S, Squibb K, McDiarmid M (2013) Pulmonary health effects in Gulf War I service members exposed to depleted uranium. *J Occup Environ Med* **55**(8)**:** 937-44

HLEG (2009) *High Level Expert Group, Report on European low dose risk research*. EC: Brussels

Hoving S, Heeneman S, Gijbels MJ, te Poele JA, Bolla M, Pol JF, Simons MY, Russell NS, Daemen MJ, Stewart FA (2010) NO-donating aspirin and aspirin partially inhibit age-related atherosclerosis but not radiation-induced atherosclerosis in ApoE null mice. *PLoS One* **5**(9)**:** 0012874

Hoving S, Heeneman S, Gijbels MJ, te Poele JA, Pol JF, Gabriels K, Russell NS, Daemen MJ, Stewart FA (2011) Anti-inflammatory and anti-thrombotic intervention strategies using atorvastatin, clopidogrel and knock-down of CD40L do not modify radiation-induced atherosclerosis in ApoE null mice. *Radiother Oncol* **101**(1)**:** 100-8

IAEA (2004) *International Atomic Energy Agency. Methods for assessing occupational radiation doses due to intakes of radionuclides, publication 37.* IAEA: Vienna

IARC (2014) *International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, volume 106. Trichloroethylene, tetrachloroethylene, and some other chlorinated agents.* IARC: Lyon

ICRP (1989) International Commission on Radiological Protection Age-dependent doses to members of the public from intake of radionuclides: Part 1. A report of a Task

Group Committee of the International Commission on Radiological Protection. *Ann ICRP* **20**(2)**:** 1-122

ICRP (1993) International Commission on Radiological Protection Age-dependent doses to members of the public from intake of radionuclides: Part 2. Ingestion dose coefficients. A report of a Task Group of Committee 2 of the International Commission on Radiological Protection. *Ann ICRP* **23**(3-4)**:** 1-167

ICRP (1994) *International Commission on Radiological Protection. Publication 66. Human Respiratory Tract Model for Radiological Protection*. Oxford: Pergamon Press

ICRP (1995) International Commission on Radiological Protection Age-dependent doses to members of the public from intake of radionuclides: Part 3. Ingestion dose coefficients. A report of a Task Group of Committee 2 of the International Commission on Radiological Protection. *Ann ICRP* **25**(1)**:** 1-74

ICRP (2002) International Commission on Radiological Protection. Basic anatomical and physiological data for use in radiological protection: reference values. ICRP Publication 89. *Ann ICRP* **32** (3/4)

ICRP (2006) Human alimentary tract model for radiological protection. ICRP Publication 100. A report of The International Commission on Radiological Protection. *Ann ICRP* **36**(1-2)**:** 25-327, iii

ICRP (2007) International Commission on Radiological Protection. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. *Ann ICRP* **37**(2-4)**:** 1-332

IRSN (2014) *Instutut de Radioprotection et de Sûreté Nucléaire. La radioprotection des travailleurs. Exposition professionnelle aux rayonnements ionisants : bilan 2013,Rapport PRP-HOM/2014-007.* IRSN: Fontenay-aux-Roses

Ivanov VK, Maksioutov MA, Chekin SY, Petrov AV, Biryukov AP, Kruglova ZG, Matyash VA, Tsyb AF, Manton KG, Kravchenko JS (2006) The risk of radiation-induced cerebrovascular disease in Chernobyl emergency workers. *Health Phys* **90**(3)**:** 199-207

Journy N, Rehel JL, Ducou Le Pointe H, Lee C, Brisse H, Chateil JF, Caer-Lorho S, Laurier D, Bernier MO (2015) Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France. *Br J Cancer* **112**(1)**:** 185-93

Kannel WB, Castelli WP, Gordon T, McNamara PM (1971) Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham study. *Ann Intern Med* **74**(1)**:** 1-12

Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes 3rd J (1961) Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. *Ann Intern Med* **55:** 33-50

Kannel WB, McGee D, Gordon T (1976) A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol* **38**(1)**:** 46-51

Karpov AB, Semenova YV, Takhauov RM, Litvinenko TM, Kalinkin DE (2012) The risk of acute myocardial infarction and arterial hypertension in a cohort of male employees of a Siberian Group of Chemical Enterprises exposed to long-term irradiation. *Health Phys* **103**(1)**:** 15-23

Krestinina LY, Epifanova S, Silkin S, Mikryukova L, Degteva M, Shagina N, Akleyev A (2013) Chronic low-dose exposure in the Techa River Cohort: risk of mortality from circulatory diseases. *Radiat Environ Biophys* **52**(1)**:** 47-57

Kreuzer M, Auvinen A, Cardis E, Hall J, Jourdain JR, Laurier D, Little MP, Peters A, Raj K, Russell NS, Tapio S, Zhang W, Gomolka M (2015a) Low-dose ionising radiation

and cardiovascular diseases--Strategies for molecular epidemiological studies in Europe. *Mutat Res Rev Mutat Res* **764:** 90-100

Kreuzer M, Dufey F, Laurier D, Nowak D, Marsh JW, Schnelzer M, Sogl M, Walsh L (2015b) Mortality from internal and external radiation exposure in a cohort of male German uranium millers, 1946-2008. *Int Arch Occup Environ Health* **88**(4)**:** 431-41

Kreuzer M, Dufey F, Sogl M, Schnelzer M, Walsh L (2013) External gamma radiation and mortality from cardiovascular diseases in the German WISMUT uranium miners cohort study, 1946-2008. *Radiat Environ Biophys* **52**(1)**:** 37-46

Kurttio P, Harmoinen A, Saha H, Salonen L, Karpas Z, Komulainen H, Auvinen A (2006) Kidney Toxicity of Ingested Uranium From Drinking Water. *Am J Kidney Dis* **47**(6)**:** 972-982

Kurttio P, Komulainen H, Leino A, Salonen L, Auvinen A, Saha H (2005) Bone as a possible target of chemical toxicity of natural uranium in drinking water. *Environ Health Perspect* **113**(1)**:** 68-72

Laurent O, Gomolka M, Haylock R, Blanchardon E, Giussani A, Atkinson WD, Baatout S, Bingham D, Cardis E, Hall J, Tomasek L, Laurier D (2015) *Task 5.8 CURE final report. D5.17: Report for an integrated (biology-dosimetry-epidemiology) research project on occupational uranium exposure*. IRSN: Fontenay-aux-Roses

Laurier D, Guseva Canu I, Baatout S, Bertho JM, Blanchardon E, Bouffler S, Cardis E, Gomolka M, Hall J, Kesminiene A, Kreuzer M, Rage E (2012) DoReMi workshop on multidisciplinary approaches to evaluating cancer risks associated with low-dose internal contamination. *Radioprotection* **47**(1)**:** 119-148

Laurier D, Hill C (2013) Cancer risk associated with ionizing radiation [in French]. *Rev Prat* **63**(8)**:** 1126-32

Le Gallic C, Phalente Y, Manens L, Dublineau I, Benderitter M, Gueguen Y, Lehoux S, Ebrahimian TG (2015) Chronic Internal Exposure to Low Dose 137Cs Induces Positive Impact on the Stability of Atherosclerotic Plaques by Reducing Inflammation in ApoE-/- Mice. *PLoS One* **10**(6)

Leach LJ, Yuile CL, Hodge HC (1973) A five year inhalation study with natural uranium dioxide (UO2) dust. II. Postexposure retention and biologic effects in the monkey, dog and rat. *Health Phys* **25**(3)**:** 239-258

Leggett RW (1994) Basis for the ICRP's age-specific biokinetic model for uranium. *Health Phys* **67**(6)**:** 589-610

Leggett RW, Eckerman KF, Boice Jr JD (2005) A respiratory model for uranium aluminide based on occupational data. *J Radiol Prot* **25**(4)**:** 405-416

Leggett RW, Eckerman KF, McGinn RA (2012) *Controlling intake of uranium in the workplace: applications of biokinetic modeling and occupational monitoring data*. Oak Ridge National Laboratory (ORNL): Oak Ridge

Lestaevel P, Bussy C, Paquet F, Dhieux B, Clarencon D, Houpert P, Gourmelon P (2005a) Changes in sleep-wake cycle after chronic exposure to uranium in rats. *Neurotoxicol Teratol* **27**(6)**:** 835-40

Lestaevel P, Houpert P, Bussy C, Dhieux B, Gourmelon P, Paquet F (2005b) The brain is a target organ after acute exposure to depleted uranium. *Toxicology* **212**(2-3)**:** 219-26

Lestaevel P, Romero E, Dhieux B, Ben Soussan H, Berradi H, Dublineau I, Voisin P, Gourmelon P (2009) Different pattern of brain pro-/anti-oxidant activity between depleted and enriched uranium in chronically exposed rats. *Toxicology* **258**(1)**:** 1-9

Leuraud K, Schnelzer M, Tomasek L, Hunter N, Timarche M, Grosche B, Kreuzer M, Laurier D (2011) Radon, smoking and lung cancer risk: Results of a joint analysis of three European case-control studies among uranium miners. *Rad Res* **176**(3)**:** 375-387

Little MP (2013) A review of non-cancer effects, especially circulatory and ocular diseases. *Rad Environ Biophys* **52**(4): 435-49

Little MP, Azizova TV, Bazyka D, Bouffler SD, Cardis ESC, Chekin S, Chumak VV, Cucinotta FA, de Vathaire F, Hall P, Harrison JD, Hildebrandt G, Ivanov V, Kashcheev VV, Klymenko SV, Kreuzer M, Laurent O, Ozasa K, Schneider T, Tapio S, Taylor AM, Tzoulaki I, Vandoolaeghe WL, Wakeford R, Zablotska LB, Zhang W, Lipshultz SE (2012a) Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. *Environ Health Perspect* **120**(11)**:** 1503-1511

Little MP, Bazyka D, Bouffler SD, Harrison JD, Cardis E, Cucinotta FA, Kreuzer M, Laurent O, Tapio S, Wakeford R, Zablotska L, Lipshultz SE (2012b) Estimating risk of circulatory disease: Little et al. respond. *Environ Health Perspect* **120**(12)**:** A453-A454

Little MP, Gola A, Tzoulaki I (2009) A model of cardiovascular disease giving a plausible mechanism for the effect of fractionated low-dose ionizing radiation exposure. *PLoS Comput Biol* **5**(10)**:** 23

Little MP, Tawn EJ, Tzoulaki I, Wakeford R, Hildebrandt G, Paris F, Tapio S, Elliott P (2008) A systematic review of epidemiological associations between low and moderate doses of ionizing radiation and late cardiovascular effects, and their possible mechanisms. *Rad Res* **169**(1)**:** 99-109

Little MP, Tawn EJ, Tzoulaki I, Wakeford R, Hildebrandt G, Paris F, Tapio S, Elliott P (2010) Review and meta-analysis of epidemiological associations between low/moderate doses of ionizing radiation and circulatory disease risks, and their possible mechanisms. *Rad Environ Biophys* **49**(2)**:** 139-153

Little MP, Zablotska LB, Brenner AV, Lipshultz SE (2015) Circulatory disease mortality in the Massachusetts tuberculosis fluoroscopy cohort study. *Eur J Epidemiol* **9**, doi 10.1007/s10654-015-0075-9

Loomis DP, Wolf SH (1996) Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennessee, 1947-1990. *Am J Ind Med* **29**(2)**:** 131-141

Marsh JW, Blanchardon E, Gregoratto D, Hofmann W, Karcher K, Nosske D, Tomášek L (2012) Dosimetric calculations for uranium miners for epidemiological studies. *Radiat Prot Dosimetry* **149**(4)**:** 371-383

Marsh JW, Harrison JD, Laurier D, Birchall A, Blanchardon E, Paquet F, Tirmarche M (2014) Doses and lung cancer risks from exposure to radon and plutonium. *Int J Radiat Biol* **90**(11)**:** 1080-7

McDiarmid MA, Gaitens JM, Hines S, Breyer R, Wong-You-Cheong JJ, Engelhardt SM, Oliver M, Gucer P, Kane R, Cernich A, Kaup B, Hoover D, Gaspari AA, Liu J, Harberts E, Brown L, Centeno JA, Gray PJ, Xu H, Squibb KS (2013) The Gulf War depleted uranium cohort at 20 years: Bioassay results and novel approaches to fragment surveillance. *Health Phys* **104**(4)**:** 347-361

McGeoghegan D, Binks K (2000a) The mortality and cancer morbidity experience of workers at the Capenhurst uranium enrichment facility 1946-95. *J Radiol Prot* **20**(4)**:** 381-401

McGeoghegan D, Binks K (2000b) The mortality and cancer morbidity experience of workers at the Springfields uranium production facility, 1946-95. *J Radiol Prot* **20**(2)**:** 111-137

McGeoghegan D, Binks K, Gillies M, Jones S, Whaley S (2008) The non-cancer mortality experience of male workers at British Nuclear Fuels plc, 1946-2005. *Int J Epidemiol* **37**(3)**:** 506-518

McNamee R, Burgess G, Dippnall WM, Cherry N (2006) Occupational noise exposure and ischaemic heart disease mortality. *Occup Environ Med* **63**(12)**:** 813-9

Metz-Flamant C, Guseva Canu I, Laurier D (2011) Malignant pleural mesothelioma risk among nuclear workers: A review. *J Radiol Prot* **31**(1)**:** 9-23

Metz-Flamant C, Laurent O, Samson E, Caër-Lorho S, Acker A, Hubert D, Richardson DB, Laurier D (2013) Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers. *Occup Environ Med* **70**(9)**:** 630-638

Milgram S, Carriere M, Malaval L, Gouget B (2008a) Cellular accumulation and distribution of uranium and lead in osteoblastic cells as a function of their speciation. *Toxicology* **252**(1-3)**:** 26-32

Milgram S, Carriere M, Thiebault C, Malaval L, Gouget B (2008b) Cytotoxic and phenotypic effects of uranium and lead on osteoblastic cells are highly dependent on metal speciation. *Toxicology* **250**(1)**:** 62-9

Mitchel RE, Jackson JS, Heinmiller B (1999) Inhaled uranium ore dust and lung cancer risk in rats. *Health Phys* **76**(2)**:** 145-55

Monleau M, De Meo M, Paquet F, Chazel V, Dumenil G, Donnadieu-Claraz M (2006) Genotoxic and inflammatory effects of depleted uranium particles inhaled by rats. *Toxicol Sci* **89**(1)**:** 287-95

Morvan P (2004) *Nucléaire, les chemins de l'uranium*. Ellipses: Paris

Moulis G, Lapeyre-Mestre M, Palmaro A, Pugnet G, Montastruc JL, Sailler L (2015) French health insurance databases: What interest for medical research? *Rev Med Interne* **36**(6)**:** 411-7

Muirhead CR, O'Hagan JA, Haylock RGE, Phillipson MA, Willcock T, Berridge GLC, Zhang W (2009) Mortality and cancer incidence following occupational radiation exposure: Third analysis of the National Registry for Radiation Workers. *Br J Cancer* **100**(1)**:** 206-212

NCRP (2006) *United States National Council on Radiation Protection and Measurements. Development of a biokinetic model for radionuclide-contaminated wounds and procedures for their assessment, dosimetry and tratment. Report No. 156*. NCRP: Bethesda

Neuman WF (1950) Urinary Uranium as a Measure of Exposure Hazard. *Ind Med Surg* **19**(4)**:** 185-191

NRC (2006) *National Research Council Health risks from exposure to low levels of ionizing radiation (BEIR VII phase2)*. National Academies Press: Washington

Nusinovici S, Vacquier B, Leuraud K, Metz-Flamant C, Caer-Lorho S, Acker A, Laurier D (2010) Mortality from circulatory system diseases and low-level radon exposure in the French cohort study of uranium miners, 1946-1999. *Scand J Work Environ Health* **36**(5)**:** 373-83

O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusoff K, Truelsen T, Diener HC, Sacco RL, Ryglewicz D, Czlonkowska A, Weimar C, Wang X, Yusuf S (2010) Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* **376**(9735)**:** 112-23

Orona NS, Tasat DR (2012) Uranyl nitrate-exposed rat alveolar macrophages cell death: influence of superoxide anion and TNF alpha mediators. *Toxicol Appl Pharmacol* **261**(3)**:** 309-16

OSHA (2006) *Occupational Safety and Health Administration, OSHA Fact Sheet, Personal Protective Equipment*. OSHA: Washington

Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, Sakata R, Sugiyama H, Kodama K (2012) Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: an overview of cancer and noncancer diseases. *Radiat Res* **177**(3)**:** 229-43

Paquet F, Houpert P, Blanchardon E, Delissen O, Maubert C, Dhieux B, Moreels AM, Frelon S, Gourmelon P (2006) Accumulation and distribution of uranium in rats after chronic exposure by ingestion. *Health Phys* **90**(2)**:** 139-47

Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Sir Craft AW, Parker L, Berrington de Gonzalez A (2012) Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* **380**(9840)**:** 499-505

Pernot E, Cardis E, Badie C (2014) Usefulness of saliva samples for biomarker studies in radiation research. *Cancer Epidemiol Biomarkers Prev* **23**(12)**:** 2673-80

Pernot E, Hall J, Baatout S, Benotmane MA, Blanchardon E, Bouffler S, El Saghire H, Gomolka M, Guertler A, Harms-Ringdahl M, Jeggo P, Kreuzer M, Laurier D, Lindholm C, Mkacher R, Quintens R, Rothkamm K, Sabatier L, Tapio S, de Vathaire F, Cardis E (2012) Ionizing radiation biomarkers for potential use in epidemiological studies. *Mutat Res - Rev Mutat Res* **751**(2)**:** 258-286

Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ (2005) Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* **45**(1)**:** 142-61

Pinkerton LE, Bloom TF, Hein MJ, Ward EM (2004) Mortality among a cohort of uranium mill workers: An update. *Occup Environ Med* **61**(1)**:** 57-64

Pinney SM, Freyberg RW, Levine GE, Brannen DE, Mark LS, Nasuta JM, Tebbe CD, Buckholz JM, Wones R (2003) Health effects in community residents near a uranium plant at Fernald, Ohio, USA. *Int J Occup Med Environ Health* **16**(2)**:** 139-53

Poisson C, Stefani J, Manens L, Delissen O, Suhard D, Tessier C, Dublineau I, Gueguen Y (2014) Chronic uranium exposure dose-dependently induces glutathione in rats without any nephrotoxicity. *Free Radic Res* **48**(10)**:** 1218-31

Polednak AP, Frome EL (1981) Mortality among men employed between 1943 and 1947 at a uranium-processing plant. *J Occup Med* **23**(3)**:** 169-178

Preston DL, Lubin JH, Pierce DA, McConney ME (1993) *EPICURE User's Guide*. HiroSoft International Corporation: Seattle

Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K (2003) Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiat Res* **160**(4)**:** 381-407

Puska P (2010) From Framingham to North Karelia: from descriptive epidemiology to public health action. *Prog Cardiovasc Dis* **53**(1)**:** 15-20

Rage E, Caer-Lorho S, Drubay D, Ancelet S, Laroche P, Laurier D (2015) Mortality analyses in the updated French cohort of uranium miners (1946-2007). *Int Arch Occup Environ Health* **88**(6)**:** 717-30

Rage E, Vacquier B, Blanchardon E, Allodji RS, Marsh JW, Caer-Lorho S, Acker A, Laurier D (2012) Risk of lung cancer mortality in relation to lung doses among French uranium miners: follow-up 1956-1999. *Radiat Res* **177**(3)**:** 288-97

Richardson DB (2004) An incidence density sampling program for nested case-control analyses. *Occup Environ Med* **61**(12): e59

Richardson DB, Wing S (2006) Lung cancer mortality among workers at a nuclear materials fabrication plant. *Am J Ind Med* **49**(2)**:** 102-111

Ritz B, Morgenstern H, Crawford-Brown D, Young B (2000) The effects of internal radiation exposure on cancer mortality in nuclear workers at Rocketdyne/Atomics International. *Environ Health Perspect* **108**(8)**:** 743-751

Rothman KJ, Greenland S, Lash TL (2008) *Modern Epidemiology, 3rd edition*. Lippincott Williams & Wilkins: Philadelphia

Samson E, Piot I, Zhivin S, Acker A, Laroche P, Laurier D (2014) 0184 Mortality profile of the French cohort of uranium processing workers. *Occup Environ Med* **71**(1)**:** 2014-102362

Sasaki H, Wong FL, Yamada M, Kodama K (2002) The effects of aging and radiation exposure on blood pressure levels of atomic bomb survivors. *J Clin Epidemiol* **55**(10)**:** 974-981

Schultz-Hector S, Trott KR (2007) Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? *Int J Radiat Oncol Biol Phys* **67**(1)**:** 10-8

Sera N, Hida A, Imaizumi M, Nakashima E, Akahoshi M (2013) The association between chronic kidney disease and cardiovascular disease risk factors in atomic bomb survivors. *Radiat Res* **179**(1)**:** 46-52

Shimizu Y, Kato H, Schull WJ, Hoel DG (1992) Studies of the mortality of A-bomb survivors. 9. Mortality, 1950-1985: Part 3. Noncancer mortality based on the revised doses (DS86). *Radiat Res* **130**(2)**:** 249-66

Shimizu Y, Kodama K, Nishi N, Kasagi F, Suyama A, Soda M, Grant EJ, Sugiyama H, Sakata R, Moriwaki H, Hayashi M, Konda M, Shore RE (2010) Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. *BMJ (Online)* **340**(7739)**:** 193

Silver SR, Bertke SJ, Hein MJ, Daniels RD, Fleming DA, Anderson JL, Pinney SM, Hornung RW, Tseng CY (2013) Mortality and ionising radiation exposures among workers employed at the Fernald Feed Materials Production Center (1951-1985). *Occup Environ Med* **70**(7)**:** 453-463

Snipes MB, McClellan RO, Mauderly JL, Wolff RK (1989) Retention patterns for inhaled particles in the lung: comparisons between laboratory animals and humans for chronic exposures. *Health Phys* **57**(SUPPL. 1)**:** 69-78

Stewart FA (2012) Mechanisms and dose-response relationships for radiation-induced cardiovascular disease. *Ann ICRP* **41**(3-4)**:** 72-9

Stewart FA, Akleyev AV, Hauer-Jensen M, Hendry JH, Kleiman NJ, Macvittie TJ, Aleman BM, Edgar AB, Mabuchi K, Muirhead CR, Shore RE, Wallace WH (2012) ICRP publication 118: ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs--threshold doses for tissue reactions in a radiation protection context. *Ann ICRP* **41**(1-2)**:** 1-322

Tager IB (2000) Current view of epidemiologic study designs for occupational and environmental lung diseases. *Environ Health Perspect* **4:** 615-23

Takahashi I, Abbott RD, Ohshita T, Takahashi T, Ozasa K, Akahoshi M, Fujiwara S, Kodama K, Matsumoto M (2012) A prospective follow-up study of the association of radiation exposure with fatal and non-fatal stroke among atomic bomb survivors in Hiroshima and Nagasaki (1980-2003). *BMJ Open* **2**(1)

Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, Sugimoto S, Ikeda T, Terasaki M, Izumi S, et al. (1994) Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958-1987. *Radiat Res* **137**(2 Suppl)**:** S17-67

Tirmarche M, Laurier D, Bochicchio F, Cardis E, Binks K, Hofmann W, Muirhead CR, Canu IG (2009) *Quantification of cancer and non-cancer risks associated with multiple radiation exposures: Epidemiologic studies, organ dose calculation and risk*

assessment. Final scientific report in the Frame of the European project "Alpha Risk" N° 516483, period 2005-2009. European Commission (EC): Brussels

Tournier BB, Frelon S, Tourlonias E, Agez L, Delissen O, Dublineau I, Paquet F, Petitot F (2009) Role of the olfactory receptor neurons in the direct transport of inhaled uranium to the rat brain. *Toxicol Lett* **190**(1)**:** 66-73

UNSCEAR (2006) *United Nations Scientific Committee on the Effects of Atomic Radiation Sources and Effects of Ionizing Radiation. Volume I. Annex A: Epidemiological studies of radiation and cancer*. United Nations (UN): New York

UNSCEAR (2008) *United Nations Scientific Committee on the Effects of Atomic Radiation Sources and Effects of Ionizing Radiation. Volume I. Annex B: Exposures of the public and workers from various sources of radiation.* United Nations (UN): New York

Vandenbroucke JP, Pearce N (2012) Case-control studies: basic concepts. *Int J Epidemiol* **41**(5)**:** 1480-9

Voegtlin C, Hodge HC (1949) *Pharmacology and toxicology of uranium compounds*. Mcgraw-Hill: New York

Vrijheid M, Cardis E, Ashmore P, Auvinen A, Bae JM, Engels H, Gilbert E, Gulis G, Habib R, Howe G, Kurtinaitis J, Malker H, Muirhead C, Richardson D, Rodriguez-Artalejo F, Rogel A, Schubauer-Berigan M, Tardy H, Telle-Lamberton M, Usel M, Veress K (2007) Mortality from diseases other than cancer following low doses of ionizing radiation: results from the 15-Country Study of nuclear industry workers. *Int J Epidemiol* **36**(5)**:** 1126-35

Wachholz BW, Casarett GW (1970) Radiation hypertension and nephrosclerosis. *Rad Res* **41**(1)**:** 39-56

Wade-Gueye NM, Delissen O, Gourmelon P, Aigueperse J, Dublineau I, Souidi M (2012) Chronic exposure to natural uranium via drinking water affects bone in growing rats. *Biochim Biophys Acta* **1820**(7)**:** 1121-7

Wagner SE, Burch JB, Bottai M, Pinney SM, Puett R, Porter D, Vena JE, Hebert JR (2010) Hypertension and hematologic parameters in a community near a uranium processing facility. *Environ Res* **110**(8)**:** 786-97

Whitaker JM (2005) *Uranium enrichment plant characteristics: a manual for the IAEA*

WHO (2003) *World Health Organization, MONIKA, World's largest study of heart disease, stroke, risk factors, and population trends 1979-2002.* WHO: Geneva

Wong FL, Yamada M, Sasaki H, Kodama K, Hosoda Y (1999a) Effects of radiation on the longitudinal trends of total serum cholesterol levels in the atomic bomb survivors. *Rad Res* **151**(6)**:** 736-746

Wong FL, Yamada M, Sasaki H, Kodama K, Hosoda Y (1999b) Effects of radiation on the longitudinal trends of total serum cholesterol levels in the atomic bomb survivors. *Radiat Res* **151**(6)**:** 736-46

Wrenn ME, Durbin PW, Howard B, Lipsztein J, Rundo J, Still ET, Willis DL (1985) Metabolism of ingested U and Ra. *Health Phys* **48**(5)**:** 601-33

Yamada M, Wong FL, Fujiwara S, Akahoshi M, Suzuki G (2004) Noncancer disease incidence in atomic bomb survivors, 1958-1998. *Rad Res* **161**(6)**:** 622-632

Yiin JH, Anderson JL, Daniels RD, Seel EA, Fleming DA, Waters KM, Chen PH (2009) A nested case-control study of multiple myeloma risk and uranium exposure among workers at the Oak Ridge Gaseous Diffusion Plant. *Rad Res* **171**(6)**:** 637-645

Yiin JH, Schubauer-Berigan MK, Silver SR, Daniels RD, Kinnes GM, Zaebst DD, Couch JR, Kubale TL, Chen PH (2005) Risk of lung cancer and leukemia from exposure to ionizing radiation and potential confounders among workers at the Portsmouth Naval Shipyard. *Rad Res* **163**(6)**:** 603-613

Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* **364**(9438)**:** 937-52

Zablotska LB, Bazyka D, Lubin JH, Gudzenko N, Little MP, Hatch M, Finch S, Dyagil I, Reiss RF, Chumak VV, Bouville A, Drozdovitch V, Kryuchkov VP, Golovanov I, Bakhanova E, Babkina N, Lubarets T, Bebeshko V, Romanenko A, Mabuchi K (2013a) Radiation and the risk of chronic lymphocytic and other leukemias among chornobyl cleanup workers. *Environ Health Perspect* **121**(1)**:** 59-65

Zablotska LB, Lane RSD, Frost SE (2013b) Mortality (1950-1999) and cancer incidence (1969-1999) of workers in the Port Hope cohort study exposed to a unique combination of radium, uranium and γ-ray doses. *BMJ Open* **3**(2)

Zablotska LB, Little MP, Cornett RJ (2014) Potential increased risk of ischemic heart disease mortality with significant dose fractionation in the Canadian Fluoroscopy Cohort Study. *Am J Epidemiol* **179**(1)**:** 120-31

Zablotska LB, Ron E, Rozhko AV, Hatch M, Polyanskaya ON, Brenner AV, Lubin J, Romanov GN, McConnell RJ, O'Kane P, Evseenko VV, Drozdovitch VV, Luckyanov N, Minenko VF, Bouville A, Masyakin VB (2011) Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chornobyl accident. *Br J Cancer* **104**(1)**:** 181-7

Zhivin S, Laurier D, Caër-Lorho S, Acker A, Guseva Canu I (2013) Impact of chemical exposure on cancer mortality in a French cohort of uranium processing workers. *Am J Ind Med* **56**(11)**:** 1262-1271

Zhivin S, Laurier D, Guseva Canu I (2014) Health effects of occupational exposure to uranium: Do physicochemical properties matter? *Int J Radiat Biol* **90**(11)**:** 1104-1113

Zhou LR, Zhou JH, Yang JC (1999) Effects of Cytokines Induced by Mineral Dust on Lung Fibroblasts In Vitro. *J Occup Health* **41**(3)**:** 144-148

Zhu G, Tan M, Li Y, Xiang X, Hu H, Zhao S (2009) Accumulation and distribution of uranium in rats after implantation with depleted uranium fragments. *J Radiat Res* **50**(3)**:** 183-92

Zhukovsky M, Bastrikova N, Vasilyev A (2015) Relative biological effectiveness of alpha particles at radon exposure. *Radiat Prot Dosimetry* **164**(4)**:** 467-70

APPENDIXES

Appendix 1. Résumé détaillé de la thèse[9]

Introduction

Les humains sont constamment exposés aux rayonnements ionisants d'origine naturelle tels que les rayonnements telluriques, cosmiques et le gaz radon. L'exposition artificielle majeure provient des examens médicaux à rayons X et, dans une faible mesure, des retombées nucléaires après les accidents nucléaires (Tchernobyl, Fukushima…) et des essais d'armes nucléaires. L'exposition professionnelle aux rayonnements ionisants, quant à elle, concerne des nombreux métiers comme les professionnels de santé et les travailleurs de l'industrie nucléaire.

Bien que de nombreuses données soient disponibles sur les effets sanitaires des fortes expositions aux rayonnements γ, les effets consécutifs à des contaminations chroniques internes par les émetteurs α restent beaucoup moins connus. Ces émetteurs ont tendance à s'accumuler dans des tissus particuliers et émettent une radiation très dense. L'uranium est un émetteur α omniprésent dans la nature dont les effets (chimio- et radiotoxicité) dépendent de ses propriétés physico-chimiques, notamment la solubilité (absorption pulmonaire) et sa composition isotopique.

Actuellement, les travailleurs du cycle du combustible nucléaire attirent beaucoup d'attention scientifique du fait de leur exposition chronique à des divers composés uranifères, et de la disponibilité des données de surveillance. En outre, l'évaluation d'une exposition interne est sujette à de grandes incertitudes, et la majorité des travailleurs de l'uranium sont exposés à plusieurs composés uranifères ce qui complique l'analyse des risques associés à chacun des types d'uranium. C'est pour ces raisons que la littérature récente suggère d'effectuer les études chez les sous-groupes des travailleurs du cycle du combustible avec une exposition homogène, ainsi que de collecter des données précises sur les propriétés physico-chimiques de l'uranium.

Une étude-pilote des travailleurs d'AREVA NC Pierrelatte a été initiée en 2005 par l'Institut de Radioprotection et de Sûreté Nucléaire (IRSN) pour étudier une association potentielle

[9] This section is a summary of the PhD manuscript in the French language. To avoid repetions, the text has no references or citations. These can be found in the corresponding chapters of the thesis. / Cette section est un résumé détaillé en français de la thèse. Pour éviter des répétitions, le texte n'inclut ni reference ni citation. Celles-ci peuvent être trouvées dans les chapitres correspondants de la thèse.

entre mortalité et contamination interne due à l'uranium. Cette étude-pilote a conduit à la construction d'une cohorte française (TRACY U cohorte) de plus de 12 000 travailleurs potentiellement exposés à l'uranium à : Pierrelatte (AREVA NC, CEA, Eurodif, Comurhex, Socatri, FBFC), Malvési (Comurhex), Romans (FBFC), Marcoule (Melox).

Mon projet de thèse intègre la poursuite de ces travaux avec trois objectifs principaux :

Objectif 1 : Effectuer une revue critique de la littérature concernant l'impact de l'uranium sur la mortalité. Nous avons effectué une revue critique des études épidémiologiques réalisant un suivi de travailleurs du cycle du combustible nucléaire. Cette revue nous a amené à concentrer la thèse sur deux axes de travail.

Objectif 2 : Analyser la mortalité dans la cohorte des travailleurs impliqués dans l'étape d'enrichissement. Cet objectif porte sur le risque de mortalité par maladies cancéreuses et non-cancéreuses chez les travailleurs français de l'enrichissement d'uranium. Contrairement aux autres travailleurs du cycle du combustible du nucléaire, cette population est exposée à l'uranium très soluble: hexafluorure d'uranium (UF_6) et fluorure d'uranyle (UO_2F_2). Cette étude permet de mieux comprendre les risques spécifiquement associés à l'exposition à l'uranium soluble.

Objectif 3 : Analyser la relation entre la mortalité par maladies d'appareil circulatoire et la dose interne due à l'uranium chez les travailleurs d'AREVA NC Pierrelatte. Cet objectif porte sur l'analyse du risque de décès par pathologies cardiovasculaires suite à l'exposition à l'uranium dans l'étude cas-témoins nichée des travailleurs d'AREVA NC Pierrelatte, après la prise en compte des facteurs classiques de risque cardiovasculaire.

Plan du manuscrit

Ce manuscrit de thèse se compose de six chapitres.

Le chapitre 1 introduit la problématique de l'exposition aux rayonnements ionisants chez l'homme, décrit les concepts de dose et les effets biologiques, et souligne les intérêts majeurs de la recherche sur les effets des rayonnements ionisants.

Le chapitre 2 présente les différentes étapes du cycle du combustible nucléaire en France. Ce chapitre met l'accent sur la variété des risques radiologiques et non-radiologiques rencontrés par ces travailleurs. L'état actuel de la surveillance médico-professionnelle de l'exposition interne due à l'uranium est détaillé.

Le chapitre 3 concerne les connaissances acquises sur les effets sanitaires après exposition chronique à l'uranium dans les études toxicologiques. Ce chapitre présente également la revue critique de la littérature de l'association entre mortalité et exposition à l'uranium interne qui a été effectuée dans le cadre de cette thèse. En outre, ce chapitre met en évidence l'influence des propriétés physico-chimiques des composés uranifères sur les effets sanitaires, identifie les lacunes actuelles, et propose des actions afin d'améliorer les futures études portant sur les travailleurs du cycle du combustible nucléaire.

Le chapitre 4 présente l'analyse de la mortalité au sein de la cohorte française des travailleurs de l'enrichissement de l'uranium. Une caractéristique unique de cette population est son exposition à des composés uranifères très solubles. Ce chapitre fournit des détails sur la construction de la cohorte et la méthodologie de la reconstruction de l'exposition professionnelle pour les polluants radiologiques et non-radiologiques. En premier lieu, la mortalité a été comparée à celle de la population française. En second lieu, les analyses exposition-réponse ont été effectuées pour certaines causes de décès définies à priori.

Le chapitre 5 examine la relation entre mortalité par maladies d'appareil circulatoire et dose interne due à l'uranium. Ces résultats reposent sur une étude cas-témoins nichée des travailleurs d'AREVA NC Pierrelatte. Un protocole dosimétrique a été développé spécifiquement pour cette étude, ce qui a permis l'estimation des doses individuelles dues à l'uranium fondées sur les données individuelles de surveillance radiotoxicologique et des données sur la solubilité de l'uranium (absorption pulmonaire). Des données individuelles sur les principaux facteurs de risque des maladies cardiovasculaires ont été extraites des dossiers médicaux.

Le chapitre 6 présente une discussion générale sur les limites et les avantages du travail effectué. Ce chapitre traite des questions soulevées par ce travail et ouvre des perspectives.

Revue critique de la littérature concernant l'impact de l'uranium sur la mortalité (objectif 1)

La toxicité de l'uranium dépend de ses propriétés physico-chimiques, y compris la composition isotopique et la solubilité.

Les travailleurs du cycle du combustible nucléaire sont potentiellement exposés à des formes diverses physico-chimiques de l'uranium. De ce fait et en raison de l'exposition mesurable, c'est une population d'intérêt pour les effets de l'uranium sur la santé.

Le lien entre exposition à l'uranium et mortalité par cancer avait déjà analysé par le Docteur Irina Guseva Canu pour les études portant sur les travailleurs du nucléaire et publiées entre 1980 et 2006. Pour mettre à jour la revue mentionnée ci-dessus et étudier l'impact des propriétés physico-chimiques de l'uranium (composition isotopique, solubilité), nous avons analysé la mortalité par maladies cancéreuses et non-cancéreuses dans les études épidémiologiques du personnel civil (travailleurs du cycle du combustible nucléaire) et militaire (travailleurs déployés dans les guerres du Golfe et des Balkans) publiées entre 1980 et 2013. Notre thèse ne discute pas les résultats de mortalité du personnel militaire, mais ils peuvent être trouvés dans l'article publié.

Questions scientifiques

Notre revue a cherché à répondre aux questions suivantes :

- Y-a-t-il un taux élevé de mortalité entre les différents groupes de travailleurs du cycle du combustible nucléaire ?
- Y-a-t-il une relation dose-réponse entre exposition à l'uranium et cause de décès définie ?
- Dans quelle mesure les propriétés physico-chimiques expliquent les associations observées ?

Matériels et Méthodes

Recherche documentaire

Deux bases de données biomédicales (PubMed et Scopus) ont été utilisées pour rechercher les articles anglophones publiés entre 1980 et 2013. Les mots-clés étaient : mortality, morbidity, incidence, cancer, lymphatic, lymphoid, leukemia, hematopoietic, lymphohematopoietic, multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's disease, kidney, circulatory, cardiovascular, cerebrovascular, ischemic, disease, uranium, workers, processing. Les

bibliographies de chacun des articles récupérés ont ensuite été analysées comme un moyen d'identifier des études supplémentaires.

Critères d'exclusion

Notre revue était dédiée à l'analyse des effets de l'uranium. Pour cette raison, nous avons exclu les études où l'uranium n'était pas la source majeure de l'exposition: travailleurs américains de Rocketdyne/Atomics International (plus de 14 radionucléides différents, y compris uranium, plutonium, strontium, thorium, polonium, americium, cesium…), travailleurs américains de Savannah River Site (exposition interne, y compris uranium, plutonium, tritium et les produits de fission) et travailleurs français du Commissariat à l'énergie atomiques et aux énergies alternatives (CEA) (mélange d'exposition interne et externe).

Résultats

Vingt articles ont été identifiés. En moyenne, la période de suivi était de 43,6 ans. En raison d'un manque d'informations détaillées, nous avons supposé que la plupart des travailleurs ont été exposés aux composés solubles et insolubles. Pour les travailleurs d'enrichissement, nous avons supposé une exposition homogène à l'uranium soluble.

Comparaison avec la population générale

Un excès significatif de mortalité par cancer du poumon a été observé chez les travailleurs de fabrication de combustible américains embauchés à Y-12 Oak Ridge, à Fernald Feed Materials Production Center et les travailleurs français à Pierrelatte. La plupart des études ont noté une baisse de mortalité (effet du travailleur sain) par rapport à la population générale. Cet effet était plus remarquable pour les maladies de l'appareil circulatoire.

Analyse dose-réponse

Sur les 20 articles examinés, seulement 9 études ont permis une analyse dose-réponse. Seulement 7 études ont évalué l'exposition interne due à l'uranium (dose interne, intake d'uranium, score d'exposition…) ; d'autres ont utilisé des proxis d'exposition.

Seule l'étude des travailleurs de l'enrichissement américains de Paducah a suggéré une augmentation de mortalité par cancer du poumon et des tissus lymphohématopoïétiques, malgré une faible puissance statistique.

Impact des propriétés physico-chimiques

Les propriétés physico-chimiques de l'uranium sont rarement prises en compte dans les études analysées. Bien que le type de travail puisse être un substitut raisonnable des propriétés physico-chimiques de l'uranium, il n'y avait pas d'indication d'excès de mortalité entre différents groupes des travailleurs du cycle du combustible nucléaire. Néanmoins, deux études américaines de travailleurs de fabrication du combustible et une étude américaine de travailleurs de l'enrichissement ont montré respectivement une augmentation de mortalité par cancer du poumon et des tissus lymphohématopoïétiques. Une étude française des travailleurs d'AREVA NC Pierrelatte a signalé un impact de l'isotopie et de la solubilité car le risque de mortalité par cancer (poumon, tissus lymphohématopoïétiques) et par maladies d'appareil circulatoire était plus élevé pour les composés uranifères de retraitement insolubles par rapport aux composés naturels solubles.

Discussion

Notre revue critique de la littérature a montré les points suivants : (1) Les travailleurs du cycle du combustible nucléaire ont une mortalité inférieure (« effet du travailleur sain ») à celle de la population générale ; (2) La mortalité par cancer du poumon et des tissus lymphohématopoïétiques semble être élevée dans certains groupes de travailleurs (enrichissement d'uranium et fabrication du combustible) ; (3) L'impact des propriétés physico-chimiques ne peut pas être défini sur la base des études actuelles.

En conclusion, les caractéristiques physico-chimiques de l'uranium sont rarement prises en compte dans les études épidémiologiques et les résultats disponibles ne sont pas concluants quant à leur association avec des effets sanitaires. De plus, la majorité des travailleurs d'uranium sont exposés à plusieurs composés uranifères, ce qui complique l'analyse des risques associés à chacun des types d'uranium. Les études futures portant sur les travailleurs de l'enrichissement (exposition à l'hexafluorure d'uranium) et de fabrication du combustible (exposition au dioxyde d'uranium) auront le plus grand potentiel pour déterminer les risques de santé après exposition chronique à l'uranium, en raison de leur exposition homogène à des formes physico-chimiques spécifiques.

Analyse de la mortalité dans la cohorte des travailleurs impliqués dans l'étape d'enrichissement de l'uranium (objectif 2)

L'enrichissement de l'uranium est une des étapes du cycle du combustible nucléaire. Les travailleurs impliqués dans cette étape sont une population d'intérêt pour la communauté scientifique en raison de l'exposition homogène à des composés uranifères très solubles (UF_6, UO_2F_2). C'était la motivation principale pour mettre en place et analyser la mortalité dans la cohorte française des travailleurs de l'enrichissement de l'uranium.

Matériels et Méthodes

Construction de la cohorte et suivi épidémiologique

Une liste préliminaire des travailleurs de l'enrichissement a été identifiée à partir de la cohorte TRACY U (TRAvailleurs du CYcle du combustible potentiellement exposés à l'uranium) de 12 739 travailleurs. Les critères d'inclusion ont été définis comme suit :

- Emploi aux usines d'enrichissement AREVA NC Pierrelatte, CEA Pierrelatte et Eurodif ;
- Travail au moins six mois entre 1964 et 2008 ;
- Vivant au 01/01/1968.

Par ailleurs, nous avons exclu les catégories suivantes : travailleurs ayant des contrats temporaires et anciens mineurs d'uranium. La base de données définitive, utilisée dans les analyses statistiques, a inclu 4688 travailleurs.

La date d'entrée dans la cohorte a été définie comme la date de la première embauche à l'usine d'enrichissement plus six mois ou le 01/01/1968. La date de sortie de la cohorte était la date de décès, la date de dernières nouvelles pour les perdus de vue ou le 31/12/2008.

Données d'exposition

L'exposition annuelle aux composés uranifères solubles (de base de l'uranium naturel, enrichi ou appauvri) et aux produits non-radiologiques (trichloréthylène, chaleur, bruit) a été reconstituée pour chaque individu grâce à une matrice emplois-expositions. Un produit multiplicatif de la fréquence, l'intensité d'exposition et la durée d'emploi, issu de la matrice emplois-expositions, a permis de dériver un score d'exposition individuelle à l'échelle annuelle, qui peut être utilisé dans les analyses statistiques.

Les doses d'irradiation externe (en mGy) ont été reconstituées pour chaque année à partir des archives dosimétriques du Système d'Information de la Surveillance de l'Exposition aux

Rayonnements Ionisants (SISERI) mis en place par l'Institut de Radioprotection et de Sûreté Nucléaire (IRSN).

Statuts vitaux et causes de décès

Les statuts vitaux ont été obtenus auprès du Répertoire National d'Identification des Personnes Physiques (RNIPP) de l'Institut National de la Statistique et des Études Économiques (INSEE). Les causes de décès ont été obtenues auprès du Centre d'épidémiologie sur les Causes Médicales de Décès (CépiDC) de l'Institut National de la Santé et de la Recherche Médicale (INSERM) pour la période de 1968 à 2008. Les causes de décès sont codées selon la Classification Internationale des Maladies (CIM) définie par l'Organisation Mondiale de la Santé (OMS). Pour les décès survenant avant 1978, les causes de décès sont codées selon la version 8 de la CIM (CIM-8), puis selon la CIM-9 pour les décès survenant jusqu'en 1999 et finalement selon la CIM-10 pour les décès survenant après 2000.

Méthodes d'analyse

Une première étape dans l'analyse était la comparaison entre la mortalité de la cohorte et de la population française. La mortalité observée a été comparée à celle attendue d'après les taux de mortalité de la population française, par calcul du rapport de mortalité standardisé (Standardized Mortality Ratio, SMR) par cause spécifique.

En deuxième lieu, des modèles de Poisson log-linéaires et les modèles linéaires d'excès risque relatif (ERR) ont été employés pour étudier la mortalité par cancers solides, par tissus lymphohématopoïétiques, ainsi que par maladies de l'appareil circulatoire en lien avec l'exposition interne à l'uranium ou à l'exposition externe gamma.

Résultats

Comparaison avec la population générale

La mortalité par toutes causes de décès (SMR=0,69, 95% intervalles de confiance (IC) 0,65 à 0,74) et tous cancers (SMR=0,79, 95% IC 0,72 à 0,87) était inférieure par rapport à celle de population française. On a observé un excès significatif de mortalité par cancer de la plèvre (SMR=2,32, 95% IC 1,06 à 4,41). D'autres excès non-significatifs ont été observés pour le cancer du rein (SMR=1,12, 95% IC 0,60 à 1,91), du pancréas (SMR=1,30, 95% IC 0,87 à 1,85), du système biliaire (SMR=1,55, 95% IC 0,50 à 3,62), des tumeurs malignes du système

nerveux central (SMR=1,62, 95% IC 0,94 à 2,59), du mélanome de la peau (SMR=1,93, 95% IC 0,83 à 3,81) et du sein chez les femmes (SMR=1,46, 95% IC 0,63 à 2,88). Des déficits de mortalité ont été observés pour les cancers liés au tabagisme (SMR=0,73, 95% IC 0,64 à 0,83), le cancer du poumon (SMR=0,74, 95% IC 0,60 à 0,90), les maladies respiratoires non malignes (SMR=0,64, 95% IC 0,47 à 0,84), les maladies de l'appareil circulatoire (SMR=0,79, 95% IC 0,70 à 0,89) et la mortalité due à des causes externes (SMR=0,53, 95% IC 0,42 à 0,66).

Analyse dose-réponse

L'exposition à des composés uranifères très solubles (issus de l'uranium naturel) n'était pas significativement associée aux causes de décès étudiées (cancers du poumon, cancers solides et des tissus lymphohématopoïétiques, maladies d'appareil circulatoire). Une tendance à la baisse a été observée pour les cancers du poumon et les tissus lymphohématopoïétiques. Une association non significative a été notée entre la dose externe γ et la mortalité par maladies de l'appareil circulatoire (ERR/100 mGy=0,13, 95% IC <0 à 1,97) et les maladies ischémiques (ERR/100 mGy=1,11, 95% IC <0 à 3,86). La magnitude de l'association liée à l'uranium enrichi et appauvri était comparable à celle de l'uranium naturel.

Discussion

Dans son ensemble, l'analyse de la cohorte des travailleurs français de l'enrichissement montre un effet du travailleur sain en comparaison avec la population française, à l'exception d'un excès de mortalité par cancer de la plèvre. Aucune des causes de mortalité étudiée n'a été associée significativement, ni avec l'exposition aux composés uranifères rapidement solubles ni avec l'exposition externe γ.

Les résultats obtenus dans notre étude mériterait d'être réévalués après un suivi supplémentaire, la réalisation de nouvelles analyses utilisant les doses absorbées dues à l'uranium, et une mise en commun des données avec d'autres cohortes similaires afin d'augmenter la puissance statistique.

Analyse de la relation entre la mortalité par maladies de l'appareil circulatoire et la dose interne due à l'uranium chez les travailleurs d'AREVA NC Pierrelatte (objectif 3)

Une étude de cohorte de 2897 travailleurs d'AREVA NC Pierrelatte réalisée en 2005–2010 a suggéré un risque accru de mortalité par maladies de l'appareil circulatoire. Cette analyse était fondée sur les scores cumulés à six formes physico-chimiques de l'uranium issus de la

matrice emplois-expositions. Une décision avait été prise de mettre en place une étude cas-témoins nichée, d'estimer les doses absorbées dues à l'uranium en prenant en compte les propriétés physico-chimiques et de collecter les données sur les facteurs individuels de risque cardiovasculaire afin d'ajuster les analyses dose-réponse.

Matériels et Méthodes

La cohorte sous-jacente pour à cette étude est celle de travailleurs d'AREVA NC Pierrelatte. L'établissement AREVA NC Pierrelatte est situé sur le site nucléaire du Tricastin. Ce site a été construit par le CEA qui dès 1960 utilisait le procédé d'enrichissement par diffusion gazeuse, d'abord dans des usines-pilotes, puis dans des usines militaires. En 1976, le procédé et le personnel de certaines installations ont été intégrés à la COGEMA (devenue AREVA en 2006) pour produire de l'uranium enrichi civil jusqu'à l'apparition de l'usine Eurodif en 1978. A partir de ce moment, la chimie de l'uranium est devenue l'activité dominante du site. L'uranium a été la seule matière radioactive manipulée. La cohorte des travailleurs de la transformation de l'uranium d'AREVA NC Pierrelatte a été créée en 2005 comme une étude-pilote. La cohorte comprenait 2897 travailleurs employés à l'usine pendant au moins six mois entre 1960 et 2006. Les statuts vitaux et les causes de décès ont été collectés à partir de registres nationaux de mortalité (RNIPP et CépiDC) jusqu'en 2006.

L'analyse de l'étude cas-témoins nichée porte sur 102 décès par maladies d'appareil circulatoire (dont 44 décès par maladies ischémiques et 31 pathologies cérébrovasculaires) et 416 témoins. Les cas et les témoins ont été appariés sur l'âge atteint, le sexe, la période de naissance et le statut socio-professionnel. Les doses absorbées (mGy) ont été estimées en tenant compte des profils de solubilité des composés uranifères extraits de la matrice emploi-expositions. Les facteurs de risques cardiovasculaires individuels (tabagisme, pression artérielle, indice de masse corporelle, cholestérol, glycémie) ont été recueillis à partir des dossiers médicaux. La mortalité a été analysée par régression logistique conditionnelle afin d'estimer l'Excess Odds Ratio (EOR) par mGy de la dose interne due à l'uranium.

Résultats

<u>Association avec facteurs de risque</u>

Des associations positives non-significatives ont été observées entre la mortalité par maladies de l'appareil circulatoire et tous les facteurs de risque biologiques ou de comportement considérés. L'ajustement sur la dose interne due à l'uranium n'a pas modifié ces associations.

La mortalité était significativement associée avec l'hypertension (Odds Ratio ajusté (AOR)=3,89, 95% IC 2,16 à 7,02) et à la limite du seuil de signification avec la glycémie (AOR=1,09, 95% IC 0,98 à 1,22).

Analyse dose-réponse

Une tendance linéaire non-significative (p-value=0.4) a été observée entre la mortalité par maladies de l'appareil circulatoire et les catégories de dose absorbée due à l'uranium. Nous avons observé une association significative dans en utilisant un modèle linéaire (EOR/mGy=0,2, 95% IC 0,004 à 0,5). Il y avait peu de signe de confusion par les facteurs de risque cardiovasculaires individuels ou l'exposition externe γ.

Discussion

C'est la première étude qui suggère une augmentation de la mortalité par maladies de l'appareil circulatoire avec la dose absorbée cumulée due à l'uranium. Afin de disposer de la dose interne et d'étudier l'influence des facteurs de risque biologiques et de comportement sur la relation dose-réponse, un investissement important a été réalisé pour l'estimation des doses et le recueil des données concernant les facteurs de risque à partir des dossiers médicaux des travailleurs. L'ajustement des modèles sur les facteurs de risque cardiovasculaires classiques ne modifie pas l'association. L'association observée conforme les résultats de l'analyse précédente au sein de la cohorte d'AREVA NC Pierrelatte.

Conclusion générale

En raison de l'omniprésence de l'uranium dans la nature, plus de données sont nécessaires pour évaluer les effets potentiels de cette exposition sur la santé. Les travailleurs du cycle du combustible nucléaire constituent une population d'intérêt afin d'étudier l'exposition à faible dose et faible débit dose par inhalation d'uranium. L'interprétation des études antérieures a été entravée par les limites suivantes : mauvaise qualité de l'évaluation de l'exposition, non-prise en compte des propriétés physico-chimiques des composés uranifères, puissance statistique limitée et non-prise en compte des facteurs de confusion potentiels.

Dans ce travail de thèse, nous avons tenté de répondre à certaines limites citées ci-dessous : (1) en construisant une cohorte française des travailleurs de l'enrichissement d'uranium exposés à des composés uranifères très solubles et (2) en analysant le risque de décès par maladies de l'appareil circulatoire en relation avec la dose absorbée estimée chez les

travailleurs d'AREVA NC Pierrelatte et en recueillant des informations individuelles sur les facteurs de risque classiques de maladie cardiovasculaire.
L'exposition à des composés uranifères très solubles n'a été associée significativement à aucune des causes de décès étudiée. L'association entre le risque de décès par maladies d'appareil circulatoire persiste après ajustement sur les facteurs de risque biologiques ou de comportement et l'exposition externe γ. Néanmoins, la magnitude de cette association apparait particulièrement élevée et associée à de grandes incertitudes et ce résultat doit être interprété avec prudence.

Le niveau d'exposition faible à l'uranium et le petit nombre de travailleurs sont les causes principales de la puissance statistique limitée de notre travail. Le suivi de 12 739 travailleurs du cycle du combustible potentiellement exposés à l'uranium (cohorte TRACY U), le développement de collaborations internationales permettant de mener des études combinées et la collecte de matériel biologique permettant la recherche de les biomarqueurs permettra d'améliorer notre connaissance des risques associés à l'exposition chronique de l'uranium.

Appendix 2. Additional analyses for the French cohort of uranium enrichment workers

The following additional analyses were performed for the French cohort of uranium enrichment workers: (1) sensitivity analysis of the relationship between mortality and natural soluble uranium compounds after exclusion of 246 workers with potential exposure to insoluble uranium compounds (Table A1) and (2) additional analysis of the relationship between mortality and exposure to non-radiological hazards (Table A2).

Table A1. Summary of within-cohort Poisson regression models for exposure-response between exposure to natural soluble uranium compounds lagged by five years, and selected causes of death in the French cohort of uranium enrichment workers after exclusion of 246 with potential exposure to insoluble uranium compounds (n=4,442)

		Exposure categories			
Outcome		**Unexposed**	**Low**	**Medium**	**High**
	Cases	116	64	111	109
Solid cancers	RR (95%CI)	ref.	1.13 (0.82 to 1.55)	1.04 (0.80 to 1.36)	1.03 (0.79 to 1.35)
	Cases	30	19	27	23
Lung cancer	RR (95%CI)	ref.	1.10 (0.60 to 1.96)	0.93 (0.55 to 1.59)	0.73 (0.41 to 1.26)
	Cases	6	5	10	7
Lymphohematopoietic cancers	RR (95%CI)	ref.	1.92 (0.54 to 6.59)	1.78 (0.65 to 5.31)	1.24 (0.40 to 3.95)
	Cases	82	36	73	86
Circulatory diseases	RR (95%CI)	ref.	0.94 (0.62 to 1.40)	1.03 (0.74 to 1.43)	1.24 (0.90 to 1.70)
	Cases	30	16	21	26
Ischemic heart diseases	RR (95%CI)	ref.	1.15 (0.60 to 2.12)	0.73 (0.41 to 1.28)	0.94 (0.54 to 1.61)
	Cases	23	6	22	20
Cerebrovascular diseases	RR (95%CI)	ref.	0.56 (0.20 to 1.34)	1.26 (0.68 to 2.33)	1.06 (0.57 to 1.97)

All models are stratified by sex, attained age, calendar period, socio-economic status at hire, and subcohort.
CI, confidence intervals; RR, relative risk.

Conclusion: Exclusion of workers with potential exposure to insoluble uranium compounds does not change our results obtained in Chapter 4 (see Table 14).

Table A2. Summary of within-cohort Poisson regression models for exposure-response between TCE, heat, and noise lagged by five years, and selected causes of death in a French cohort of uranium enrichment workers (n=4,688)

			Exposure categories			
Outcome			**Unexposed**	**Low**	**Medium**	**High**
Solid cancer		Cases	124	45	116	121
	TCE	RR (95%CI)	ref.	1.01 (0.70 to 1.41)	1.06 (0.82 to 1.38)	1.06 (0.82 to 1.37)
Lung cancer		Cases	34	11	25	30
	TCE	RR (95%CI)	ref.	0.75 (0.36 to 1.44)	0.80 (0.47 to 1.35)	0.85 (0.51 to 1.39)
Lymphohematopoietic cancer		Cases	5	5	11	7
	TCE	RR (95%CI)	ref.	3.05 (0.83 to 11.21	2.55 (0.91 to 8.20)	1.57 (0.49 to 5.36)
Circulatory diseases		Cases	44	25	156	56
	Heat	RR (95%CI)	ref.	1.26 (0.75 to 2.08)	1.03 (0.74 to 1.48)	0.95 (0.63 to 1.44)
		Cases	120			161
	Noise*	RR (95%CI)	ref.			0.86 (0.66 to 1.22)
Ischemic heart diseases		Cases	14	8	52	21
	Heat	RR (95%CI)	ref.	1.48 (0.58 to 3.55)	1.05 (0.59 to 1.99)	1.08 (0.55 to 2.20)
		Cases	34			61
	Noise*	RR (95%CI)	ref.			1.16 (0.72 to 1.87)
Cerebrovascular diseases		Cases	11	6	45	9
	Heat	RR (95%CI)	ref.	1.31 (0.44 to 3.55)	1.23 (0.64 to 2.57)	0.70 (0.28 to 1.75)
		Cases	32			39
	Noise*	RR (95%CI)	ref.			0.88 (0.52 to 1.48)

* Noise exposure assessed as "never-exposed" vs. never-exposed.
CI, confidence interval; RR, relative risk; TCE, trichloroethylene.

Conclusion: A decreasing trend across exposure categories of TCE exposure was observed for lung and lymphohematopoietic cancer mortality. Noise exposure was positively associated with IHD, but not with all CSD or CVD mortality.

Appendix 3. Additional analyses for the nested case-control study of the AREVA NC Pierrelatte uranium processing workers

The following additional analyses were performed for the nested case-control study of the AREVA NC Pierrelatte uranium processing workers: (1) distribution of cumulative uranium lung and external γ-radiation whole-body doses (Figure A1), and (2) analysis of actual confounding by CSD risk factors (Table A3).

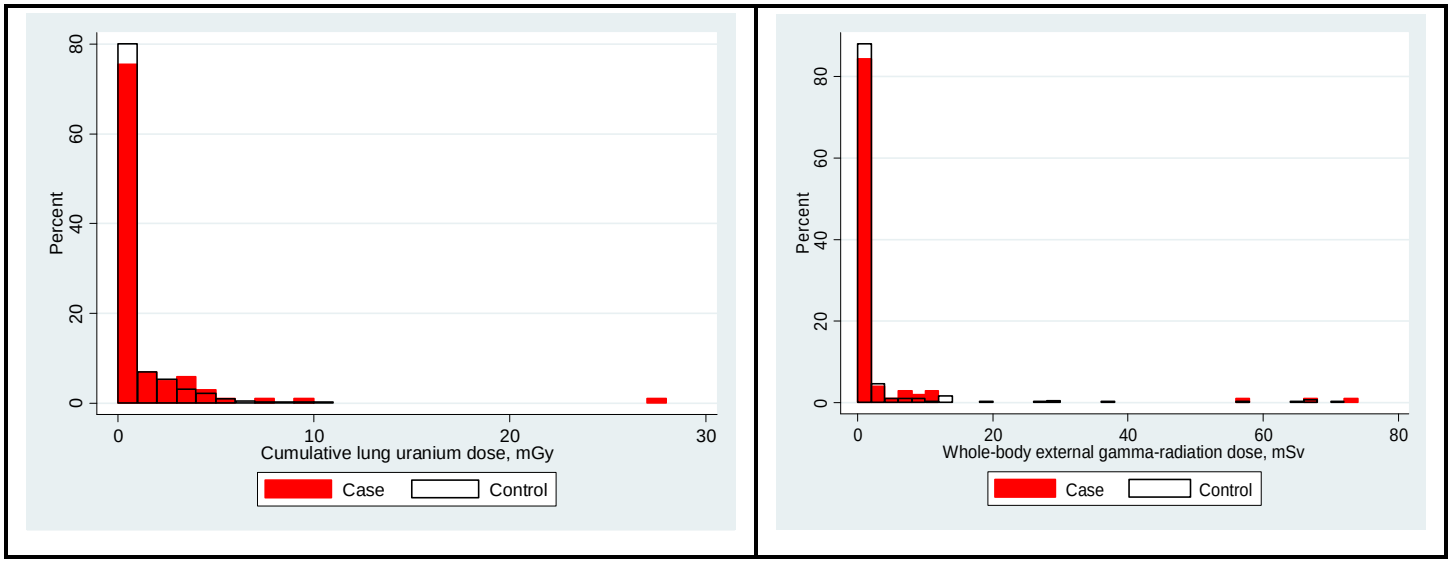

Figure A1. Distribution of radiation doses among cases and controls in the nested case-control study of AREVA NC Pierrelatte uranium processing workers

Conclusion: Distributions of both cumulative uranium and γ-radiation doses were highly skewed to the left, as was previously suggested by a descriptive statistics in Chapter 5 (Table 21). There was no difference between cases and controls.

To be an actual confounder, three formal criteria should be satisfied: (i) a confounding factor is an extraneous risk factor for the disease among unexposed group, (ii) a confounding factor should be associated with the exposure under study in the source population (among controls in a case-control study), and (iii) a confounding factor is not an intermediate step in the causal path between the exposure and the disease (Rothman *et al*, 2008).

We checked the first two criteria within the nested case-control study (Table A3). The third criterion was assumed to be held.

Table A3. Confounding criteria verification in the nested case-control study of AREVA NC Pierrelatte workers

		Association with disease among unexposed	Association with exposure among controls
Variable		**OR (95% CI)**	**OR (95% CI)**
Smoking		3.63 (0.97 to 13.56)	0.78 (0.48 to 1.27)
BMI			
	Overweight	0.86 (0.25 to 2.95)	1.09 (0.68 to 1.75)
	Obese	6.29 (1.17 to 33.68)	1.50 (0.84 to 2.69)
BP		1.84 (0.63 to 5.35)	0.82 (0.51 to 1.32)
Total cholesterol		0.61 (0.17 to 2.12)	1.15 (0.66 to 1.99)
Glycemia		2.65 (1.02 to 6.88)	0.81 (0.50 to 1.32)
External γ-radiation dose		1.03 (0.99 to 1.07)	0.97 (0.94 to 1.01)

BMI, body mass index; BP, blood pressure; CI, confidence intervals; OR, odds ratio.

Conclusion: None of considered risk factors was associated with disease among unexposed, and with exposure among controls. These results confirmed the absence of substantial confounding presented in Chapter 5 (Table 28).

Appendix 4. Article 1

Article: Impact of chemical exposure on cancer mortality in a French cohort of uranium processing workers

Impact of Chemical Exposure on Cancer Mortality in a French Cohort of Uranium Processing Workers

Sergey Zhivin, MD, MPH,[1]* Dominique Laurier, PhD,[1] Sylvaine Caër-Lorho, MSc,[1] Alain Acker, MD,[2] and Irina Guseva Canu, PhD[1]

Background *Nuclear workers may be exposed to a variety of chemical hazards, in addition to radiation. We examined the effect of chemical exposures on cancer mortality among French uranium processing workers at the AREVA NC Pierrelatte facility.*
Methods *A cohort of 2,897 uranium processing workers employed for at least 6 months was followed from 1968 through 2006. Exposure to uranium and potentially carcinogenic chemicals was assessed with a plant-specific job-exposure matrix. Mortality hazard ratios (HRs) for cancers of the lung, lymphohematopoietic system, kidney and bladder, brain and central nervous system (BCNS), and prostate were estimated for each specific chemical exposure, with Cox regression models stratified for sex and calendar period and adjusted for socioeconomic status. Additional adjustments enabled us to examine the effect of co-exposure to uranium and other chemicals.*
Results *Exposure to aromatic solvents was associated with increased risk of BCNS malignancies after adjustment for other chemicals (HR = 6.53, 95% CI = 1.14–37.41; n = 6) and for other chemicals and uranium (HR = 7.26, 95% CI = 0.90–58.19) in the annual exposure status model. Selected groups of lymphohematopoietic cancers were found associated with solvent exposure. Inconclusive results were found regarding chromium (VI) exposure, since only 2 workers died from lung cancer among 109 exposed.*
Conclusion *Based on our pilot study, it seemed important to take into account chemical exposures in the analyses of cancer mortality among French uranium processing workers.*
Am. J. Ind. Med. 2013. © *2013 Wiley Periodicals, Inc.*

KEY WORDS: nuclear workers; uranium; chemicals; epidemiology; solvents; chromium; ionizing radiation

INTRODUCTION

Nuclear workers at the AREVA NC Pierrelatte uranium processing plant in France are exposed predominantly to internal sources of radiation, specifically, different types of uranium. These workers have been found to be at increased risk of cancer, notably lung and lymphohematopoietic cancers [Canu et al., 2010b, 2011]. However, in addition to this radiation exposure from uranium, they are likely to have been exposed to chemical pollutants, because uranium processing includes various chemical conversion processes. Chemical hazards at uranium processing plants have been studied at similar U.S. nuclear facilities—Rocketdyne/Atomics International [Ritz et al., 2000], the Oak Ridge gaseous diffusion plant [Yiin et al., 2009], the Paducah

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Contract grant sponsor: Institut de Radioprotection et de Sûreté Nucléaire (IRSN) and AREVA NC.
Disclosure Statement: Collaborative research program in the area of Epidemiology developed by IRSN and AREVA NC.
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Accepted 2 July 2013
DOI 10.1002/ajim.22231. Published online in Wiley Online Library (wileyonlinelibrary.com).

gaseous diffusion plant [Chan et al., 2010], and Fernald Feed Materials Production Center [Anderson et al., 2012].

A previous comprehensive review of cancer risk among uranium processing workers ascertained that they were at risk for lung, larynx, and lymphohematopoietic cancers [Canu et al., 2008]. In addition, recent findings among various groups of radiation workers co-exposed to chemicals suggest that they are at increased risk for lung, lymphohematopoietic, central nervous system, and prostate cancers. As such, lung cancer has been associated with exposure to hydrazine [Ritz et al., 2006], asbestos and welding fumes [Yiin et al., 2005], and mineral oils [Zhao et al., 2005]. Lymphohematopoietic cancers have been related to exposure to hydrazine [Ritz et al., 2006], mineral oils [Zhao et al., 2005], cutting fluids [Ritz, 1999], aromatic hydrocarbons [Wing et al., 2000], benzene [Schubauer-Berigan et al., 2007], and trichloroethylene (TCE) [Zhao et al., 2005]. Central nervous system cancer has been associated with cutting fluids [Ritz, 1999], and prostate cancer with exposure to kerosene [Ritz, 1999] and TCE [Krishnadasan et al., 2007].

The reviewed literature suggests that chemical exposure might be an important component of the occupational hazards associated with cancer risk among uranium processing workers. Thus, in this study, we aimed at assessing the impact of chemical exposure on cancer mortality in a cohort of French uranium processing workers.

MATERIALS AND METHODS

Study Population and Follow-Up

The AREVA NC Pierrelatte facility was built in 1960 by the French Atomic Energy Commission to produce highly enriched uranium for military purposes, by the gaseous diffusion process. Uranium enrichment continued there through 1999, although the main activity changed to production of low- and medium-enriched uranium in 1976. Most of uranium conversion processes necessitated the use of chemicals. Uranium was the only radioactive material handled at this facility. Specific tasks performed there included handling uranium hexafluoride (UF_6) during uranium enrichment, processing UF_6, producing uranium dioxide (UO_2), transforming uranyl nitrate ($UO_2(NO_3)_2$) to oxide (U_3O_8), and converting $UO_2(NO_3)_2$ to uranium tetrafluoride (UF_4) and to uranium salt (UF_4NH_4F). In addition, general and specific maintenance operations were performed including cleaning, decontamination of leaks and repairing of industrial devices.

The cohort includes 2,897 workers employed at the establishment for at least 6 months between January 1968 and December 2006. All workers were followed for the outcome from the later of 6 months after employment began or January 1, 1968, until the earlier of the end of employment, death, or December 31, 2006. Workers with a history of employment in uranium mines were excluded. Vital status and causes of deaths for deceased individuals were extracted from the National Natural Persons Identification Index and the National Cause of Death Registry, respectively. The National Cause of Death Registry contains anonymized records of all deaths in France since 1968 and their causes. Death records were matched to cohort members by date of birth, gender, and date and place of death. The first deaths in the AREVA NC Pierrelatte cohort occurred in 1978. All causes of death were coded according to the International Classification of Diseases (ICD): the 9th revision (ICD-9) for deaths through 1999, and the 10th revision (ICD-10) for those from 2000 through 2006.

Exposure Assessment

A plant-specific job-exposure matrix (JEM) was constructed to assess annual and cumulative exposure to uranium and 15 categories of chemicals from 1960 to 2006 [Guseva Canu et al., 2008, 2009]. These included chlorinated agents, fluoride agents, nitrogenous agents, aromatic solvents, welding fumes, vitreous (rock and glass) fibers, asbestos, refractive ceramic fibers, chromium (VI) compounds (potassium dichromate, chromium trioxide), chlorine trifluoride, TCE, lead, mercury, silica gel, hydrazine, and other fuels. While the toxicity of fibers (including asbestos) is presumably of a physical (mechanical damage) rather than chemical nature [IARC, 2012b], we considered them in this study. Welding fumes consist of mixtures of different metals [Antonini, 2003], and therefore, are believed to have chemical effects on humans. Heat was also considered in the JEM. Uranium compounds in this JEM were classified as natural uranium-bearing compounds (NU) and reprocessed uranium-bearing compounds (RPU). Both NU and RPU were further classified according to their solubility (fast, moderate, and slow) on the basis of the ICRP Human Respiratory Tract Model [ICRP, 1994] and other specific workstation analytical studies [Chazel et al., 2000, 2001].

Exposure to each type of chemical and uranium compound was described in terms of frequency and relative exposure level (on a four-point scale) at each job and for different time periods during which exposure was considered constant. The results produced by the JEM were reviewed by a group of experts and validated by comparing them with data from the medical records of a random sample of workers. This review found that the sensitivity of the JEM was 73% and the specificity 83% [Guseva Canu et al., 2009]. A comparison of exposure estimators for uranium compounds based on the JEM cumulative exposure scores with internal uranium intake based on the monitoring data showed moderate to strong correlation [Guseva Canu et al., 2010]. We have described the JEM in detail in earlier publications [Guseva Canu et al., 2008, 2009, 2010].

Of the 15 chemicals in the JEM, we focused on the 7 chemicals most prevalent at the plant, most of them mentioned in previous peer-reviewed literature on nuclear workers: asbestos, TCE, aromatic solvents, hydrazine and other fuels, ceramic refractive fibers, welding fumes, and chromium (VI) compounds. Exposure to chromium (VI) and ceramic refractive fibers has not been described in previous studies of radiation workers; however, workers at this plant handled these substances.

Selection of Cancer Outcomes

Our research concentrated on cancer sites or cancers of organ groups for which associations with chemical exposures have been already described in the literature. We considered cancers with a minimum of 10 cases, but made exceptions for brain and other central nervous system (BCNS) cancers (n = 9) and for non-Hodgkin's lymphoma (n = 9). The exception for BCNS cancers was based on the probability and plausibility of the biological mechanism of direct transfer of uranium to the brain by the olfactory receptor neurons [Tournier et al., 2009]. The following cancers of a priori interest did not meet the inclusion criterion of 10 cases: cancer of the larynx (n = 6), pleural cancer (n = 5), kidney cancer (n = 5), bladder cancer (n = 5), Hodgkin's disease (no deaths), multiple myeloma (n = 4), all types of leukemia except chronic lymphocytic leukemia (n = 8), chronic lymphocytic leukemia (n = 4). We chose, however, to consider cancers of some organ groups based on similar effects of carcinogenic substances in cases of functional and/or anatomical proximity (kidney and bladder cancer) and in the case of lymphohematopoietic cancers, especially in view of the uncertainty about grouping the latter for epidemiologic investigations [EPA, 2012]. The malignancies considered were: lung (n = 53, ICD-9 162; ICD-10 C33–C34), lymphohematopoietic (n = 21, ICD-9 200, 202–208; ICD-10 C82–C85, C90–C96), kidney and bladder (n = 10, ICD-9 188–189; ICD-10 C64–C68), BCNS (n = 9, ICD-9 191–192, 225, 239.6; ICD-10 C70–C72, D32, D33, D43.0–D43.2), and prostate cancers (n = 19, ICD-9 185; ICD-10 C61). No cases of Hodgkin's disease (ICD-9 201; ICD-10 C81), malignant immunoproliferative diseases and other B-cell lymphomas (ICD-10 C88), or other specified types of T/NK-cell lymphoma (ICD-10 C86) were observed in our cohort. Chronic lymphocytic leukemia (ICD-9 204.1; ICD-10 91.1) and pleural cancer (malignant mesothelioma, ICD-9 163; ICD-10 C38.4, C45.0) were treated as separate cancer groups and not grouped with the lymphohematopoietic cancers or lung cancer, respectively.

We reviewed the peer-reviewed literature to choose in advance the chemicals to be tested in associations with specific types of cancer: lung cancer (asbestos, chromium (VI) compounds, hydrazine and other fuels, and welding fumes), lymphohematopoietic cancers (hydrazine and other fuels, solvents, TCE, and welding fumes), kidney and bladder cancer (hydrazine and other fuels, solvents), BCNS cancers (solvents and TCE), and prostate cancers (TCE).

Statistical Analysis

Three types of exposure variables were used in the analyses. The binary variable (ever vs. never exposed) allowed us to differentiate ever-exposed (annual exposure score >0) from never-exposed workers. The cumulative exposure duration variables enabled us to examine risk per year of exposure. The cumulative exposure score was used as a log-transformed continuous variable to analyze the risk per step of cumulative exposure. Zero values were attributed to unexposed workers during log-transformation. Time-lagged log-transformed continuous exposure scores accounted for a latency period. Short latency periods (2 and 5 years) were chosen for lymphohematopoietic cancers, while a 10-year lag was applied for solid cancers, as in external radiation studies. Each exposure variable was treated as time-dependent.

Cox regression models with age as the main time variable [Korn et al., 1997] were used to estimate the hazard ratios (HRs) and corresponding 95% confidence intervals (95% CI) for the associations between each type of cancer and chemical. Final models consisted of: a model adjusted for socioeconomic status and stratified by sex and 10-year calendar period, another further adjusted for other chemicals, and a third further adjusted for organ-specific uranium compounds. Models of lung cancer mortality risk were adjusted for insoluble uranium since insoluble uraniferous compounds are deposited primarily in the lungs [Leach et al., 1970, 1973]. Soluble uranium can be transported to other organs before its renal elimination and is partially retained in the bones, kidneys, and liver [ATSDR, 2012]. Therefore, statistical models of other malignancies were adjusted for soluble uranium compounds. Statistical models for lymphohematopoietic cancers were adjusted for insoluble uranium compounds because of probable uranium retention in lymphatic ganglions and nodes. Socioeconomic class was used as a proxy measurement for exposures and life-style factors that could not be assessed. Complementary analyses based on cumulative exposure levels to solvents (three-class categorical: no exposure, low to medium, and high) were run separately for different groups (1—non-Hodgkin's lymphoma (n = 9); 2—all leukemias excluding chronic lymphocytic leukemia (n = 8); and 3—non-Hodgkin's lymphoma, multiple myeloma, and chronic lymphocytic leukemia (n = 17)) [EPA, 2012] of lymphohematopoietic cancers. The cumulative exposure level used cutoff points at 0 and the 75th percentile of the cumulative exposure score. No analyses were performed for Hodgkin's disease since there were no deaths from this malignancy in our cohort. The

effect of tobacco smoking was assessed in a sub-cohort of 345 workers with available smoking data.

Statistical analyses were performed with Stata statistical software, version 11 (Stata Corporation, College Station, TX). The use of the individual data was approved by the French Data Protection Authority (CNIL) and the Pierrelatte Plant Committee of Hygiene, Safety and Working Conditions (CHSCT).

RESULTS

Descriptive Results

The AREVA NC Pierrelatte cohort consisted of 2,897 employees, mostly men (n = 2,709, 93.5%), who were followed for a mean of 27.6 years. There were 79,892 accumulated person-years during the follow-up. The study population was characterized by a high percentage of skilled workers (almost 65%) and a young age at the end of follow-up (mean: 59.9 years). The cause of death was found for 99% of the deaths: of the 460 deaths, 214 were due to cancer. A fuller description of the cohort with an external mortality analysis (SMRs) has been published elsewhere [Canu et al., 2010a, 2011; Guseva Canu et al., 2012].

Most AREVA NC Pierrelatte workers were exposed to natural uranium compounds (n = 2,337, 81%) [Canu et al., 2011]. In addition to uranium, the most common chemical exposures in the cohort were asbestos (67%), TCE (59%), aromatic solvents (43%), and hydrazine and other fuels (41%). Duration of exposure to these chemicals varied, ranging from 7.5 to 12 years (Table I).

Exposure-Risk Estimators

Table II shows HRs for mortality from lung cancer and exposure to chemicals. The risk of lung cancer among workers exposed to asbestos, ceramic refractive fibers, or welding fumes did not differ from that of unexposed workers. A non-significantly increased risk of lung cancer among workers exposed to hydrazine and other fuels was seen in models based on all three types of exposure variables. Adjusting for uranium and other chemicals showed that insoluble uranium compounds had a small confounding effect (8%). The association between lung cancer risk and exposure to hydrazine and other fuels remained unchanged after allowing for 10-year latency (HR = 1.05 per step of log-transformed cumulative exposure score, 95% CI = 0.95–1.15). A significant association between lung cancer mortality and exposure to chromium (VI) compounds was observed in univariate models and after adjustment for other types of exposure. This association was seen in the models with annual exposure status (HR = 31, 95% CI = 3.64–257.1), with cumulative exposure duration (HR = 1.31, 95% CI = 1.06–1.62), and with log-transformed cumulative exposure scores, regardless of the corresponding lag-time (Table II). It should be emphasized that analysis of the

TABLE I. Distribution of Exposed Individuals, Person-Years at Risk and Number of Observed Deaths From Specific Cancers by Type of Chemical in the AREVA NC Pierrelatte Workers Cohort (n = 2,897)

Type of chemical	Number of ever exposed workers, N (%)	Person-years at risk[a]	No. of all cancer deaths[b]	No. of lung cancer deaths[c]	No. of LH cancer deaths[d]	No. of KB cancer deaths[e]	No. of BCNS cancers deaths[f]	No. of prostate cancer deaths[g]	Cumulative exposure duration (years)[h], mean (SD)
Asbestos	1,933 (66.72)	52,759	162	41	17	7	8	15	12.13 (8.38)
Trichloroethylene	1,717 (59.27)	46,265	153	35	16	8	5	13	10.09 (7.52)
Solvents	1,258 (43.42)	31,841	86	17	12	1	6	7	10.10 (8.03)
Hydrazine and other fuels	1,175 (40.56)	25,598	72	19	7	4	2	7	9.36 (7.13)
Ceramic refractive fibers	688 (23.75)	14,616	37	7	5	0	2	3	8.32 (7.53)
Welding fumes	418 (14.43)	8,875	24	8	2	1	3	1	8.38 (7.34)
Chromium (VI) compounds	109 (3.76)	1,423	2	2	0	0	0	0	7.50 (5.66)

LH, lymphohematopoietic; KB, kidney and bladder; BCNS, brain and other central nervous system.
[a]Collected from 1968 to 2006.
[b]Two hundred fourteen (n = 214) in the cohort.
[c]Fifty three (n = 53) in the cohort.
[d]Twenty one (n = 21) in the cohort.
[e]Ten (n = 10) in the cohort.
[f]Nine (n = 9) in the cohort.
[g]Nineteen (n = 19) in the cohort.
[h]Collected from 1960 to 2006.

TABLE II. Hazard Ratios and 95% Confidence Intervals for Lung Cancer (n = 53) Mortality Associated With Exposure to Chemicals in the AREVA NC Pierrelatte Workers Cohort

Exposure variables	Asbestos	Ceramic refractive fibers	Chromium (VI) compounds	Hydrazine and other fuels	Welding fumes
Annual exposure status (ever exposed vs. never exposed)					
Model 1	0.77 (0.38–1.56)*	0.64 (0.29–1.44)	18 (3.96–82.03)	1.21 (0.68–2.17)	0.96 (0.43–2.13)
Model 2	0.72 (0.33–1.57)*	0.52 (0.21–1.29)	29 (5.37–152.5)	1.20 (0.63–2.31)	1.08 (0.47–2.49)
Model 3	0.85 (0.42–1.75)*	0.60 (0.26–1.36)	31 (3.64–257.1)	1.10 (0.61–2.00)	1.02 (0.46–2.26)
Cumulative exposure duration (continuous, per year)					
Model 1	1.01 (0.97–1.05)	1.03 (0.97–1.10)	1.31 (1.10–1.57)	1.03 (0.98–1.08)	0.99 (0.90–1.09)
Model 2	1.00 (0.96–1.05)	1.00 (0.92–1.08)	1.34 (1.11–1.63)	1.02 (0.97–1.07)	1.01 (0.91–1.12)
Model 3	1.01 (0.96–1.06)	1.00 (0.92–1.08)	1.31 (1.06–1.62)	1.02 (0.96–1.07)	1.01 (0.92–1.12)
Log-transformed cumulative exposure score (continuous, per step of score)					
Model 1	0.96 (0.88–1.06)	0.95 (0.85–1.06)	1.56 (1.23–1.98)	1.03 (0.95–1.12)	1.00 (0.88–1.13)
Model 2	0.95 (0.86–1.05)	0.92 (0.81–1.04)	1.67 (1.28–2.17)	1.03 (0.94–1.13)	1.02 (0.89–1.16)
Model 3	0.96 (0.86–1.07)	0.92 (0.81–1.04)	1.67 (1.20–2.32)	1.02 (0.93–1.12)	1.02 (0.89–1.16)
Model 3a (lag = 5 years)	0.99 (0.89–1.10)	0.93 (0.82–1.06)	1.45 (1.01–2.08)	1.04 (0.94–1.14)	1.02 (0.89–1.17)
Model 3b (lag = 10 years)	1.04 (0.94–1.16)	0.95 (0.83–1.08)	1.52 (1.05–2.19)	1.05 (0.95–1.15)	1.06 (0.92–1.22)

Model 1: Model adjusted for socio-economic status, and stratified by 10-year calendar period and sex (lag = 0 years).
Model 2: Model 1 + adjusted for other chemicals presented in the table (lag = 0 years).
Model 3: Model 2 + adjusted for insoluble uranium compounds (lag = 0 years).
*Model does not meet the proportional hazard assumption.

association between exposure to chromium (VI) compounds and lung cancer risk was based on only two lung cancer cases among 109 workers exposed to chromium (VI). A separate analysis of pleural cancer mortality with cumulative exposure scores lagged by 30 and 40 years did not show any significant association (data not shown).

In the analyses of lymphohematopoietic cancer mortality (Table III), only exposure to solvents increased the risk, and not significantly (model based on a 5-year lagged exposure score, HR = 1.11 per step of score, 95% CI = 0.97–1.28). The risk estimates related to TCE exposure were rather inconsistent. A significant association between solvent

TABLE III. Hazard Ratios and 95% Confidence Intervals for Lymphohematopoietic Cancer (n = 21) Mortality Associated With Exposure to Chemicals in the AREVA NC Pierrelatte Workers Cohort

Exposure variables	Hydrazine and other fuels	Solvents	Trichloroethylene	Welding fumes
Annual exposure status (ever exposed vs. never exposed)				
Model 1	1.11 (0.44–2.80)	1.61 (0.66–3.91)	1.07 (0.36–3.18)	0.60 (0.13–2.69)
Model 2	1.04 (0.40–2.66)	1.62 (0.61–4.28)	0.88 (0.27–2.94)	0.66 (0.14–3.08)
Model 3	0.82 (0.30–2.19)	1.66 (0.57–4.85)	0.91 (0.27–3.08)	0.71 (0.15–3.35)
Cumulative exposure duration (continuous, per year)				
Model 1	1.01 (0.92–1.11)	1.04 (0.97–1.11)	1.07 (0.99–1.15)	0.95 (0.77–1.18)
Model 2	1.01 (0.91–1.11)	1.04 (0.96–1.12)	1.07 (0.98–1.15)	0.96 (0.78–1.19)
Model 3	0.98 (0.89–1.08)	1.02 (0.94–1.10)	1.06 (0.98–1.15)	0.98 (0.80–1.21)
Log-transformed cumulative exposure score (continuous, per step of score)				
Model 1	1.01 (0.89–1.15)	1.08 (0.96–1.22)	1.04 (0.90–1.20)	0.92 (0.72–1.17)
Model 2	1.00 (0.88–1.15)	1.08 (0.95–1.23)	1.03 (0.88–1.20)	0.93 (0.73–1.19)
Model 3	0.97 (0.84–1.12)	1.08 (0.94–1.25)	1.03 (0.88–1.21)	0.94 (0.74–1.21)
Model 3a (lag = 2 years)	0.98 (0.85–1.13)	1.09 (0.95–1.26)	1.06 (0.90–1.24)	0.95 (0.74–1.23)
Model 3b (lag = 5 years)	0.97 (0.84–1.12)	1.11 (0.97–1.28)	1.10 (0.94–1.29)	0.97 (0.75–1.24)

Model 1: Model adjusted for socio-economic status, and stratified by 10-year calendar period and sex (lag = 0 years).
Model 2: Model 1 + adjusted for other chemicals presented in the table (lag = 0 years).
Model 3: Model 2 + adjusted for insoluble uranium compounds (lag = 0 years).

exposure and risk of non-Hodgkin's lymphoma was observed in the dose–response analysis among workers with high exposure (>last tertile of cumulative exposure score) (HR = 4.38, 95% CI = 1.01–18.97) (data not shown). Associations were also observed between exposure to solvents and (a) all leukemia except chronic lymphocytic leukemia (HR = 14.39, 95% CI = 2.04–101.40) and (b) a selected group of lymphohematopoietic cancers (non-Hodgkin's lymphoma, multiple myeloma, and chronic lymphocytic leukemia) (HR = 4.80, 95% CI = 0.94–24.54).

A significant excess risk of BCNS malignancies (Table IV) was observed in the binary solvent-exposure analysis, adjusted for TCE exposure (HR = 6.53, 95% CI = 1.14–37.41). After adjustment for soluble uranium compounds, the risk was higher, but no longer statistically significant (HR = 7.26, 95% CI = 0.90–58.19). The risk of kidney and bladder cancer mortality associated with exposure to hydrazine and other fuels was elevated, but not significantly so, in all models (Table IV). No association was observed between the risk of prostate cancer and TCE exposure (Table IV).

An additional adjustment for smoking in the subcohort of 345 workers whose smoking status was known did not show significant associations between chemical hazards and lung and kidney and bladder cancers (Table SI). HRs were higher for smokers, but the width of the confidence intervals appears to indicate greater uncertainty.

DISCUSSION

In this study, we examined the effects of chemical exposure on cancer mortality among French nuclear workers potentially exposed to uranium at the AREVA NC Pierrelatte facility. The results showed that exposure to aromatic solvents may increase the risk of BCNS cancer mortality. An elevated risk of lung cancer was associated with exposure to chromium (VI) compounds, but was based on only two cases. A non-significant elevated risk of mortality was observed from lung and kidney and bladder cancers after exposure to hydrazine and other fuels, and from lymphohematopoietic malignancies after exposure to aromatic solvents. It should be noted that lymphohematopoietic cancer mortality was increased in this cohort for non-Hodgkin lymphoma (SMR = 1.35, 95% CI = 0.58–2.66), and multiple myeloma (SMR = 1.10, 95% CI = 0.23–3.23) in comparison with French population [Canu et al., 2010a].

A limited number of articles have investigated associations between chemical hazards and BCNS cancer [Gomes et al., 2011], and a few of them have focused on nuclear workers [Carpenter et al., 1987, 1988]. Carpenter et al. [1988] found a positive but not significant association (odds ratio = 2.0, 95% CI = 0.7–5.5) in a binary analysis of exposure to aromatic solvents (toluene, xylene, and methyl ethyl ketone) and BCNS cancer, while no association of BCNS cancer was observed among the same population of Oak Ridge nuclear workers exposed to inhaled uranium, even

TABLE IV. Hazard Ratios and 95% Confidence Intervals From Kidney and Bladder (KB) (n = 10), Brain and Other Central Nervous System (BCNS) (n = 9), Prostate (n = 19) Cancers Associated With Exposure to Chemicals in the AREVA NC Pierrelatte Workers Cohort

	KB cancer		BCNS cancer		Prostate cancer
Exposure variables	**Hydrazine and other fuels**	**Solvents**	**Solvents**	**Trichloroethylene**	**Trichloroethylene**
Annual exposure status (ever exposed vs. never exposed)					
Model 1	1.85 (0.47–7.32)	0.15 (0.02–1.24)	2.93 (0.69–12.50)	0.48 (0.11–1.98)	0.71 (0.25–2.02)
Model 2	2.43 (0.57–10.40)	0.13 (0.01–1.10)	6.53 (1.14–37.41)	0.18 (0.03–0.97)	NA
Model 3	2.37 (0.55–10.21)	0.15 (0.02–1.32)	7.26 (0.90–58.19)	0.18 (0.03–1.17)	1.26 (0.22–7.34)
Cumulative exposure duration (continuous, per year)					
Model 1	1.03 (0.90–1.17)	0.50 (0.14–1.73)	1.03 (0.93–1.14)	1.00 (0.89–1.11)	0.99 (0.91–1.09)
Model 2	1.05 (0.91–1.20)	0.48 (0.07–3.77)	0.97 (0.84–1.11)	1.06 (0.92–1.22)	NA
Model 3	1.04 (0.91–1.20)	0.56 (0.18–1.68)	1.04 (0.93–1.17)	0.98 (0.86–1.11)	1.01 (0.92–1.12)
Log-transformed cumulative exposure score (continuous, per step of score)					
Model 1	1.09 (0.90–1.32)	0.71 (0.49–1.03)	1.11 (0.93–1.32)	0.91 (0.76–1.09)	0.95 (0.83–1.09)
Model 2	1.12 (0.91–1.36)	0.70 (0.48–1.01)	1.22 (0.98–1.52)	0.82 (0.66–1.02)	NA
Model 3	1.12 (0.92–1.36)	0.71 (0.49–1.04)	1.20 (0.94–1.52)	0.82 (0.64–1.04)	1.00 (0.82–1.24)
Model 3a (lag = 5 years)	1.12 (0.92–1.36)	0.71 (0.49–1.04)	1.08 (0.86–1.35)	0.87 (0.69–1.11)	1.01 (0.82–1.24)
Model 3b (lag = 10 years)	1.13 (0.93–1.38)	0.72 (0.49–1.05)	0.98 (0.78–1.22)	0.82 (0.65–1.04)	1.00 (0.84–1.21)

Model 1: Model adjusted for socio-economic status, and stratified by 10-year calendar period and sex (lag = 0 years).
Model 2: Model 1 + adjusted for other chemicals presented in the table (lag = 0 years).
Model 3: Model 2 + adjusted for soluble uranium compounds (lag = 0 years).
NA, not applicable.

after adjustment for chemical co-exposures [Carpenter et al., 1987]. Adjustment for soluble uranium compounds increased the BCNS cancer risk in our study, but the result was more consistent in the model based on annual exposure status. Although no excess mortality from BCNS cancers was noted in the literature review on uranium processing workers [Canu et al., 2008] and our result was based on only six BCNS cancer deaths, data exist to support the biological plausibility of our finding [Tournier et al., 2009].

The magnitude of the lung cancer risk related to chromium (VI) exposure in this cohort was high, presumably due to small sample size. Chromium (VI) compounds are considered a Group 1 carcinogen by the International Agency on Cancer Research, that is, an agent for which sufficient evidence shows that it causes cancer in humans [IARC, 2012a]. Until now, its carcinogenicity has been studied mostly among highly exposed chromium production workers [Holmes et al., 2008]. While workers in chromate production industries are exposed to a mix of different chromate salts, workers in the AREVA NC Pierrelatte cohort handled only specific chromium (VI) compounds—potassium dichromate and chromate trioxide. Although the potential carcinogenicity of chromium (VI) compounds might depend on their solubility, both insoluble and soluble chromate salts are established carcinogens [Holmes et al., 2008; Mancuso, 1997a, b]. It should be noted that our JEM classified only 109 workers as potentially exposed to chromium (VI) compounds, and only 2 cases of lung cancer occurred among them. The cumulative exposure score and cumulative duration of exposure to chromium (VI) of these two workers did not differ significantly from those of other workers. Moreover, one of these workers was a smoker. Dose–response relationship to chromium (VI) is therefore too limited for any conclusion.

Chromium is also one of the metals that might be found in welding fumes. The HRs for lung cancer mortality and exposure to welding fumes were elevated in our study, but not significantly. Two previous studies of this association among U.S. naval shipyard workers with predominantly external radiation exposure yielded inconsistent results [Yiin et al., 2005; Zaebst et al., 2009].

A non-significant increase in lung cancer mortality among workers exposed to hydrazine and other fuels was observed. Similar findings have previously been reported in both mortality and incidence studies among aerospace and radiation workers of Rocketdyne/Atomics International exposed to hydrazine [Ritz et al., 1999, 2006; Morgenstern and Ritz, 2001], although one extension of the Rocketdyne aerospace workers cohort showed no association [Boice et al., 2006]. The association between hydrazine and lung cancer risk remains controversial, even in cohorts of hydrazine production workers [Wald et al., 1984; Morris et al., 1995]. It is important to note that the workers in the AREVA NC Pierrelatte cohort were exposed to a mix of hydrazine and other fuels including kerosene and gas oil. These fuels contain polycyclic aromatic hydrocarbons (PAHs), some of which are confirmed lung carcinogens [IARC, 1989]. Nonetheless, their exposure is unlikely to be sufficient to cause an observable effect on lung cancer deaths. According to De Matteis et al. [2012], a carcinogenic effect by PAHs in the lungs might only be evident at high levels of exposure.

We did not observe an association between exposure to asbestos or ceramic refractive fibers and lung cancer risk in our study; however, when we allowed for a 10-year lag of a log-transformed cumulative exposure score, the risk rose above 1 for lung cancer and asbestos exposure (HR = 1.04, 95% CI = 0.94–1.16). Asbestos remains one of the main occupational risk factors for lung cancer in France [Wild et al., 2012]. A previous study among naval shipyard workers [Yiin et al., 2005] exposed to asbestos reported an excess risk of lung cancer, though only in univariate statistical models. Pleural cancer is also known as malignant mesothelioma and is strongly associated with asbestos exposure [Price and Ware, 2004]. Nonetheless, the impact of low-level radiation exposure to nuclear workers on their risk of malignant mesothelioma remains uncertain [Metz-Flamant et al., 2011]. Asbestos-induced malignant mesothelioma may have a latent period of 40 years or more years [Kamp, 2009], and the burden of malignant mesothelioma mortality continues to rise in France [Gilg Soit Ilg et al., 1998]. Thus, a further follow-up of AREVA NC Pierrelatte workers for this disease will be necessary.

Our results showing an elevated risk of lymphohematopoietic cancers among workers exposed to aromatic solvents seem consistent with previous studies. Solvents are strongly suspected to cause lymphatic and hematopoietic malignancies [Clapp et al., 2008]. Few articles have mentioned specific chemical types of solvents; however, aromatic solvents (and particularly benzene) are more prone to be associated with lymphohematopoietic cancers [Descatha et al., 2005]. Benzene is a Group 1 carcinogen based on evidence for leukemia [IARC, 1982]. Many workers in this cohort are likely to have been exposed to a mix of known carcinogenic aromatic solvents (benzene, toluene, and xylene), and the association we observed thus seems to be true. A nested case-control study conducted among five U.S. cohorts of radiation workers showed a dose-effect association between leukemia risk and benzene exposure [Schubauer-Berigan et al., 2007]. The risk of death from lymphohematopoietic cancer in our study remained elevated (albeit not significantly) when a 5-year lagged log-transformed cumulative exposure score was used (HR = 1.11, 95% CI = 0.97–1.28). A limitation of the analysis of these lymphohematopoietic malignancies in our study is that we considered all lymphatic and hematopoietic malignancies in one category, because of the small number of cases. These cancers might have different etiologies [EPA, 2012]. All dose-effect

associations for the different groups of lymphohematopoietic cancers were increased, especially for leukemia, as seen in previous studies among nuclear workers [Schubauer-Berigan et al., 2007]. An association between the risk of lymphohematopoietic cancers and TCE exposure was less clear. An increased risk of non-Hodgkin's lymphoma has been suggested among aerospace workers [Zhao et al., 2005], but the association was not significant, as it was in our study.

An association between exposure to hydrazine and other fuels and kidney and bladder cancers was also positive, but non-significant. There were some indications of an increased risk of kidney cancer among Rocketdyne aerospace workers in the United States [Boice et al., 2006; Ritz et al., 2006], but their level of hydrazine exposure is much higher than that of the nuclear workers in our cohort.

The risk of prostate cancer mortality associated with TCE exposure was not elevated, even after adjustment for uranium compounds. A positive and significant association between TCE exposure and prostate cancer incidence was reported among Rocketdyne aerospace workers [Krishnadasan et al., 2007]. Our results, however, are based exclusively on mortality data. Prostate cancer is generally not fatal, and an incidence study might well be more appropriate.

Impact of Uranium and Chemical Exposures

We updated our previous analysis of lung and lymphohematopoietic cancer mortality and exposure to uranium (Table SII). HRs were similar to those based on chemical exposure; higher risks were observed for slowly soluble uraniferous compounds, as in our previous publication [Canu et al., 2011]. We also examined the mortality from cancers of the kidney and bladder, BCNS, and prostate related to uranium (Table SIII). Analysis of cancers of the kidney and bladder and BCNS was limited, however, because most individuals were exposed only to natural uranium. There was, however, a trend towards increasing risk with decreasing solubility of the uranium compounds. Workers exposed to slowly soluble reprocessed uranium had the highest risk of prostate cancer mortality in multivariate models, according to every exposure model: annual exposure status (HR = 4.45, 95% CI = 0.46–43.20), cumulative duration exposure (HR = 1.18, 95% CI = 0.98–1.42), or log-transformed cumulative exposure score (HR = 1.17, 95% CI = 0.91–1.50).

Magnitude of HRs associated with chemical exposure shows that chemical exposures might also have an impact on cancer mortality among AREVA NC Pierrelatte workers. This finding underlines the importance of not neglecting chemical exposures among nuclear workers [Wing et al., 2000; Richardson et al., 2013]. Increasing the awareness of potentially exposed workers is a necessary goal in the workplace. A recent study on attitudes towards the use of personal protective equipment among uranium processing workers found that they generally pay more attention to protecting themselves against radiological compared with chemical risks [Guseva Canu et al., 2013].

CONCLUSION

To best of our knowledge, our study is the first European study to consider the impact of chemical exposure and uranium compounds of different solubility on cancer mortality among nuclear workers.

This was a pilot epidemiologic investigation among French uranium processing workers; as such, our findings are subject to important limitations: only a small percentage of the cohort has thus far died (14%), and the number of cancer deaths is small (n = 214). Using three exposure definitions and several models for each cancer outcome might lead to a problem of multiple comparisons; however, we sought to minimize this problem by choosing specific outcomes and specific exposures based on biological knowledge and a literature review. We consider our findings as preliminary results that should be confirmed by continuing the follow-up of the AREVA NC Pierrelatte cohort and in the analyses of the French cohort of uranium cycle workers (TRACY U cohort, n = 12,657) [Samson et al., 2009]. In conclusion, our findings were consistent with the previous data. Both chemical hazards and uranium compounds may have an impact on cancer mortality among French uranium processing workers, but these results should be considered cautiously.

ACKNOWLEDGMENTS

This study was carried out and funded as part of the collaborative research program in the area of Epidemiology developed by Institut de Radioprotection et de Sûreté Nucléaire (IRSN) and AREVA NC. Authors state that AREVA NC had no control over the design, description of results, and publication of the results. The authors wish to acknowledge the help of Professor David Richardson (University of North Carolina at Chapel Hill) for his careful review of the earlier versions of this manuscript.

REFERENCES

Anderson JL, Daniels RD, Fleming DA, Tseng CY. 2012. Exposure assessment for a cohort of workers at a former uranium processing facility. J Expo Sci Environ Epidemiol 22:324–330.

Antonini JM. 2003. Health effects of welding. Crit Rev Toxicol 33:61–103.

ATSDR. 2012. Toxicological profile for uranium. Atlanta: U.S. Department of Health and Human Services.

Boice JD Jr, Marano DE, Cohen SS, Mumma MT, Blot WJ, Brill AB, Fryzek JP, Henderson BE, McLaughlin JK. 2006. Mortality among Rocketdyne workers who tested rocket engines, 1948–1999. J Occup Environ Med 48:1070–1092.

Canu IG, Ellis ED, Tirmarche M. 2008. Cancer risk in nuclear workers occupationally exposed to uranium-emphasis on internal exposure. Health Phys 94:1–17.

Canu IG, Cardis E, Metz-Flamant C, Caër-Lorho S, Auriol B, Wild P, Laurier D, Tirmarche M. 2010a. French cohort of the uranium processing workers: Mortality pattern after 30-year follow-up. Int Arch Occup Environ Health 83:301–308.

Canu IG, Jacob S, Cardis E, Wild P, Caër-Lorho S, Auriol B, Laurier D, Tirmarche M. 2010b. Reprocessed uranium exposure and lung cancer risk. Health Phys 99:308–313.

Canu IG, Jacob S, Cardis E, Wild P, Caër S, Auriol B, Garsi JP, Tirmarche M, Laurier D. 2011. Uranium carcinogenicity in humans might depend on the physical and chemical nature of uranium and its isotopic composition: Results from pilot epidemiological study of French nuclear workers. Cancer Causes Control 22:1563–1573.

Carpenter AV, Flanders WD, Frome EL. 1987. CNS cancers and radiation exposure: A case-control study among workers at two nuclear facilities. J Occup Med 29:601–604.

Carpenter AV, Flanders WD, Frome EL, Tankersley WG, Fry SA. 1988. Chemical exposures and central nervous system cancers: A case-control study among workers at two nuclear facilities. Am J Ind Med 13:351–362.

Chan C, Hughes TS, Muldoon S, Aldrich T, Rice C, Hornung R, Brion G, Tollerud DJ. 2010. Mortality patterns among Paducah Gaseous Diffusion Plant Workers. J Occup Environ Med 52:725–732.

Chazel V, Houpert P, Ansoborlo E, Henge-Napoli MH, Paquet F. 2000. Variation of solubility, biokinetics and dose coefficient of industrial uranium oxides according to specific surface area. Radiat Prot Dosimetry 88:223–231.

Chazel V, Houpert P, Paquet F, Ansoborlo E. 2001. Effect of absorption parameters on calculation of the dose coefficient: Example of classification of industrial uranium compounds. Radiat Prot Dosimetry 94:261–268.

Clapp RW, Jacobs MM, Loechler EL. 2008. Environmental and occupational causes of cancer: New evidence 2005–2007. Rev Environ Health 23:1–37.

De Matteis S, Consonni D. Lubin JH. Tucker M. Peters S. Vermeulen RC. Kromhout H, Bertazzi PA, Caporaso NE, Pesatori AC, Wacholder S, Landi MT. 2012. Impact of occupational carcinogens on lung cancer risk in a general population. Int J Epidemiol 41(3):711–721.

Descatha A, Jenabian A, Conso F, Ameille J. 2005. Occupational exposures and haematological malignancies: Overview on human recent data. Cancer Causes Control 16:939–953.

EPA. 2012. Lymphohematopoietic cancers induced by chemicals and other agents: Overview and implications for risk assessment. Washington, DC: U.S. National Center for Environmental Assessment.

Gilg Soit Ilg A, Bignon J, Valleron AJ. 1998. Estimation of the past and future burden of mortality from mesothelioma in France. Occup Environ Med 55:760–765.

Gomes J, Al Zayadi A, Guzman A. 2011. Occupational and environmental risk factors of adult primary brain cancers: A systematic review. Int J Occup Environ Med 2:82–111.

Guseva Canu I, Molina G, Goldberg M, Collomb P, David JC, Perez P, Paquet F, Tirmarche M. 2008. Development of a job exposure matrix for the epidemiological follow-up of workers in the French nuclear industry. Results of a pilot study. Rev Epidemiol Sante Publique 56:21–29.

Guseva Canu I, Paquet F, Goldberg M, Auriol B, Bérard P, Collomb P, David JC, Molina G, Perez P, Tirmarche M. 2009. Comparative assessing for radiological, chemical, and physical exposures at the French uranium conversion plant: Is uranium the only stressor? Int J Hyg Environ Health 212:398–413.

Guseva Canu I, Laurier D, Caër-Lorho S, Samson E, Timarche M, Auriol B, Bérard P, Collomb P, Quesne B, Blanchardon E. 2010. Characterisation of protracted low-level exposure to uranium in the workplace: A comparison of two approaches. Int J Hyg Environ Health 213:270–277.

Guseva Canu I, Garsi JP, Caër-Lorho S, Jacob S, Collomb P, Acker A, Laurier D. 2012. Does uranium induce circulatory diseases? First results from a French cohort of uranium workers. Occup Environ Med 69:404–409.

Guseva Canu I, Faust S, Canioni P, Collomb P, Samson E, Laurier D. 2013. Attitude towards personal protection equipment in the French nuclear fuel industry. Arh Hig Rada Toksikol 64(2):285–293.

Holmes AL, Wise SS, Wise JP Sr. 2008. Carcinogenicity of hexavalent chromium. Indian J Med Res 128:353–372.

IARC. 1982. Some industrial chemicals and dyestuffs. IARC Monogr Eval Carcinog Risk Chem Hum, volume 29.

IARC. 1989. Crude oil and major petroleum fuels. IARC Monogr Eval Carcinog Risk Chem Hum, volume 45.

IARC. 2012a. Chromium (VI) compounds. A review of human carcinogens: Chemical agents and related occupations. IARC Monogr Eval Carcinog Risk Chem Hum, volume 100C.

IARC. 2012b. A review of human carcinogens: Arsenic, metals, fibres, and dusts. IARC Monogr Eval Carcinog Risk Chem Hum, volume 100C.

ICRP. 1994. Human respiratory tract model for radiological protection. Publication 66. Oxford: Pergamon Press.

Kamp DW. 2009. Asbestos-induced lung diseases: An update. Transl Res 153:143–152.

Korn EL, Graubard BI, Midthune D. 1997. Time-to-event analysis of longitudinal follow-up of a survey: Choice of the time-scale. Am J Epidemiol 145:72–80.

Krishnadasan A, Kennedy N, Zhao Y, Morgenstern H, Ritz B. 2007. Nested case-control study of occupational chemical exposures and prostate cancer in aerospace and radiation workers. Am J Ind Med 50:383–390.

Leach LJ, Maynard EA, Hodge HC, Scott JK, Yuile CL, Sylvester GE, Wilson HB. 1970. A five-year inhalation study with natural uranium dioxide (UO 2) dust. I. Retention and biologic effect in the monkey, dog and rat. Health Phys 18:599–612.

Leach LJ, Yuile CL, Hodge HC. 1973. A five year inhalation study with natural uranium dioxide (UO2) dust. II. Postexposure retention and biologic effects in the monkey, dog and rat. Health Phys 25:239–258.

Mancuso TF. 1997a. Chromium as an industrial carcinogen: Part I. Am J Ind Med 31:129–139.

Mancuso TF. 1997b. Chromium as an industrial carcinogen: Part II. Chromium in human tissues. Am J Ind Med 31:140–147.

Metz-Flamant C, Guseva Canu I, Laurier D. 2011. Malignant pleural mesothelioma risk among nuclear workers: A review. J Radiol Prot 31:9–23.

Morgenstern H, Ritz B. 2001. Effects of radiation and chemical exposures on cancer mortality among Rocketdyne workers: A review of three cohort studies. Occup Med 16:219–237.

Morris J, Densem JW, Wald NJ, Doll R. 1995. Occupational exposure to hydrazine and subsequent risk of cancer. Occup Environ Med 52:43–45.

Price B, Ware A. 2004. Mesothelioma trends in the United States: An update based on surveillance, epidemiology, and end results program data for 1973 through 2003. Am J Epidemiol 159:107–112.

Richardson DB, Wine S, Keil A, Wolf S. 2013. Mortality among workers at Oak Ridge National Laboratory. Am J Ind Med 56(7):725–732.

Ritz B. 1999. Cancer mortality among workers exposed to chemicals during uranium processing. J Occup Environ Med 41:556–566.

Ritz B, Morgenstern H, Froines J, Moncau J. 1999. Chemical exposures of rocket-engine test-stand personnel and cancer mortality in a cohort of aerospace workers. J Occup Environ Med 41:903–910.

Ritz B, Morgenstern H, Crawford-Brown D, Young B. 2000. The effects of internal radiation exposure on cancer mortality in nuclear workers at Rocketdyne/Atomics International. Environ Health Perspect 108:743–751.

Ritz B, Zhao Y, Krishnadasan A, Kennedy N, Morgenstern H. 2006. Estimated effects of hydrazine exposure on cancer incidence and mortality in aerospace workers. Epidemiology 17:154–161.

Samson E, Guseva Canu I, Acker A, Laurier D, Tirmarche M. 2009. TRACY U: The French cohort of uranium cycle workers. 10th International Conference on the Health Effects of Incorporated Radionuclides (HEIR), Santa Fe, USA, 10–14 May 2009.

Schubauer-Berigan MK, Daniels RD, Fleming DA, Markey AM, Couch JR, Ahrenholz SH, Burphy JS, Anderson JL, Tseng CY. 2007. Risk of chronic myeloid and acute leukemia mortality after exposure to ionizing radiation among workers at four U.S. nuclear weapons facilities and a nuclear Naval Shipyard. Radiat Res 167:222–232.

Tournier BB, Frelon S, Tourlonias E, Agez L, Delissen O, Dublineau I, Paquet F, Petitot F. 2009. Role of the olfactory receptor neurons in the direct transport of inhaled uranium to the rat brain. Toxicol Lett 190: 66–73.

Wald N, Boreham J, Doll R, Bonsall J. 1984. Occupational exposure to hydrazine and subsequent risk of cancer. Br J Ind Med 41:31–34.

Wild P, Gonzalez M, Bourgkard E, Courouble N, Clément-Duchêne C, Martinet Y, Févotte J, Paris C. 2012. Occupational risk factors have to be considered in the definition of high-risk lung cancer populations. Br J Cancer 106:1346–1352.

Wing S, Richardson D, Wolf S, Mihlan G, Crawford-Brown D, Wood J. 2000. A case control study of multiple myeloma at four nuclear facilities. Ann Epidemiol 10:144–153.

Yiin JH, Schubauer-Berigan MK, Silver SR, Daniels RD, Kinnes GM, Zaebst DD, Couch JR, Kubale TL, Chen PH. 2005. Risk of lung cancer and leukemia from exposure to ionizing radiation and potential confounders among workers at the Portsmouth Naval Shipyard. Radiat Res 163:603–613.

Yiin JH, Anderson JL, Daniels RD, Seel EA, Fleming DA, Waters KM, Chen PH. 2009. A nested case-control study of multiple myeloma risk and uranium exposure among workers at the Oak Ridge Gaseous Diffusion Plant. Radiat Res 171:637–645.

Zaebst DD, Seel EA, Yiin JH, Nowlin SJ, Chen P. 2009. Summary of retrospective asbestos and welding fume exposure estimates for a nuclear naval shipyard and their correlation with radiation exposure estimates. J Occup Environ Hyg 6:404–414.

Zhao Y, Krishnadasan A, Kennedy N, Morgenstern H, Ritz B. 2005. Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers. Am J Ind Med 48:249–258.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.

TABLE SI. Risk of Mortality From Lung (n = 19) and Kidney and Bladder (KB) (n = 6) Cancers by Exposure (Ever vs. Never Exposed) to Cancer-Specific Chemicals in the Subcohort of 345 AREVA NC Pierrelatte Workers With Available Smoking Data (Hazard Ratios and Their 95% Confidence Intervals)

TABLE SII. Hazard Ratios and 95% Confidence Intervals for Mortality From Lung Cancer (n = 53) and Lymphohematopoietic Cancers (n = 21) Associated With Exposure to Different Types of Uranium Compounds in the AREVA NC Pierrelatte Workers Cohort

TABLE SIII. Hazard Ratios and 95% Confidence Intervals for Mortality From Cancers of the Kidney and Bladder (KB) (n = 10), Brain and Other Central Nervous System (BCNS) (n = 9), and Prostate (n = 19) Associated With Exposure to Different Types of Uranium Compounds in the AREVA NC Pierrelatte Workers Cohort.

Supplementary table I. Risk of Mortality from Lung (n=19) and Kidney and Bladder (KB) (n=6) Cancers by Exposure (Ever vs. Never Exposed) to Cancer-Specific Chemicals in the Subcohort of 345 AREVA NC Pierrelatte Workers with Available Smoking Data (Hazard Ratios and their 95% Confidence Intervals)

Exposure variables	Asbestos	Ceramic refractive fibers	Chromium (VI) compounds	Hydrazine and other fuels	Welding fumes
			Lung cancer		
Model 1	0.28 (0.08-0.98)	0.28 (0.03-2.39)	16.29 (0.70-380)	0.99 (0.28-3.57)	0.31 (0.03-2.65)
Model 2	0.26 (0.07-0.94)	0.27 (0.03-2.31)	13.53 (0.55-329)	0.98 (0.26-3.66)	0.35 (0.04-3.22)
Smoking	4.43 (0.58-33.8)	4.30 (0.56-32.7)	4.59 (0.61-34.8)	4.60 (0.61-34.9)	3.68 (0.48-28.2)
			KB cancer*		
Model 1	NA	NA	NA	2.25 (0.29-17.6)	NA
Model 1	NA	NA	NA	2.32 (0.29-18.6)	NA
Smoking	NA	NA	NA	2.18 (0.27-17.4)	NA

Model 1: Model, adjusted for socio-economic status, soluble/insoluble uranium compounds, other chemicals, and stratified by 10-year calendar period and sex (lag=0 years)
Model 2: Model, adjusted for socio-economic status, soluble/insoluble uranium compounds, other chemicals and smoking, and stratified by 10-year calendar period and sex (lag=0 years)
Smoking: Model, adjusted for socio-economic status, and stratified by 10-year calendar period and sex (only among smokers) (lag=0 years)
NA: not applicable

***** Model 1 for KB cancer was adjusted for soluble uranium compounds

Supplementary Table II. Hazard Ratios and 95% Confidence Intervals for Mortality from Lung Cancer (n=53) and Lymphohematopoietic Cancers (n=21) Associated with Exposure to Different Types of Uranium Compounds in the AREVA NC Pierrelatte Workers Cohort

	Exposure variables	Natural uranium			Reprocessed uranium		
		Type F	Type M	Type S	Type F	Type M	Type S
Lung cancer	**Annual exposure status (ever exposed vs. never exposed)**						
	Model 1	0.60 (0.30-1.18)	0.81 (0.46-1.44)	0.87 (0.46-1.65)	0.75 (0.31-1.80)	1.76 (0.60-5.21)	1.89 (0.56-6.41)
	Model 2	0.63 (0.30-1.34)	0.75 (0.39-1.42)	0.79 (0.39-1.61)	0.80 (0.23-2.73)	1.15 (0.28-4.65)	0.96 (0.16-5.56)
	Model 3	0.64 (0.31-1.36)	0.81 (0.43-1.52)	0.92 (0.48-1.77)	1.02 (0.34-3.07)	2.03 (0.67-6.11)	2.02 (0.65-7.80)
	Cumulative exposure duration (continuous, per year)						
	Model 1	1.02 (0.98-1.06)	1.03 (0.98-1.07)	1.02 (0.96-1.07)	1.02 (0.93-1.13)	1.12 (1.02-1.24)	1.11 (1.00-1.24)
	Model 2	1.04 (0.99-1.10)	1.03 (0.98-1.09)	0.99 (0.92-1.06)	0.99 (0.86-1.13)	1.02 (0.87-1.20)	1.00 (0.85-1.18)
	Model 3	1.03 (0.99-1.07)	1.04 (0.99-1.09)	1.03 (0.97-1.09)	1.07 (0.96-1.19)	1.13 (1.03-1.25)	1.13 (1.01-1.25)
	Log-transformed cumulative exposure score (continuous, per step of score)						
	Model 1	0.95 (0.90-1.02)	0.99 (0.93-1.06)	0.99 (0.92-1.07)	0.97 (0.88-1.07)	1.08 (0.96-1.21)	1.09 (0.96-1.24)
	Model 2	0.98 (0.91-1.05)	1.01 (0.94-1.09)	1.03 (0.94-1.13)	0.98 (0.84-1.14)	1.04 (0.89-1.23)	1.02 (0.84-1.24)
	Model 3	0.96 (0.90-1.03)	1.00 (0.93-1.07)	1.00 (0.93-1.08)	1.01 (0.90-1.14)	1.10 (0.97-1.24)	1.11 (0.98-1.26)
Lymphohematopoietic cancer	**Annual exposure status (ever exposed vs. never exposed)**						
	Model 1	1.05 (0.30-3.75)	1.05 (0.43-2.60)	1.13 (0.43-2.97)	1.24 (0.35-4.42)	1.26 (0.15-10.61)	7.38 (1.71-31.91)
	Model 2	0.88 (0.15-4.97)	0.97 (0.34-2.71)	0.89 (0.30-2.67)	1.08 (0.29-4.03)	1.07 (0.12-9.38)	6.66 (1.42-31.22)
	Model 3	0.85 (0.15-4.78)	0.87 (0.33-2.34)	0.88 (0.30-2.62)	1.05 (0.28-3.89)	1.04 (0.12-9.09)	6.81 (1.45-31.90)
	Cumulative exposure duration (continuous, per year)						
	Model 1	1.03 (0.96-1.11)	1.04 (0.97-1.12)	1.07 (0.99-1.15)	0.95 (0.75-1.21)	0.78 (0.33-1.89)	1.16 (1.01-1.33)
	Model 2	1.04 (0.96-1.14)	1.06 (0.98-1.15)	1.07 (0.98-1.15)	0.93 (0.73-1.19)	0.76 (0.30-1.89)	1.15 (1.00-1.33)
	Model 3	1.04 (0.95-1.13)	1.04 (0.97-1.13)	1.06 (0.98-1.15)	0.92 (0.73-1.19)	0.75 (0.30-1.89)	1.15 (1.00-1.33)
	Log-transformed cumulative exposure score (continuous, per step of score)						
	Model 1	1.03 (0.91-1.16)	1.02 (0.92-1.12)	1.02 (0.92-1.14)	1.00 (0.86-1.17)	0.98 (0.75-1.29)	1.21 (1.03-1.43)
	Model 2	1.03 (0.87-1.23)	1.01 (0.91-1.14)	1.00 (0.88-1.13)	0.98 (0.84-1.15)	0.96 (0.73-1.27)	1.20 (1.01-1.43)
	Model 3	1.03 (0.87-1.23)	1.00 (0.90-1.12)	1.00 (0.88-1.13)	0.98 (0.84-1.15)	0.96 (0.73-1.27)	1.20 (1.01-1.43)

Model 1: Univariate model, adjusted for socio-economic status, and stratified by 10-year calendar period and sex (lag=0 years)
Model 2: Model 1+adjusted for cancer-specific chemicals (lag=0 years)
Model 3: Model 2, but adjusted for other selected chemicals as in [I. Guseva Canu et al., 2012] (lag=0 years)

Uranium compounds were classified in terms of absorption types (F fast; M moderate; S slow solubility) according to [ICRP, 1994] and [Chazel et al., 2000; Chazel et al., 2001].

Supplementary Table III. Hazard Ratios and 95% Confidence Intervals for Mortality from Cancers of the Kidney and Bladder (KB) (n=10), Brain and Other Central Nervous System (BCNS) (n=9), and Prostate (n=19) Associated with Exposure to Different Types of Uranium Compounds in the AREVA NC Pierrelatte Workers Cohort

	Exposure variables	Natural uranium			Reprocessed uranium		
		Type F	Type M	Type S	Type F	Type M	Type S
KB cancer	**Annual exposure status (ever exposed vs. never exposed)**						
	Model 1	0.83 (0.16-4.36)	0.44 (0.10-1.85)	0.39 (0.05-3.23)	NA	NA	NA
	Model 2	1.20 (0.23-6.31)	0.72 (0.16-3.33)	1.36 (0.13-14.59)	NA	NA	NA
	Cumulative exposure duration (continuous, per year)						
	Model 1	1.02 (0.93-1.13)	0.93 (0.80-1.09)	0.67 (0.26-1.71)	NA	NA	NA
	Model 2	1.04 (0.94-1.16)	0.97 (0.83-1.12)	0.81 (0.37-1.79)	NA	NA	NA
	Log-transformed cumulative exposure score (continuous, per step of score)						
	Model 1	0.98 (0.84-1.14)	0.90 (0.77-1.07)	0.86 (0.64-1.15)	NA	NA	NA
	Model 2	1.02 (0.87-1.19)	0.95 (0.80-1.13)	0.98 (0.71-1.35)	NA	NA	NA
BCNS cancer	**Annual exposure status (ever exposed vs. never exposed)**						
	Model 1	0.75 (0.13-4.19)	1.34 (0.30-6.01)	1.25 (0.30-5.19)	2.63 (0.58-11.90	NA	NA
	Model 2	0.64 (0.06-6.40)	1.09 (0.21-5.67)	0.86 (0.17-4.19)	2.21 (0.45-10.86)	NA	NA
	Cumulative exposure duration (continuous, per year)						
	Model 1	0.98 (0.89-1.08)	1.05 (0.95-1.15)	1.04 (0.93-1.15)	1.04 (0.86-1.25)	NA	NA
	Model 2	1.01 (0.90-1.12)	1.05 (0.95-1.16)	1.01 (0.90-1.14)	1.01 (0.83-1.21)	NA	NA
	Log-transformed cumulative exposure score (continuous, per step of score)						
	Model 1	0.94 (0.81-1.09)	1.02 (0.87-1.19)	1.02 (0.87-1.20)	1.11 (0.94-1.31)	NA	NA
	Model 2	0.91 (0.72-1.14)	1.00 (0.84-1.20)	0.98 (0.82-1.17)	1.08 (0.91-1.28)	NA	NA
Prostate cancer	**Annual exposure status (ever exposed vs. never exposed)**						
	Model 1	0.51 (0.17-1.52)	1.08 (0.41-2.85)	0.37 (0.08-1.63)	1.46 (0.40-5.36)	2.68 (0.28-25.17)	4.04 (0.42-38.59)
	Model 2	0.41 (0.07-2.47)	1.19 (0.43-3.28)	0.38 (0.08-1.75)	1.59 (0.42-6.01)	2.96 (0.31-28.45)	4.45 (0.46-43.20)
	Cumulative exposure duration (continuous, per year)						
	Model 1	0.98 (0.92-1.06)	1.00 (0.92-1.09)	1.01 (0.91-1.13)	1.14 (0.99-1.30)	1.17 (0.97-1.40)	1.17 (0.97-1.41)
	Model 2	1.00 (0.91-1.10)	1.01 (0.92-1.10)	1.02 (0.91-1.13)	1.15 (1.00-1.31)	1.17 (0.98-1.41)	1.18 (0.98-1.42)
	Log-transformed cumulative exposure score (continuous, per step of score)						
	Model 1	0.93 (0.84-1.03)	1.02 (0.91-1.13)	0.90 (0.76-1.06)	1.05 (0.91-1.21)	1.12 (0.87-1.43)	1.16 (0.90-1.48)
	Model 2	0.88 (0.73-1.05)	1.03 (0.92-1.15)	0.90 (0.76-1.07)	1.06 (0.91-1.23)	1.13 (0.88-1.45)	1.17 (0.91-1.50)

Model 1: Univariate model, adjusted for socio-economic status, and stratified by 10-year calendar period and sex (lag=0 years)
Model 2: Model 1+adjusted for cancer-specific chemicals (lag=0 years)
NA: not applicable

Appendix 5. Article 2

Article: Health effects of occupational exposure to uranium: Do physicochemical properties matter?

International Journal of Radiation Biology, November 2014; 90(11): 1104–1113

ISSN 0955-3002 print / ISSN 1362-3095 online
DOI: 10.3109/09553002.2014.943849

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healthcare

Health effects of occupational exposure to uranium: Do physicochemical properties matter?

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Abstract

***Purpose*: Physicochemical properties of uranium, including isotopic composition and solubility, are determinants of its toxicity. We reviewed epidemiological studies in civilian and military workers known to be exposed to uranium with different physicochemical properties to investigate its long-term effects, such as cancerous and circulatory diseases.**

***Materials and methods:* We systematically searched the Pubmed and the Scopus databases to identify studies of uranium-processing workers (published between 1980 and 2013) and veterans of the wars in the Persian Gulf and the Balkans (published between 1991 and 2013) in which defined outcomes, such as lung, lymphohematopoietic, kidney cancers, and circulatory diseases were examined. Results from these studies in terms of risk of each health outcome (mortality or incidence) and analyses of dose-response relationship were examined to present the impact of uranium physicochemical properties on the observed results.**

***Results:* Twenty-seven articles were reviewed. There is some evidence for increased lung cancer risk among uranium-processing workers. The evidence is less strong for lymphohematopoietic cancer. We found that most of the studies insufficiently assessed the physicochemical properties of uranium and some of them used proxies for the exposure assessment and risk estimation analyses. Studies of veterans of the wars in the Persian Gulf and the Balkans are uninformative in respect to internal uranium exposure.**

***Conclusions:* Existing epidemiological data on the physicochemical properties of uranium and associated health outcomes are inconclusive. Further studies among certain groups of uranium-processing workers (uranium-enrichment and fuel-fabrication workers) could contribute to our knowledge of the health effects of uranium with respect to its physicochemical properties.**

Keywords: Review, uranium, physicochemical, ionizing radiation, occupational, epidemiology

Introduction

External exposure of humans to low doses of gamma-radiation is suspected to increase the risk of several cancers (Muirhead et al. 2009) and induce circulatory diseases (Advisory Group on Ionising Radiation [AGIR] 2010, Little et al. 2012). Strong worldwide evidence exists for an association between lung cancer risk and internal radiation exposure to radon gas and its decay products (Tirmarche et al. 2010). By contrast, there is little information available on associations between the risk of health effects and internal radiation exposure after inhalation of uranium dusts (Laurier et al. 2012). In particular, there is very little known about the impact of different physicochemical properties of uranium on such health risks.

Uranium is a ubiquitous element in the Earth's crust, and most of uranium isotopes emit alpha radiation when undergoing radioactive decay (Agency for Toxic Substances & Disease Registry [ATSDR] 2012). Uranium can exist as one of four broad industrial isotopic forms: Natural (99% of ^{238}U, 0.711% of ^{235}U and 0.005 of ^{234}U), enriched (increased ratio of ^{235}U and ^{234}U), depleted (decreased ratio of ^{235}U and ^{234}U), and reprocessed (^{236}U, neptunium, plutonium, americium and other transuranium elements ingrown in the nuclear fuel during reactor operations). Specifically related to inhalation of uranium, solubility is a characteristic that relates to clearance from the human lung. The International Commission of Radiological Protection (ICRP) lists three types of solubility (fast, moderate, and slow) that determine the uranium absorption rate of the blood (ICRP 1994).

Uranium toxicity depends on its physicochemical properties, including isotopic composition and solubility (Leggett et al. 2012). Enriched uranium ($>3\%$ enriched for civil use or $>90\%$ enriched for military use) is mostly radiotoxic because ^{235}U and ^{234}U are more radioactive than ^{238}U. Chemical toxicity, on the other hand, is the main concern for natural and depleted uranium (DU). Insoluble forms of uranium always

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(Received 1 November 2013; revised 20 May 2014; accepted 7 July 2014)

represent a higher radiotoxic potential because of their longer retention in the human lung.

Uranium-processing workers handle uranium compounds with various physicochemical properties, while war veterans have been only exposed to DU. The latter group include veterans of wars in the Persian Gulf and in the Balkans which took place in the 1990s (hereafter referred as 'war veterans'), and in which DU was extensively used. Epidemiological studies of these two specific populations are of particular interest since they represent the major occupationally exposed groups with exposure to uranium with different physicochemical forms. In addition, the uranium exposure among these groups may occur at measurable level, as opposed to the general population.

A previous literature review of workers occupationally exposed to uranium found that these workers were at risk for lung, lymphohematopoietic, but not kidney cancers (Canu et al. 2008). More recent studies have shown that exposure to specific types of uranium is associated with increased mortality from lung and lymphohematopoietic cancers (Canu et al. 2011). More recently still, associations between uranium exposure and risk of circulatory diseases have been reported in workers carrying out milling, refining, and processing (Guseva Canu et al. 2012, Zablotska et al. 2013).

We performed a systematic literature review relating to the two occupationally exposed groups to determine the impact of the physicochemical properties of uranium on health risks. In so doing, we aimed to answer the following three questions:

(1) Is there an elevated rate of mortality or incidence of the defined outcomes of interest among different groups of uranium-processing workers and war veterans?
(2) Do epidemiological studies demonstrate a dose-response relationship between internal uranium exposure and any of the defined outcomes of interest?
(3) To what extent do the physicochemical properties of the uranium to which these populations were exposed explain any of the reported associations?

Materials and methods

Literature search

We searched the *Pubmed* (www.ncbi.nlm.nih.gov/pubmed) and the *Scopus* (www.scopus.com) databases for English-language peer-reviewed articles. Keywords of the outcomes of interest were the following: Mortality, morbidity, incidence, cancer, lymphatic, lymphoid, leukemia, hematopoietic, lymphohematopoietic, multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's disease, kidney, circulatory, cardiovascular, cerebrovascular, ischemic and disease. Literature search was performed separately for uranium-processing workers (combinations of the keywords 'uranium', 'workers', 'processing') and war veterans (combinations with the key words 'Gulf', 'Balkan', 'war', 'veterans'). Further literature search was restricted to articles published in the period 1980–2013 for uranium-processing workers, and to articles published in the period 1991–2013 for war veterans, since the first ground Persian Gulf War started in 1991. The bibliographies of each of the retrieved articles were subsequently scanned as a means of identifying additional studies. Figure 1 presents a summary how studies were selected for inclusion in our systematic literature review.

Health outcomes of interest

The identified studies were screened for the following outcomes of interest in our review according to the 9th and 10th revisions of International Classification of Diseases (ICD): Lung cancer (ICD-9 162; ICD-10 C33-C34), all leukemias (ICD-9 204-208; ICD-10 C91-C95), non-Hodgkin's lymphoma (ICD-9 200, 202; ICD-10 C82-C85), Hodgkin's disease (ICD-9 201; ICD-10 C81), multiple myeloma (ICD-9 203; ICD-10 C90), kidney cancer (ICD-9 189; ICD-10 C64-C66), all circulatory diseases (ICD-9 390-459; ICD-10 I00-I99), ischemic heart diseases (ICD-9 420-414; ICD-10 I20-I25) and cerebrovascular diseases (ICD-9 430–438; ICD-10 I60-I69) (World Health Organization [WHO] 1998, 2004). The articles that ascertained disease studies by ICD classifications other than ICD-9 and ICD-10 were included, but disease categories were carefully checked.

Data considered in our review

The uranium production cycle typically includes seven steps between uranium mining and fuel reprocessing (Figure 2). Exposure to external ionizing radiation and radon decay products (RDP) is possible at every step of this cycle. Some of these steps include far more significant exposure to RDP (uranium mining), plutonium and other transuranium elements (fuel reprocessing), or external ionizing radiation exposure (reactor operation), compared to other steps of uranium processing. We were specifically interested in potential health effects associated with internal radiation exposure to uranium, and, thus, did not consider studies of uranium miners, reactor operators, or workers where uranium was not the major source of exposure (Figure 1). We, however, included an article by Zablotska et al. (2013), because the authors managed to distinguish uranium and radium workers in some of their analyses. We have also included a portion of a study by Boice et al. (2007) concerning uranium millers, though that study analyzed the health effects of uranium exposure among both uranium mill workers and nearby resi-

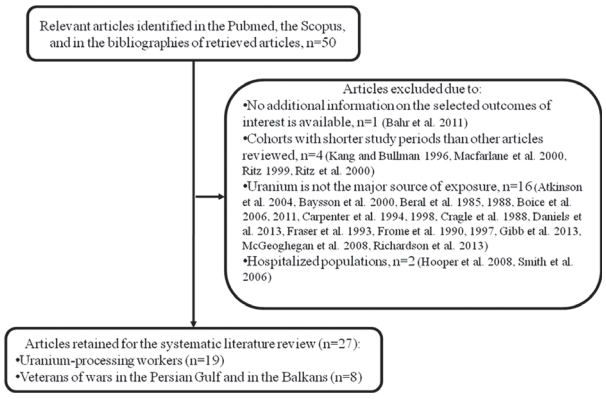

Figure 1. A summary of the selection of articles.

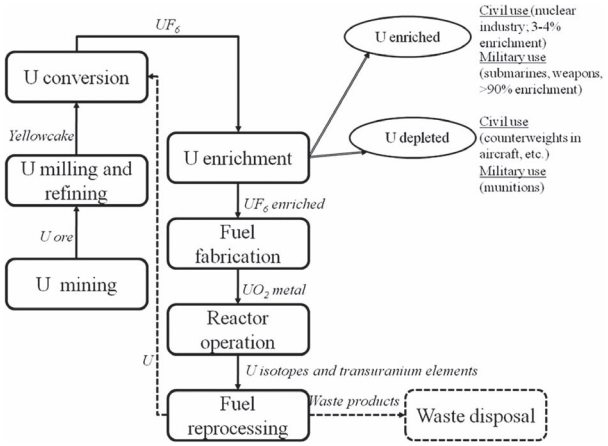

Figure 2. A simplified schema of the nuclear fuel cycle. Italicized words represent the forms of uranium at each stage of processing. Two end-products of uranium enrichment (enriched and depleted uranium) are presented. Dotted lines represent the additional stages of uranium processing.

dents. Where several studies had been performed on any one population, we included the study with the longest follow-up period; the only exception to this rule were the articles carried out on uranium-processing workers (Checkoway et al. 1988, Loomis and Wolf 1996, Richardson and Wing 2006), and war veterans (Macfarlane et al. 2003, Macfarlane et al. 2005), because each study provided specific data on outcomes of interest not covered by the other studies.

General mortality and incidence experience were analyzed using the Standardized Mortality Ratio (SMR), Standardized Incidence Ratio (SIR) and the Proportional Incidence Ratio (PIR), together with their confidence intervals (CI). Associations between uranium exposure and health outcomes of interest were assessed using analyses of dose-response (within cohort) provided in the reviewed articles. Internal uranium doses, cumulative scores derived from job-exposure matrix (JEM) and indirect substitutes (external doses such as Sv and Gy) or RDP dose expressed as working level month (WLM) were considered. We selected the analyses of dose-response relationship in the form of ERR (excess relative risk), HR (hazard ratio), OR (odds ratio), and RR (rate ratio or relative risk). Finally, studies were reviewed to ascertain if they addressed quantification of the impact of the physicochemical properties of uranium on the risk of defined health outcomes. The impact of the physicochemical properties of uranium on the risk of health effects in uranium-exposed populations was assessed using information provided on the type of work performed (uranium milling, conversion, enrichment, fuel fabrication, and war veterans), and using results of risk calculations and dose-response analyses. Results for uranium-processing workers and war veterans are described separately.

Results

We identified 27 relevant articles among uranium-processing workers ($n = 19$); (Polednak and Frome 1981, Dupree et al. 1987, Checkoway et al. 1988, Dupree et al. 1995, Loomis and Wolf 1996, Dupree-Ellis et al. 2000, McGeoghegan and Binks 2000a, 2000b, Pinkerton et al. 2004, Richardson and Wing 2006, Boice et al. 2007, 2008, Yiin et al. 2009, Canu et al. 2010, 2011, Chan et al. 2010, Guseva Canu et al. 2012, Silver et al. 2013, Zablotska et al. 2013) and war veterans ($n = 8$); (Kang and Bullman 2001, Macfarlane et al. 2003, Gustavsson et al. 2004, Macfarlane et al. 2005, Storm et al. 2006, Peragallo et al. 2010, Young et al. 2010, Bogers et al. 2013), and reviewed them in detail (Table I). All articles pertaining to uranium-processing workers are mortality studies (study by Zablotska et al. (2013) considered both mortality and incidence), while there are six incidence articles out of eight among Gulf and Balkan war veterans. Maximal follow-up periods among uranium-processing workers (average = 42.7 years) are higher than among war veterans (average = 11.1 years). Due to a lack of detailed information, we assumed that most of the workers would have been exposed to both soluble and insoluble forms of uranium, except for those working in uranium enrichment, where we considered exposure to soluble uranium compounds to be more plausible (Table I). Table II shows other relevant characteristics of the uranium-processing workers and the war veterans.

Mortality and incidence

Health outcomes of uranium-processing workers. Figure 3 shows plotted SMR for lung and kidney cancer, and all leukemias. Figure 4 describes SMR of lymphohematopoietic cancer other than leukemia such as non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HD), and multiple myeloma (MM). Uranium-processing workers employed in milling and conversion, enrichment, and fuel fabrication present an excess in mortality from lung cancer in comparison with the general population (Polednak and Frome 1981, Dupree-Ellis et al. 2000, Boice et al. 2007, Silver et al. 2013, Zablotska et al. 2013). This excess is statistically significant in two of those populations of fuel-fabrication workers at the United States Y-12 Oak Ridge and Fernald uranium-processing facilities exposed predominantly to insoluble uranium compounds (Loomis and Wolf 1996, Silver et al. 2013). There is no pattern of increased mortality from any type of lymphohematopoietic cancer (all leukemias, NHL, HD, and MM) among uranium-processing workers when compared to mortality in the general population. Three articles of uranium-processing workers employed in milling (exposure to more soluble uranium) and fuel fabrication (exposure to insoluble uranium) found a non-significant increase in kidney cancer mortality in comparison with the general population (Loomis and Wolf 1996, Dupree-Ellis et al. 2000, Boice et al. 2008). Most of the articles of uranium-processing workers observed decreased mortality in comparison with the general population from all circulatory diseases (CSD), ischemic heart (IHD), and cerebrovascular diseases (CVD) (Figure 5).

Health outcomes of war veterans. The majority of studies analyzing war veterans reported mortality or incidence from all causes and all cancers, possibly due to a limited number of cases. A significant increase (PIR = 1.15, 95% CI = 1.03–1.29) in lung cancer incidence was identified in one article studying veterans of the Gulf Wars when compared to veterans where DU was not used (Young

Table I. Description of reviewed studies on occupational exposure to uranium.

Reference	Country	Work type	Uranium	Solubility	Study design, max period of follow-up (years)	No. of workers	No. of all deaths/ cancer cases	ICD in use	No. of lung/L/NHL/HD/MM/K cancers[¶]	No. of CSD/ IHD/CVD cases
Part A. Studies of uranium-processing workers ($n = 19$)										
[1] Boice et al. 2007	USA	1	NU	S/IS*	CM, 25	450	186/48	9	24/1/1/NA/0/1	>65/<65/9
[2] Boice et al. 2008	USA	1	NU	S/IS*	CM, 26	718	220/56	9	18/3/1/0/0/3	>63/<63/12
[3] Pinkerton et al. 2004	USA	1	NU	S/IS*	CM, 58	1485	810/184	9	78/5/>4/4/<8/4[†]	362/236/<69
[4] Zablotska et al. 2013b	Canada	1	NU	S/IS*	CM/CI, 49	2472	1097/266	9	78/6/7/NA/NA/6	514/346/71
[5] Canu et al. 2010	France	2/3	NU/EU/DU/RPU	S/IS	CM, 37	2709	411/193	9–10	48/7/8/NA/3/5	101/NA/NA
[6] Canu et al. 2011	France	2/3	NU/EU/DU/RPU	S/IS	CM, 38	2897	460/214	9–10	53/<21/<21/<21/<21/NA	NA/NA/NA
[7] Dupree et al. 1987	USA	2	NU	S/IS*	CM, 36	995	429/74	8	<21/NA/<6/<6/<6/NA	<227/>159/NA
[8] Dupree et al. 1995	USA	2/4	NU	S/IS*	NCCM, 46	1574	787/787	8	787/NA/NA/NA/NA/NA	NA/NA/NA
[9] Guseva Canu et al. 2012	France	2/3	NU/EU/DU/RPU	S/IS	CM, 38	2897	NA/NA	9–10	NA/NA/NA/NA/NA/NA	111/48/31
[10] Chan et al. 2010	USA	3	NU/EU/DU	S*	CM, 51	6759	1638/461	8	146/24/32/2/10/14	NA/NA/NA
[11] McGeoghegan and Binks 2000a	UK	3	NU	S/IS*	CM, 49	3244	585/178	8	67/4/5/2/3/<2	289/213/37
[12] Polednak and Frome 1981	USA	3	NU	S/IS*	CM, 34	18869	5394/886	8	324/40/>17/9/NA/20	2571/NA/NA
[13] Yiin et al. 2009	USA	3	NU/EU/DU	S*	NCCM, 53	588	98/98	8	NA/NA/NA/NA/98/NA	NA/NA/NA
[14] Checkoway et al. 1988	USA	4	NU/EU/DU/RPU*	S/IS*	CM, 32	6781	862/196	8	<89/<4/<12/>3/4/6	NA/<292/44
[15] Dupree-Ellis et al. 2000	USA	4/2	NU	S/IS*	CM, 51	2514	1013/283	8	98/11/>1/2/5/8	474/NA/NA
[16] Loomis and Wolf 1996	USA	4	NU/EU/DU/RPU*	S/IS*	CM, 43	8116	1861/503	8	202/11/>4/3/<22/16	810/NA/NA
[17] McGeoghegan and Binks 2000b	UK	4	NU/EU/DU/RPU*	S/IS*	CM, 49	13960	3476/971	8	360/32/15/9/11/<13	1763/1191/327
[18] Richardson and Wing 2006	USA	4	NU/EU/DU/RPU*	S/IS*	CM, 43	3864	880/NA	8	111/NA/NA/NA/NA/NA	NA/NA/NA
[19] Silver et al. 2013	USA	4/2	NU/EU/DU/RPU*	S/IS*	CM, 53	6409	2767/858	5–10	297/35/32/6/19/18	805/544/82
Part B. Studies of veterans of wars in the Persian Gulf and the Balkans ($n = 8$)										
[20] Bogers et al. 2013	Netherlands	5	DU	S/IS*	CI, 15	18175	NA/175	10	>10/5/<28/<28/NA/<55	NA/NA/NA
[21] Gustavsson et al. 2004	Sweden	5	DU	S/IS*	CI, 10	8780	NA/30	7	2/NA/>1/2/1/NA	NA/NA/NA
[22] Kang and Bullman 2001	USA	5	DU	S/IS*	CM, 7	621902	4506/526	9	NA/NA/NA/NA	522/NA/NA
[23] Macfarlane et al. 2003	UK	5	DU	S/IS*	CI, 11	51721	NA/268	10	14/<45/<45/<45/<45/<13	NA/NA/NA
[24] Macfarlane et al. 2005	UK	5	DU	S/IS*	CM, 13	53462	637/123	10	NA/NA/NA/NA	96/NA/NA/NA
[25] Peragallo et al. 2010	Italy	5	DU	S/IS*	CI, 9	58413	NA/164	10	>5/14/16/20/0/<4	NA/NA/NA
[26] Storm et al. 2006	Denmark	5	DU	S/IS*	CI, 9	14012	NA/96	7	2/>4/3/3/1/2	NA/NA/NA
[27] Young et al. 2010	USA	5	DU	S/IS*	CI, 15	621902	NA/8211	10	620/>204/<478/239/83/<264	NA/NA/NA

Work type: 1 - uranium milling and refining, 2 - uranium conversion, 3 - uranium enrichment, 4 - fuel fabrication, 5 - veterans of wars in the Persian Gulf and in the Balkans in the 1990s.
CI, Cohort incidence study; CM, Cohort mortality study; CS, Cross-sectional study; CSD, Circulatory diseases; CVD, Cerebrovascular disease; DU, Depleted uranium; EU, Enriched uranium; HD, Hodgkin's disease; ICD, International classification of diseases; IHD, Ischemic heart disease; IS, Insoluble; K, Kidney cancer; L, Leukemia; MM, Multiple myeloma; NA, Not available; NCCM, Nested case-control mortality study; NHL, Non-Hodgkin's lymphoma; NU, Natural uranium; RPU, Reprocessed uranium; S, Soluble; *, supposed.
[(a)]Only the occupational portion of the article by Boice et al. 2007 was included.
[(b)]All absolute numbers for mortality studies were presented for all male radium and uranium workers (excepting lung cancer), as in the original study by Zablotska et al. 2013.
[¶]Ninth and tenth revisions of International Classifications of Diseases were used: lung cancer (ICD-9 162; ICD-10 C33-C34), all leukemia (ICD-9 204-208; ICD-10 C91-C95), non-Hodgkin's lymphoma (ICD-9 200, 202; ICD-10 C82-C85), Hodgkin's disease (ICD-9 201; ICD-10 C81), multiple myeloma (ICD-9 203; ICD-10 C90), kidney cancer (ICD-9 189; ICD-10 C64-C66), all circulatory diseases (ICD-9 390-459; ICD-10 100-199), ischemic heart disease (ICD-9 420-414; ICD-10 120-125) and cerebrovascular disease (ICD-9 430-438; ICD-10 160-169). The articles were checked on a case-by-case basis if neither ICD-9 nor ICD-10 was used.
[†]Hereafter the symbols < or > indicate that reported ICD codes differ from those utilized in our literature review. They indicate that the authors presented broader (>) or smaller (<) group of diseases.

Table II. Main characteristics of the reviewed studies of uranium-processing workers and war veterans.

Exposure characteristics	Uranium-processing workers	War veterans
U exposure	Chronic	Acute, except for those with embedded fragments
U compound	Mixtures	Depleted U
Other important exposures	External radiation, RDP, chemicals	Nerve gases, organophosphate pesticides, pyridostigmine bromide, vaccinations
Duration of follow-up	Long	Short
Analyses of dose-response with internal U exposure	Yes	No

U, Uranium; RDP, Radon decay products.

et al. 2010). A non-significant increase (SIR = 1.4, 95% CI = 0.4–3.5) in leukemia incidence was seen in veterans of the Yugoslav Wars when compared to the general population (Storm et al. 2006). Two studies of veterans of wars in both the Persian Gulf and the Balkans also observed a non-significant increase in the incidence of kidney cancer when compared to non-Gulf War veterans (Macfarlane et al. 2003, Storm et al. 2006), but the classification used in one of the studies resulted in all urinary tract cancers being included (Macfarlane et al. 2003). Veterans of the Gulf Wars had lower mortality from CSD than other veterans without any contact with DU (Kang and Bullman 2001, Macfarlane et al. 2005).

Analyses of the dose-response relationship

Of the 19 articles of uranium-processing workers that we reviewed, only nine performed any analysis of dose-response (Table III). The most informative seven studies assessed internal uranium exposure (internal uranium dose, uranium intake or cumulative score in JEM); while others used a proxy of uranium exposure (RDP dose, external dose). Briefly, articles that performed dose-response analyses reported borderline significant or significant increases of mortality due to lung cancer ($n = 1$), NHL and MM ($n = 2$), kidney cancer ($n = 1$), and CSD and IHD ($n = 1$). Most of the articles acknowledged the limitations of their results due to small numbers of cases and related limited statistical power. None of the articles of war veterans were included in Table III, since no dose-response analyses were carried out for exposure to DU in these populations.

Impact of the physicochemical properties of uranium on risk of health effects

In spite of the fact that the type of work might be considered to serve as reasonable proxy for the physicochemical properties of uranium, we did not find any evidence of differences in uranium-processing workers, with the exception of increased mortality from lung cancer among fuel-fabrication workers that had been exposed to slowly soluble uranium compounds in comparison with the general population (Loomis and Wolf 1996, Silver et al. 2013). Two articles of uranium-enrichment workers exposed to soluble uranium reported a positive association between NHL (Chan et al. 2010), and MM (Yiin et al. 2009) in analyses of dose-response relationships, but these studies were limited by low statistical power. The physicochemical properties of uranium, its isotopic composition and solubility, were not usually reported clearly in the articles we identified (Table I). Only two articles reported on the impact of both isotopic composition and solubility on the risk of the risk of CSD mortality (Canu et al. 2011, Guseva Canu et al. 2012). The latter articles reported an increased risk for decreasing solubility and for a shift from natural to reprocessed uranium. In the identified articles of war veterans, isotopic composition of uranium exposure was known (DU), but information on solubility was not provided.

Discussion

We reviewed the literature to investigate whether the physicochemical properties of uranium influence the risk of health

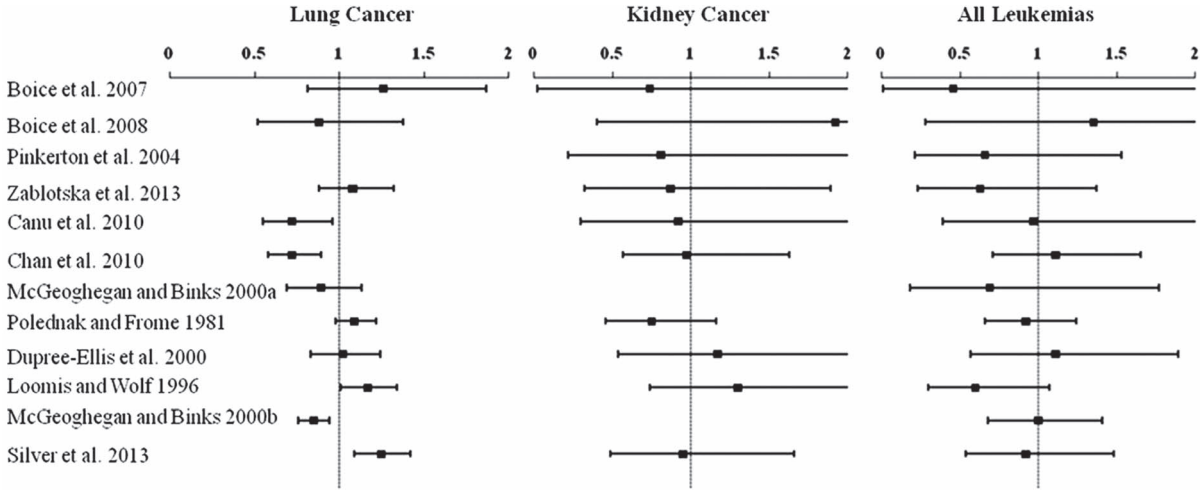

Figure 3. Standardized Mortality Ratios (SMR) and associated 95% confidence intervals for lung, kidney cancers, and all leukemias in reviewed studies of uranium-processing workers.

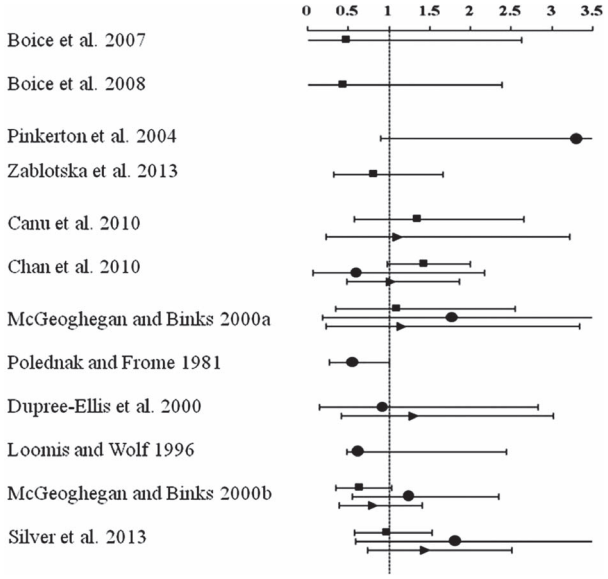

Figure 4. Standardized Mortality Ratios (SMR) and associated 95% confidence intervals for lymphohematopoietic cancers other than leukemia in reviewed studies of uranium-processing workers. ■ Non-Hodgkin's lymphoma; ● Hodgkin's disease; ▶ Multiple myeloma.

outcomes in two occupationally exposed groups, namely uranium-processing workers and veterans of wars in the Persian Gulf and the Balkans exposed to DU from munitions. Our results show that: (a) Both uranium-processing workers and war veterans exhibit lower mortality or incidence rates when compared with the general population; (b) mortality due to lung cancer and lymphohematopoietic cancer is higher in some groups of uranium-processing workers (millers, uranium-enrichment and fuel-fabrication workers) in comparison with general population and in analyses of the dose-response relationship; (c) lung cancer mortality is more pronounced among those uranium-processing workers exposed to insoluble uranium (UO_2) in comparison with the general population; and (d) the impact of the physicochemical properties of uranium on the risk of any of the defined health outcomes cannot be determined based on current studies, because of the very limited number of studies addressing this issue.

Studies of uranium-processing workers and war veterans

We found it difficult to compare uranium-processing workers and Gulf and Balkan war veterans, especially in regard to their follow-up periods, and co-exposures (Table II). This might explain differences in observed health outcomes. The most important limitation of the studies of war veterans is the lack of analyses of the dose-response relationship using either internal uranium exposure or an appropriate proxy of uranium exposure. This precludes any conclusion on associations between the diseases of interest and DU exposure. A surveillance program among 80 American veterans of the wars in the Persian Gulf with embedded DU fragments has, however, found some indication of kidney damage, but only at the level of biomarkers (McDiarmid et al. 2013). The majority of studies of war veterans used incidence data, important in studies of cancer with high survival rates, such as some of lymphohematopoietic cancers (United States Environmental Protection Agency [US EPA] 2012). The low mortality or incidence in uranium-processing workers in comparison with the general population may be explained by the healthy worker effect (HWE). This effect consists of two components (healthy worker hire and healthy worker survivor effects) and lead to the selection of a working population healthier than the general population (Checkoway et al. 2004). It proves the importance of further analyses of dose-response relationship within the same workforce, especially for very frequent outcomes like CSD.

Exposure metrics in the analyses of the dose-response relationship among uranium-processing workers

Exposure, or dose indicators chosen by the authors of the reviewed articles may well have impacted results of the dose-response analyses (Table III). RDP and external radiation exposure, often used as uranium exposure proxies, may only partially explain internal uranium exposure because of

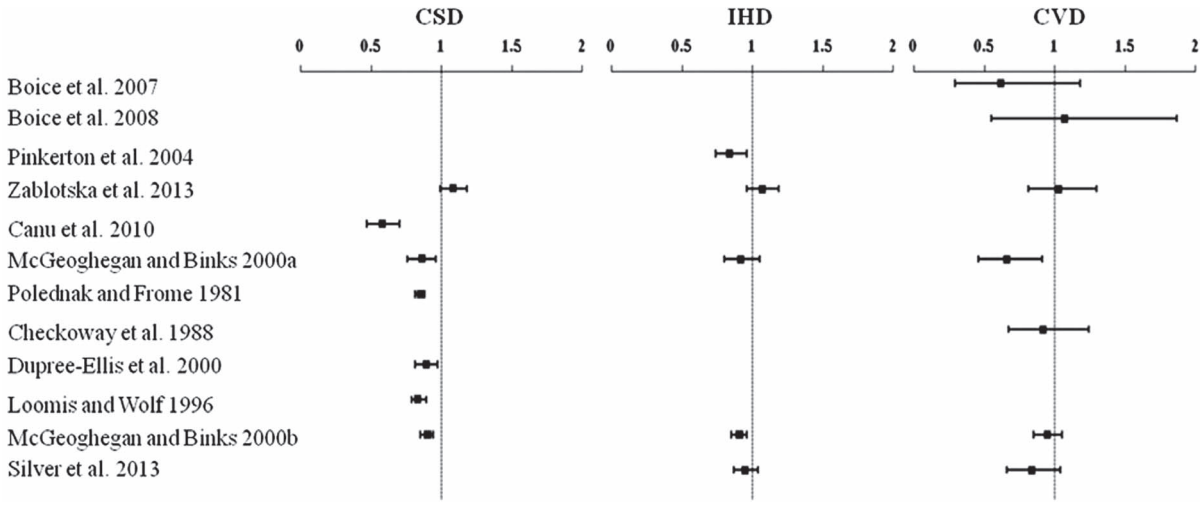

Figure 5. Standardized Mortality Ratios (SMR) and associated 95% confidence intervals for all circulatory, ischemic heart, and cerebrovascular diseases in reviewed studies of uranium-processing workers. CSD, All circulatory diseases; CVD, Cerebrovascular diseases; IHD, Ischemic heart diseases.

Table III. Analyses of dose-response relationships in reviewed studies of uranium-processing workers.

Reference	Exposure /dose indication	Dose-response analysis	Lung cancer	LHP cancer	Kidney cancer	CSD
[4] Zablotska et al. 2013	Rn dose (WLM), Ext dose (Sv)	ERR/100 WLM*, ERR/Sv	ERR/100 WLM = 0.39 (< − 1.22–4.52),	NHL - ERR/100 WLM = -0.16 (< − 0.34–10.19), ERR/ Sv = − 0.29 (< − 0.29–20.92)	ERR/100 WLM = 0.16 (< − 0.39–49.51), NA for ERR/Sv	*CSD* - ERR/100 WLM = 0.10 (− 0.05–0.32), ERR/Sv = 0.19 (− 0.07–0.55) *IHD* - ERR/100 WLM = 0.16 (− 0.05–0.50), ERR/Sv = 0.31 (− 0.05–0.88) *CVD* - ERR/100 WLM = − 0.10 (< − 0.34–0.38), ERR/Sv = − 0.29 (< − 0.29–0.33)
[6] Canu et al. 2011; [9] Guseva Canu et al. 2012	Cum exp score (JEM)	HR (Cox regression)	NU IS, HR = 1.01 (0.93–1.09); RPU IS, HR = 1.14 (1.00–1.31)	*LHP* - NU IS, HR = 1.01 (0.89–1.14); RPU IS, HR = 1.16 (0.96–1.40)	NA	*CSD* - NU IS, HR = 1.07 (1.02–1.13); RPU IS, HR = 1.17 (1.07–1.27) *IHD* - NU IS, HR = 1.13 (1.05–1.22); RPU IS, HR = 1.17 (1.03–1.33) *CVD* - NU IS, HR = 1.01 (0.92–1.12), RPU IS, HR = 1.16 (1.00–1.35)
[10] Chan et al. 2010	U intake (μg/year)	SRR (1 quart = 0–20, 2 = 21–50, 3 = 51–125, 4 = > 125)	3 = 0.95 (0.56–1.63)	*LHP* - 4 = 0.77 (0.24–2.50) *NHL* - 2 = 9.95 (1.22–81.26) *H* - 2 = 0.67 (0.04–10.73)	NA	NA
[13] Yiin et al. 2009	Int U dose (μGy)	OR (logistic regression)	NA	*MM* - OR at 10 μGy = 1.04 (1.00–1.09)	NA	NA
[14] Checkoway et al. 1988	Int U dose (rem)	RR (Poisson regression)	> = 10 rem 10-year latency, RR = 1.12 (0.47–2.65)	NA	NA	NA
[15] Dupree-Ellis et al. 2000	Ext dose (Sv)	ERR/Sv	NA	NA	ERR/Sv = 10.5 (0.6–57.4)	NA
[18] Richardson and Wing 2006	Int dose (mSv)	RR	> = 100 mSv 5-year latency, RR = 1.40 (0.65–3.01)	NA	NA	NA
[19] Silver et al. 2013	Int U dose (μGy)	ERR/100 μGy	ERR = 0.0021 (− 0.00062–0.0064)	*Non-CLL* - ERR = − 0.061 (NA-0.25) *NHL* - ERR = 0.33 (− 0.065–1.6) *MM* - ERR = 0.20 (− 0.069–2.2)	ERR = 0.033 (− 0.021–0.50)	NA

CLL, Chronic lymphocytic leukemia; CSD, Circulatory diseases; Cum, Cumulative; CVD, Cerebrovascular disease; ERR, Excess relative risk; Exp, Exposure; Ext, External; H, Hodgkin's disease; HR, Hazard ratio; IHD, Ischemic heart disease; Int, Internal; IS,Insoluble; JEM, Job-exposure matrix; LHP, Lymphohematopoietic cancer; MM, Multiple myeloma; NA, Not available; NHL, Non-Hodgkin's lymphoma; NU, Natural uranium; RPU, Reprocessed uranium; RR, Rate ratio/relative risk; SRR, Standardized rate ratio; WLM, Working level month.
*ERR estimation is based on Poisson regression in all presented articles.

differences in the RDP absorption, biokinetics, half-life periods and very low gamma-radiation potential. RDP exposure is of great importance among those uranium-processing that processed radium ore (Zablotska et al. 2013). Also, radon exposure impacts primarily the respiratory tract, very little being deposited in systemic organs, and is eliminated exclusively by the lungs (Marsh et al. 2012). External gamma-radiation is a uniform highly penetrating radiation with low linear energy transfer and cannot reflect alpha-radiation exposure; it is characterized by a high linear energy transfer, and is deposited at very short distance (about 50 μm) and limited to a few target-organs or tissues.

Radiotoxicity and chemical toxicity of uranium could be analyzed separately if internal uranium dose or uranium intake are used. Because natural and depleted uranium have a very long half-period and low specific activity, uranium intake (usually expressed in mass, μg) should be used in risk assessments of populations exposed to these types of uranium (Chan et al. 2010). It should be noted that activity (Bq) can be easily converted into intake (μg) if the isotopic composition is known. We noted, however, that precise isotopic composition was rarely available in the reviewed studies, and thus internal uranium dose in the current studies reflect both radio- and chemical toxicity. Some recent articles assessed internal uranium exposure in the frame of JEM (Canu et al. 2011, Guseva Canu et al. 2012). While JEM is very useful and widespread method of exposure assessment in occupational epidemiology, it is rarely used in radiation epidemiology. JEM allows assigning both the frequency and amount of uranium exposure in a semi-quantitative way to each given job type (Guseva Canu et al. 2008). Although JEM has lower sensitivity and specificity in comparison with internal uranium doses (Guseva Canu et al. 2010), it allows estimating the cumulative exposure scores to uranium, and, thus, makes it possible to perform analyses of dose-response by specific type of uranium.

Internal uranium dose and the influence of physicochemical properties

While uranium absorbed dose is considered a benchmark to be used in the analyses of dose-response relationship, the physicochemical properties of uranium (isotopic composition and solubility) impact on biokinetics and are thus essential parameters in estimating of the absorbed dose. There is a wealth of toxicological information available on the health effects associated with exposure to uranium compounds. These data demonstrate that the physicochemical properties of uranium may play an important role in the toxicity of uranium compounds (ATSDR 2012). Our review showed that epidemiological data are much more scarce and have only a handful of studies that have assessed the direct impact of physicochemical properties on risk (Canu et al. 2011, Guseva Canu et al. 2012).

In addition to isotopic composition and solubility, other physicochemical properties of uranium are important when considering its potential toxicity. This includes particle size, specific surface area, shape, and surface charge (zero potential) which are beyond the scope of the present review. All but particle size description are usually ignored in epidemiological studies, since they demand specialized sampling and analysis. Data on particle size are particularly important for modeling particle deposition and clearance in the respiratory tract, their further intake in the target organs, and estimation the resulting organ-specific absorbed doses. It was shown that large particles (>5 μm) are usually deposited in the upper (extra-thoracic) airways, from where they are removed into the gastrointestinal tract by mucociliary clearance. Moderate size (about 5 μm) particles may enter the deeper lung, from where they are slowly removed to thoracic lymph nodes by alveolar macrophages. Very small particles (<1 μm) may even enter directly into the circulatory system (Snipes et al. 1989) and thereby cause damage to endothelium. Slowly soluble enriched uranium compounds thus have a higher potential to deliver a larger dose to the lungs or to the lymphatic tissue, especially if the particle size is about 5 μm in diameter as found at most industrial sites (Ansoborlo et al. 2002).

Reported associations and physicochemical properties

An association between uranium exposure and lung cancer is the most plausible of the health outcomes that we reviewed, since the lung is the primary target organ following inhalation of insoluble uranium. It was confirmed in two articles of fuel-fabrication workers (Loomis and Wolf 1996, Silver et al. 2013). Although insoluble uranium might be transported to thoracic lymph nodes by macrophages, we did not observe any increase in NHL or HD among fuel-fabrication workers in analyses of dose-response relationships. In contrast, we observed increases in mortality from NHL (Chan et al. 2010) and MM (Yiin et al. 2009) among uranium-enrichment workers exposed to soluble uranium (UF_6, UO_2F_2). The authors noted, however, that their results were borderline significant and should be investigated by future studies. The kidneys are considered the organ most involved in excretion of uranium, yet we observed only one significant association for kidney cancer with a crude proxy of uranium exposure, external radiation exposure (Dupree-Ellis et al. 2000). We found that very little information was available on circulatory diseases. The possible explanation might be that CSD were considered as a deterministic outcome of exposure to acute high-dose and high dose-rate external ionizing radiation, and have been reconsidered very recently (Little et al. 2012).

While carrying out this review, we identified significant findings for other outcomes, such as gastrointestinal cancer (Silver et al. 2013). Gastrointestinal cancer may be of interest for future studies of some groups of uranium-processing workers exposed to large particles of insoluble uranium (>5 μm), which are cleared via the gastrointestinal tract. Many studies also observed an increase in mortality from pleural cancer, but a recent review showed that these results were likely confounded by asbestos exposure during the early years of nuclear industry (Metz-Flamant et al. 2011).

In summary, current literature does not allow a definitive finding in relation to the physicochemical properties of uranium. Based on the available data, a preliminary conclusion could be made that uranium-processing workers (specifically, fuel-fabrication workers) may be at risk for

lung cancer mortality, while the evidence is inconclusive for lymphohematopoietic, kidney cancers, and, especially, circulatory diseases.

Considerations for future studies examining internal uranium exposure

Our review revealed that mixtures of uranium compounds with a variety of physicochemical properties are used in most uranium fuel cycle facilities. This complicates distinguishing between the specific effects of particular physicochemical properties of uranium in future studies. Studying cohorts of workers with sufficiently homogenous soluble (uranium-enrichment workers) or insoluble (fuel-fabrication workers) uranium compounds would present the possibility of studying the effect of specific characteristics of these compounds. Nested case-control studies of internal uranium exposure that assessed important life-style related confounders would additionally enhance our knowledge of their impact upon circulatory diseases. Elaboration of a complementary JEM describing the physicochemical properties of uranium in each job type would allow better estimation of internal uranium doses, and therefore a more precise evaluation of the risk associated with uranium exposure among uranium-processing workers.

Acknowledgements

This research was funded by a research grant from the Région Île-de-France (the Health, Environment, Toxicology scientific program). We are very grateful to Dr James Grellier (CREAL, Spain) for a thorough review of the manuscript and for his helpful suggestions. We would like to thank Elizabeth Shurik, Amy Ovadia and Andrew Zega for proofreading the manuscript.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Advisory Group on Ionising Radiation (AGIR). 2010. Circulatory disease risk. Report of the Independent Advisory Group on Ionising Radiation [accessed 25 January 2014]. Available from: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1284475204588.

Ansoborlo E, Chazel V, Hengé-Napoli MH, Pihet P, Rannou A, Bailey MR, Stradling N. 2002. Determination of the physical and chemical properties, biokinetics, and dose coefficients of uranium compounds handled during nuclear fuel fabrication in France. Health Phys 82:279–289.

Atkinson WD, Law DV, Bromley KJ, Inskip HM. 2004. Mortality of employess of the United Kingdom Atomic Energy Authority, 1946–97. Occupat Environ Med 61:577–585.

Agency for Toxic Substances & Disease Registry (ATSDR). 2012. Toxicological profile for uranium [accessed 1 February 2014]. Available from: http://www.atsdr.cdc.gov/toxprofiles/tp150.pdf.

Bahr DE, Aldrich TE, Seidu D, Brion GM, Tollerud DJ. 2011. Occupational exposure to trichloroethylene and cancer risk for workers at the Paducah Gaseous Diffusion Plant. Int J Occupat Med Environ Health 24:67–77.

Baysson H, Laurier D, Tirmarche M, Valenty M, Giraud JM. 2000. Epidemiological response to a suspected excess of cancer among a group of workers exposed to multiple radiological and chemical hazards. Occupat Environ Med 57:188–194.

Beral V, Inskip H, Fraser P, Booth M, Coleman D, Rose G. 1985. Mortality of employees of the United Kingdom Atomic Energy Authority, 1946–1979. BMJ 291:440–447.

Beral V, Fraser P, Carpenter L, Booth M, Brown A, Rose G. 1988. Mortality of employees of the Atomic Weapons Establishment, 1951–82. BMJ 297:757–770.

Bogers RP, van Leeuwen FE, Grievink L, Schouten LJ, Kiemeney LALM, Schram-Bijkerk D. 2013. Cancer incidence in Dutch Balkan veterans. Cancer Epidemiol 37:550–555.

Boice JD Jr, Cohen SS, Mumma MT, Chadda B, Blot WJ. 2007. Mortality among residents of Uravan, Colorado who lived near a uranium mill, 1936–84. J Radiolog Protect 27:299–319.

Boice JD Jr, Cohen SS, Mumma MT, Chadda B, Blot WJ. 2008. A cohort study of uranium millers and miners of Grants, New Mexico, 1979–2005. J Radiolog Protect 28:303–325.

Boice JD Jr, Marano DE, Cohen SS, Mumma MT, Blot WJ, Brill AB, Fryzek JP, Henderson BE, McLaughlin JK. 2006. Mortality among Rocketdyne workers who tested rocket engines, 1948–1999. J Occupat Environ Med 48:1070–1092.

Boice JD Jr, Cohen SS, Mumma MT, Ellis ED, Eckerman KF, Leggett RW, Boecker BB, Brill AB, Henderson BE. 2011. Updated mortality analysis of radiation workers at Rocketdyne (Atomics International), 1948–2008. Radiat Res 176:244–258.

Canu IG, Ellis ED, Tirmarche M. 2008. Cancer risk in nuclear workers occupationally exposed to uranium-emphasis on internal exposure. Health Phys 94:1–17.

Canu IG, Cardis E, Metz-Flamant C, Caër-Lorho S, Auriol B, Wild P, Laurier D, Tirmarche M. 2010. French cohort of the uranium processing workers: Mortality pattern after 30-year follow-up. Int Arch Occupat Environ Health 83:301–308.

Canu IG, Jacob S, Cardis E, Wild P, Caër S, Auriol B, Garsi JP, Tirmarche M, Laurier D. 2011. Uranium carcinogenicity in humans might depend on the physical and chemical nature of uranium and its isotopic composition: Results from pilot epidemiological study of French nuclear workers. Cancer Causes Control 22:1563–1573.

Carpenter L, Higgins C, Douglas A, Fraser P, Beral V, Smith P. 1994. Combined analysis of mortality in three United Kingdom nuclear industry workforces, 1946–1988. Radiat Res 138:224–238.

Carpenter LM, Higgins CD, Douglas AJ, Maconochie NES, Omar RZ, Fraser P, Beral V, Smith PG. 1998. Cancer mortality in relation to monitoring for radionuclide exposure in three UK nuclear industry workforces. Br J Cancer 78:1224–1232.

Chan C, Hughes TS, Muldoon S, Aldrich T, Rice C, Hornung R, Brion G, Tollerud DJ. 2010. Mortality patterns among Paducah Gaseous Diffusion Plant Workers. J Occupat Environ Med 52:725–732.

Checkoway H, Pearce N, Kriebel D. 2004. Research methods in occupational epidemiology, 2nd ed. Oxford: Oxford University Press.

Checkoway H, Pearce N, Crawford-Brown DJ, Cragle DL. 1988. Radiation doses and cause-specific mortality among workers at a nuclear materials fabrication plant. Am J Epidemiol 127:255–266.

Cragle DL, McLain RW, Qualters JR, Hickey JLS, Wilkinson GS, Tankersley WG, Lushbaugh CC. 1988. Mortality among workers at a nuclear fuels production facility. Am J Industrial Med 14:379–401.

Daniels RD, Bertke S, Waters KM, Schubauer-Berigan MK. 2013. Risk of leukaemia mortality from exposure to ionising radiation in US nuclear workers: A pooled case-control study. Occupat Environ Med 70:41–48.

Dupree-Ellis E, Watkins J, Ingle JN, Phillips J. 2000. External radiation exposure and mortality in a cohort of uranium processing workers. Am J Epidemiol 152:91–95.

Dupree EA, Cragle DL, McLain RW, Crawford-Brown DJ, Teta MJ. 1987. Mortality among workers at a uranium processing facility, the Linde Air Products Company Ceramics Plant, 1943–1949. Scand J Work, Environ Health 13:100–107.

Dupree EA, Watkins JP, Ingle JN, Wallace PW, West CM, Tankersley WG. 1995. Uranium dust exposure and lung cancer risk in four uranium processing operations. Epidemiology 6:370–375.

Fraser P, Carpenter L, Maconochie N, Higgins C, Booth M, Beral V. 1993. Cancer mortality and morbidity in employees of the United Kingdom atomic energy authority, 1946–86. Br J Cancer 67: 615–624.

Frome EL, Cragle DL, McLain RW. 1990. Poisson regression analysis of the mortality among a cohort of World War II nuclear industry workers. Radiat Res 123:138–152.

Frome EL, Cragle DL, Watkins JP, Wing S, Shy CM, Tankersley WG, West CM. 1997. A mortality study of employees of the nuclear industry in Oak Ridge, Tennessee. Radiat Res 148:64–80.

Gibb H, Fulcher K, Nagarajan S, McCord S, Fallahian NA, Hoffman HJ, Haver C, Tolmachev S. 2013. Analyses of radiation and mesothelioma in the US transuranium and uranium registries. Am J Public Health 103:710–716.

Guseva Canu I, Garsi JP, Caër-Lorho S, Jacob S, Collomb P, Acker A, Laurier D. 2012. Does uranium induce circulatory diseases? First results from a French cohort of uranium workers. Occupat Environ Med 69:404–409.

Guseva Canu I, Molina G, Goldberg M, Collomb P, David JC, Perez P, Paquet F, Tirmarche M. 2008. Development of a job exposure matrix for the epidemiological follow-up of workers in the French nuclear industry. Results of a pilot study. Revue d'Epidemiologie et de Sante Publique 56:21–29.

Guseva Canu I, Laurier D, Caër-Lorho S, Samson E, Timarche M, Auriol B, Bérard P, Collomb P, Quesne B, Blanchardon E. 2010. Characterisation of protracted low-level exposure to uranium in the workplace: A comparison of two approaches. Int J Hygiene Environ Health 213:270–277.

Gustavsson P, Talbäck M, Lundin A, Lagercrantz B, Gyllestad PE, Fornell L. 2004. Incidence of cancer among Swedish military and civil personnel involved in UN missions in the Balkans 1989–99. Occupat Environ Med 61:171–173.

Hooper TI, DeBakey SF, Nagaraj BE, Bellis KS, Smith B, Smith TC, Gackstetter GD. 2008. The long-term hospitalization experience following military service in the 1991 Gulf War among veterans remaining on active duty, 1994–2004. BMC Public Health 8:60.

International Commission on Radiological Protection (ICRP). 1994. Publication 66. Human respiratory tract model for radiological protection. Oxford: Pergamon Press.

Kang HK, Bullman TA. 1996. Mortality among U.S. veterans of the Persian Gulf War. New Eng J Med 335:1498–1504.

Kang HK, Bullman TA. 2001. Mortality among US veterans of the Persian Gulf War: 7-year follow-up. Am J Epidemiol 154:399–405.

Laurier D, Guseva Canu I, Baatout S, Bertho JM, Blanchardon E, Bouffler S, Cardis E, Gomolka M, Hall J, Kesminiene A, et al. 2012. DoReMi workshop on multidisciplinary approaches to evaluating cancer risks associated with low-dose internal contamination. Radioprotection 47:119–148.

Leggett RW, Eckerman KF, McGinn RA. 2012. Controlling intake of uranium in the workplace: Applications of biokinetic modeling and occupational monitoring data. [accessed 20 February 2014]. Available from: http://ordose.ornl.gov/documents/ORNL_TM-2012-14.pdf

Little MP, Azizova TV, Bazyka D, Bouffler SD, Cardis ESC, Chekin S, Chumak VV, Cucinotta FA, de Vathaire F, Hall P, et al. 2012. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. Environ Health Perspect 120:1503–1511.

Loomis DP, Wolf SH. 1996. Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennessee, 1947–1990. Am J Industrial Med 29:131–141.

Macfarlane GJ, Biggs AM, Maconochie N, Hotopf M, Doyle P, Lunt M. 2003. Incidence of cancer among UK Gulf war veterans: Cohort study. BMJ 327:1373–1375.

Macfarlane GJ, Hotopf M, Maconochie N, Blatchley N, Richards A, Lunt M. 2005. Long-term mortality amongst Gulf War Veterans: Is there a relationship with experiences during deployment and subsequent morbidity? Int J Epidemiol 34:1403–1408.

Marsh JW, Blanchardon E, Gregoratto D, Hofmann W, Karcher K, Nosske D, Tomášek L. 2012. Dosimetric calculations for uranium miners for epidemiological studies. Radiat Protect Dosimetry 149:371–383.

McDiarmid MA, Gaitens JM, Hines S, Breyer R, Wong-You-Cheong JJ, Engelhardt SM, Oliver M, Gucer P, Kane R, Cernich A and others. 2013. The Gulf War depleted uranium cohort at 20 years: Bioassay results and novel approaches to fragment surveillance. Health Phys 104:347–361.

McGeoghegan D, Binks K. 2000a. The mortality and cancer morbidity experience of workers at the Capenhurst uranium enrichment facility 1946–95. J Radiolog Protect 20:381–401.

McGeoghegan D, Binks K. 2000b. The mortality and cancer morbidity experience of workers at the Springfields uranium production facility, 1946–95. J Radiolog Protect 20:111–137.

McGeoghegan D, Binks K, Gillies M, Jones S, Whaley S. 2008. The non-cancer mortality experience of male workers at British Nuclear Fuels plc, 1946–2005. Int J Epidemiol 37:506–518.

Metz-Flamant C, Guseva Canu I, Laurier D. 2011. Malignant pleural mesothelioma risk among nuclear workers: A review. J Radiolog Protect 31:9–23.

Muirhead CR, O'Hagan JA, Haylock RGE, Phillipson MA, Willcock T, Berridge GLC, Zhang W. 2009. Mortality and cancer incidence following occupational radiation exposure: Third analysis of the National Registry for Radiation Workers. Br J Cancer 100: 206–212.

Peragallo MS, Lista F, Sarnicola G, Marmo F, Vecchione A. 2010. Cancer surveillance in Italian army peacekeeping troops deployed in Bosnia and Kosovo, 1996–2007: Preliminary results. Cancer Epidemiol 34:47–54.

Pinkerton LE, Bloom TF, Hein MJ, Ward EM. 2004. Mortality among a cohort of uranium mill workers: An update. Occupat Environ Med 61:57–64.

Polednak AP, Frome EL. 1981. Mortality among men employed between 1943 and 1947 at a uranium-processing plant. J Occupat Med 23:169–178.

Richardson DB, Wing S. 2006. Lung cancer mortality among workers at a nuclear materials fabrication plant. Am J Industrial Med 49: 102–111.

Richardson DB, Wing S, Keil A, Wolf S. 2013. Mortality among workers at Oak Ridge National Laboratory. Am J Industrial Med 56:725–732.

Ritz B. 1999. Radiation exposure and cancer mortality in uranium processing workers. Epidemiology 10:531–538.

Ritz B, Morgenstern H, Crawford-Brown D, Young B. 2000. The effects of internal radiation exposure on cancer mortality in nuclear workers at Rocketdyne/Atomics International. Environ Health Perspect 108:743–751.

Silver SR, Bertke SJ, Hein MJ, Daniels RD, Fleming DA, Anderson JL, Pinney SM, Hornung RW, Tseng CY. 2013. Mortality and ionising radiation exposures among workers employed at the Fernald Feed Materials Production Center (1951–1985). Occupat Environ Med 70:453–463.

Smith B, Smith TC, Ryan MAK, Gray GC. 2006. A comparison of the postdeployment hospitalization experience of U.S. military personnel following service in the 1991 gulf war, southwest asia after the gulf war, and Bosnia. J Occupat Environ Hygiene 3:660–670.

Snipes MB, McClellan RO, Mauderly JL, Wolff RK. 1989. Retention patterns for inhaled particles in the lung: Comparisons between laboratory animals and humans for chronic exposures. Health Phys 57:69–78.

Storm HH, Jørgensen HO, Kejs AMT, Engholm G. 2006. Depleted uranium and cancer in Danish Balkan veterans deployed 1992–2001. Eur J Cancer 42:2355–2358.

Tirmarche M, Harrison JD, Laurier D, Paquet F, Blanchardon E, Marsh JW. 2010. International Commission on Radiological Protection (ICRP), Publication 115. Lung cancer risk from radon and progeny and statement on radon. Annals ICRP 40:1–64.

United States Environmental Protection Agency (US EPA). 2012. Lymphohematopoietic cancers induced by chemicals and other agents: Overview and implications for risk assessment. [accessed 20 February 2014]. Available from: http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id = 507128

World Health Organization (WHO). 1998. International classification of diseases, 9th revision (ICD-9). Geneva: WHO.

World Health Organization (WHO). 2004. International classification of diseases, 10th revision (ICD-10). Geneva: WHO.

Yiin JH, Anderson JL, Daniels RD, Seel EA, Fleming DA, Waters KM, Chen PH. 2009. A nested case-control study of multiple myeloma risk and uranium exposure among workers at the Oak Ridge Gaseous Diffusion Plant. Radiat Res 171:637–645.

Young HA, Maillard JD, Levine PH, Simmens SJ, Mahan CM, Kang HK. 2010. Investigating the risk of cancer in 1990–1991 US Gulf War veterans with the use of State Cancer Registry data. Annals Epidemiol 20:265–272.

Zablotska LB, Lane RSD, Frost SE. 2013. Mortality (1950–1999) and cancer incidence (1969–1999) of workers in the Port Hope cohort study exposed to a unique combination of radium, uranium and γ-ray doses. BMJ Open 3(pii):e002159. doi: 10.1136/bmjopen-2012-002159. Print 2013.

Appendix 6. Article 3

Article: Mortality (1968–2008) in a French cohort of uranium enrichment workers potentially exposed to rapidly soluble uranium compounds

ORIGINAL ARTICLE

Mortality (1968–2008) in a French cohort of uranium enrichment workers potentially exposed to rapidly soluble uranium compounds

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/oemed-2015-103142).

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Received 24 June 2015
Revised 15 October 2015
Accepted 28 October 2015

ABSTRACT

Objectives Until recently, enrichment of uranium for civil and military purposes in France was carried out by gaseous diffusion using rapidly soluble uranium compounds. We analysed the relationship between exposure to soluble uranium compounds and exposure to external γ-radiation and mortality in a cohort of 4688 French uranium enrichment workers who were employed between 1964 and 2006.

Methods Data on individual annual exposure to radiological and non-radiological hazards were collected for workers of the AREVA NC, CEA and Eurodif uranium enrichment plants from job-exposure matrixes and external dosimetry records, differentiating between natural, enriched and depleted uranium. Cause-specific mortality was compared with the French general population via standardised mortality ratios (SMR), and was analysed via Poisson regression using log-linear and linear excess relative risk models.

Results Over the period of follow-up, 131 161 person-years at risk were accrued and 21% of the subjects had died. A strong healthy worker effect was observed: all causes SMR=0.69, 95% CI 0.65 to 0.74. SMR for pleural cancer was significantly increased (2.3, 95% CI 1.06 to 4.4), but was only based on nine cases. Internal uranium and external γ-radiation exposures were not significantly associated with any cause of mortality.

Conclusions This is the first study of French uranium enrichment workers. Although limited in statistical power, further follow-up of this cohort, estimation of internal uranium doses and pooling with similar cohorts should elucidate potential risks associated with exposure to soluble uranium compounds.

What this paper adds

- During the uranium enrichment step of the nuclear fuel cycle, a protracted exposure to rapidly soluble uranium compounds (under three isotopic forms: natural, enriched and depleted uranium) may occur.
- We analysed mortality in a historical cohort of 4688 French uranium enrichment workers employed for at least 6 months between 1964 and 2006, with a median follow-up of 30 years.
- As in other studies of nuclear workers, a strong healthy worker effect was observed when comparing this worker cohort with the general population; no cause of mortality was significantly associated either with exposure to rapidly soluble uranium compounds (assessed via job-exposure matrixes) or external γ-radiation (individual doses).
- Although our study did not find strong evidence for an association between exposure to rapidly soluble uranium compounds and cause-specific mortality, a reanalysis based on extended follow-up and incorporating estimated internal uranium doses is needed.

INTRODUCTION

In recent years, research on the health of workers involved in the uranium fuel cycle has focused on relationships between internal exposures to radionuclides and health effects, including cancer and non-cancer outcomes.[1–4] When inhaled or ingested, these compounds are distributed to various organs depending on biokinetic processes specific to their physicochemical form. Internal exposure to airborne uranium compounds is of concern because they may exhibit both radiological (α-emitters) and chemical toxicity.[5] Even though a substantial amount of animal and human toxicological data exists for the radiological and chemical health effects of uranium,[6 7] data on the health impact of chronic inhalation of industrial uranium compounds on human health are limited.[7 8]

Inhalation is the main route of exposure to uranium in nuclear fuel cycle workers in the course of their work. French nuclear fuel cycle workers are subject to uranium exposure of various physicochemical forms and other chemical and physical hazards[9] during the following steps in the fuel cycle: ore milling and refining to produce a uranium concentrate powder known as 'yellow cake', conversion to uranium tetrafluoride (UF_4) and uranium hexafluoride (UF_6), enrichment of isotope ^{235}U, uranium fuel fabrication and spent fuel reprocessing and disposal. Since exposures to these workers are regularly monitored for the purposes of radiation protection, they represent one of the most pertinent groups for studying health risks associated with chronic radiation exposure.[10]

A recent literature review suggested that further studies of subgroups of nuclear fuel cycle workers with homogeneous exposure to soluble or insoluble

To cite: Zhivin S, Guseva Canu I, Samson E, *et al*. *Occup Environ Med* Published Online First: [*please include* Day Month Year] doi:10.1136/oemed-2015-103142

uranium are needed to examine whether they experience an increased risk of mortality from cancerous and non-cancerous diseases.[8]

The Tricastin nuclear site, situated in south-eastern France, is the only French nuclear site where uranium undergoes enrichment at three plants operated by AREVA NC, CEA and Eurodif. Although the main industrial enrichment technology during the period 1964 and 2008 was gaseous diffusion, some experimental work was also performed on laser enrichment in the 1970s and 1980s. During uranium enrichment by gaseous diffusion, uranium is in the form of highly soluble UF_6, containing molecules of ^{234}U, ^{235}U and ^{238}U, which are separated by mass. Enriched uranium (high weight per cent of ^{235}U) is produced in industrial quantities after many repetitions of this process. Depleted uranium, which contains a low weight per cent of ^{235}U, is a by-product of the enrichment process. Both enriched and depleted uranium are used in civil and military applications. Uranium enrichment workers constitute a specific subgroup which has protracted exposure to soluble uranium compounds of various isotopic compositions which can be categorised as natural, enriched and depleted uranium. External γ-radiation exposure in uranium enrichment workers is of lower magnitude compared with other groups of nuclear fuel cycle workers[11] In contrast to insoluble uranium compounds, which are retained in the lungs, soluble uranium compounds rapidly enter the systemic circulation where part of the uranium can be taken up by the skeleton, kidneys, liver and other tissues, and the remaining amount excreted within the following day via urine. Although previous studies in uranium enrichment workers have reported excesses in mortality from lymphohaematopoietic, bladder and stomach cancers,[12–14] until now no epidemiological study has explored long-term health effects of inhalation of different isotopic forms of uranium (natural, enriched and depleted). However, in vitro studies have shown that enriched and depleted uranium may have different toxicological profiles.[15]

Our study aimed to examine mortality risks due to cancerous and non-cancerous diseases in a national cohort of French uranium enrichment workers who were employed in enrichment of uranium by gaseous diffusion at three uranium enrichment plants, and were exposed to both radiological and non-radiological hazards. Associations with exposures to soluble uranium compounds of various isotopic compositions and external γ-radiation were examined.

MATERIALS AND METHODS

Cohort construction and follow-up

A roster of 5070 uranium workers involved in enrichment activities was identified from the French TRACY U (TRAvailleurs du CYcle du combustible potentiellement exposés à l'Uranium) cohort of 12 739 nuclear fuel cycle workers.[16] Inclusion in the cohort required that the workers should have worked for at least 6 months between 1964 and 2006 in the AREVA NC, CEA and Eurodif uranium enrichment plants. Membership of the 'uranium enrichment subcohort' (AREVA NC, CEA and Eurodif) was based on the longest employment period at these plants (see online supplementary table S1). Workers with a previous history of employment in uranium mining (n=31) were excluded. The final data set used in the statistical analyses included 4688 eligible uranium enrichment workers.

Each worker contributed person-years at risk from either the date of first employment at the uranium enrichment plant plus 6 months or 1 January 1968 (whichever occurred later), up to the date of death, last date known to be alive or 31 December 2008 (whichever occurred earlier). Sixteen deaths occurred before 1968, but the follow-up in our study began on 1 January 1968 because data on individual causes of deaths are not available in France before this date. Follow-up ended in 2008 because completeness of the death registry could not be guaranteed for more recent years at the time of the collection of individual causes of death.

Occupational radiation exposure assessment

The main exposures of interest in our study were internal radiation exposure from inhalation of uranium and external γ-radiation exposure. Ingestion of uranium in drinking water and food was considered negligible.

Estimates of annual internal exposure to uranium were reconstructed using two plant-specific job-exposure matrices (JEM) for the AREVA NC and Eurodif plants. The construction of these JEMs has been described in detail elsewhere.[17 18] The AREVA NC JEM was validated against individual bioassay data with 64% sensitivity and 80% specificity.[19] The two JEMs were constructed using the same strategy. The Eurodif JEM had additional information on current occupational exposure limits, which served to validate the intensity and frequency of exposure. The AREVA NC JEM was extrapolated to the CEA plant because of the identical nature of the work. The JEM was used to assign annual (1964–2008) levels of frequency and intensity of exposure on a four-level scale for each hazard. A multiplicative product of frequency, intensity and duration of employment (years) allowed deriving an individual exposure score which was used for epidemiological analyses.[20] Exposure to soluble uranium compounds (UF_6 and UO_2F_2) was defined as exposure to type F (rapidly soluble) uranium compounds according to the classification of the International Commission on Radiological Protection (ICRP).[21] For the Eurodif subcohort, it was possible to further distinguish between isotopic forms of uranium (natural, enriched and depleted). Exposure scores were cumulated for any worker with a history of working at uranium enrichment plants.

External γ-radiation exposure was monitored individually on either a monthly (workers susceptible to receiving between 6 and 20 mSv) or quarterly (those susceptible to receiving between 1 and 6 mSv) basis, and reported as an annual whole-body dose in mGy. External radiation dosimetry records were extracted from the plant monitoring files and the electronic SISERI system (French national database of occupational external exposure to ionising radiation).[22]

Assessment of other occupational hazards

Information on occupational exposure to trichloroethylene (TCE), heat and noise was considered because of their possible influence on cancerous[23] and circulatory diseases.[24] These were also selected due to their high prevalence and availability of monitoring data from the industrial hygiene services at uranium enrichment facilities.[12 17] Similarly to uranium exposure, exposure scores to TCE, heat and noise were estimated using JEMs. Noise was classified as a binary time-dependent variable (never exposed vs ever exposed to sound pressure of ≥80 dB(A)). Annual exposure to noise was available for the Eurodif subcohort.

Mortality ascertainment

Individual vital status and underlying causes of death were identified from the French national mortality registries by deterministic linkage via name, gender and date, and place of birth. Contributing causes of death listed on death certificates were not included as mortality events in this study. Causes of death were coded according to the eighth revision of the International

Classification of Diseases (ICD-8) from 1968 to 1977, the ninth revision (ICD-9) from 1978 to 1999 and the 10th revision (ICD-10) for the period 2000–2008.

Statistical analysis

We calculated standardised mortality ratios (SMR) for selected health outcomes using the French general population as a reference. Expected numbers of deaths for each cause were calculated using French sex-specific and age-specific mortality rates grouped in 5-year intervals from 1968 to 2008.

In addition, we performed within-cohort analyses via Poisson regression on grouped data[25] for all solid (n=406), lung (n=100) and lymphohaematopoietic (n=28) cancers, as well as circulatory (n=281), ischaemic heart (n=95) and cerebrovascular (n=71) diseases. In these analyses, person-years were cross-classified by sex, age (15–19, 20–24…80–84, 85 and over), calendar period (1968–1972, 1973–1977…1998–2003, 2004–2008), socioprofessional status at hire (managerial/professional, clerical, skilled technical, unskilled), subcohort (AREVA NC, CEA and Eurodif) and 5-year lagged cumulative exposures to soluble uranium, external γ-radiation, TCE, heat and noise. Time-dependent exposure levels were categorised (unexposed, low exposed, medium exposed and highly exposed) using quartiles of each cumulative exposure score weighted by the person-years. Cut-points for external γ-radiation were 0, 0.01, 0.13, 0.9 and 10 and more mGy so as to obtain a balanced number of deaths in each dose category. Log-linear risk models were used to obtain relative risk (RR) and corresponding 95% CI. In addition, linear excess relative risk (ERR) models were used to estimate ERR per 100 mGy and 95% CI associated with external γ-radiation dose. Models were stratified on sex, attained age, calendar period, socioeconomic status at hire and subcohort. We assessed confounding by TCE for cancer outcomes, and confounding by heat and noise for circulatory diseases. We examined the impact of the isotopic forms of rapidly soluble uranium compounds (enriched and depleted) within the Eurodif subcohort for solid cancers (n=85), lung cancer (n=23) and circulatory diseases (n=45).

A correlation between uranium compounds and external γ-radiation exposures were examined by Pearson's partial correlation coefficients controlling for the individual component effect.

All analyses were performed using Stata (StataCorp, College Station, Texas, USA) and EPICURE (HiroSoft International Corporation, Seattle, Washington, USA) statistical software.

RESULTS

Cohort description

Male workers constituted more than 90% of the study population (table 1). The median duration of follow-up was 30.2 years, and, as a whole, the cohort cumulated 136 161 person-years. Causes of death were ascertained for 99% of decedents (between 1968 and 2008). Less than 1% of the workers (n=37) were lost to follow-up. At the end of follow-up, 21% (n=1010) of the cohort had died, and 25% (n=1164) of the workers were still employed in the French nuclear industry. Almost 30% (n=1312) of the workers had been employed at more than two nuclear facilities. Seventy per cent (n=3295) of workers were potentially exposed to soluble uranium and 90% (n=4253) were monitored for external γ-radiation. Median external γ-radiation among exposed monitored workers was 0.75 mGy (minimum=0.03, maximum=230.2; table 1). More than 60% of the workers were exposed to several occupational hazards, but only 34% of the workers were exposed to both soluble uranium and external γ-radiation (data not shown). There was no correlation between exposure to rapidly soluble uranium compounds and external γ-radiation (Pearson's r=0.1). Within the Eurodif subcohort, exposure to enriched uranium was moderately correlated with depleted uranium (Pearson's r=0.7; data not shown).

Comparison of the cohort mortality with the general population

Mortality rates for all causes of death (SMR=0.69, 95% CI 0.65 to 0.74) and all cancers (SMR=0.79, 95% CI 0.72 to 0.87) were substantially below expectation based on national rates (table 2). An excess in mortality was observed for pleural cancer (SMR=2.3, 95% CI 1.06 to 4.4; based on nine deaths). A somewhat smaller mortality risk, albeit non-statistically significant, was also observed for kidney cancer (SMR=1.1, 95% CI 0.60 to 1.9), pancreatic cancer (SMR=1.3, 95% CI 0.87 to 1.8), biliary system cancer (SMR=1.5, 95% CI 0.50 to 3.6), malignant neoplasms of the central nervous system (SMR=1.6, 95% CI 0.94 to 2.6), malignant melanoma (SMR=1.9, 95% CI 0.83 to 3.8) and breast cancer (SMR=1.5, 95% CI 0.63 to 2.9) in females. Notable deficits were observed for smoking-related cancers (SMR=0.73, 95% CI 0.64 to 0.83), including lung cancer (SMR=0.74, 95% CI 0.60 to 0.90), non-malignant respiratory diseases (SMR=0.64, 95% CI 0.47 to 0.84), circulatory diseases

Table 1 Characteristics of the French cohort of uranium enrichment workers

	n (%)
Total number of workers	4688 (100)
Males	4251 (91)
Cumulated person-years	136 161
Ever exposed to soluble uranium compounds	3295 (70)
Ever exposed to insoluble uranium compounds	246 (5)
Monitored for external γ-radiation	4253 (91)
Work at more than two nuclear facilities	1312 (28)
Still employed at 31 December 2008*	1164 (25)
Subcohort†	
AREVA NC	707 (15)
CEA	1995 (43)
Eurodif	1986 (42)
Socioprofessional status at hire	
Managerial/professional	275 (6)
Clerical	798 (17)
Skilled technical	1862 (40)
Unskilled	1753 (37)
Follow-up status on 31 December 2008	
Alive	3641 (78)
Deceased	1010 (21)
Lost to follow-up	37 (1)
Age (years)	*Median (range)*
At start of follow-up	32.7 (19.1–65.5)
At end of follow-up	66.6 (22.7–95.9)
At death	67.6 (22.7–95.3)
Duration of follow-up (years)	30.2 (0.1–40.9)
Duration of employment (years)	9.2 (0.5–34.0)
Cumulative external γ-radiation dose (mGy)‡	0.8 (0.1–230.2)

*In the French nuclear industry.
†'Uranium enrichment subcohort' defined by the longest duration of employment in these plants.
‡Among monitored workers with cumulative external γ-radiation doses >0, n=2019.
DU, depleted uranium; EU, enriched uranium; NU, natural uranium.

Table 2 Observed deaths and standardised mortality ratios (SMR) in the French cohort of uranium enrichment workers

Cause of death (ICD-10)	Observed	SMR	95% CI	p Value*
All causes (A00-Y89)	1010	0.69	0.65 to 0.74	<0.001
All cancers (C00-C97)	429	0.79	0.72 to 0.87	<0.001
All cancers, except leukaemia (C00-C90, C96-C97)	418	0.79	0.72 to 0.87	<0.001
Solid cancers (C00-C80, C97)	406	0.80	0.72 to 0.88	<0.001
Smoking-related cancers (C00-C16, C22, C25, C30-C34, C53, C64-C68, C92)	242	0.73	0.64 to 0.83	<0.001
Oral cavity and pharynx (C00-C14, C46.2)	17	0.48	0.28 to 0.78	<0.001
Larynx (C32)	8	0.43	0.19 to 0.85	0.01
Lung (C33-C34)	100	0.74	0.60 to 0.90	0.02
Pleura (C38.4, C45.0)	9	2.3	1.06 to 4.4	0.04
Kidney (C64-C66, C68)	13	1.1	0.60 to 1.9	0.75
Urinary bladder (C67)	12	0.69	0.36 to 1.2	0.23
Oesophagus (C15)	19	0.66	0.40 to 1.03	0.07
Stomach (C16)	12	0.59	0.30 to 1.02	0.06
Pancreas (C25)	30	1.3	0.87 to 1.8	0.19
Liver (C22)	17	0.76	0.44 to 1.2	0.30
Biliary system (C23-C24)	5	1.5	0.50 to 3.6	0.45
Colon (C18)	28	0.83	0.55 to 1.2	0.38
Rectum (C19-C21)	11	0.81	0.40 to 1.4	0.59
Malignant melanoma (C43)	8	1.9	0.83 to 3.8	0.12
Breast, females (C50)	8	1.5	0.63 to 2.9	0.37
Prostate, males (C61)	30	0.86	0.58 to 1.2	0.48
Malignant and benign tumours of the brain and CNS (C70-C72, D32-D33, D42-D43)	21	1.3	0.80 to 1.9	0.28
Malignant tumours of the brain and CNS (C70-C72)	17	1.6	0.94 to 2.6	0.08
All lymphohaematopoietic (C46.3, C81-C96)	28	0.80	0.53 to 1.1	0.27
All leukaemia (C91.0-C91.3, C91.5, C91.7, C91.9, C92-C95)†	11	0.74	0.37 to 1.3	0.40
Non-Hodgkin's lymphoma (C46.3, C82-C85, C88.0-C88.3 C91.4, C96)	12	0.95	0.49 to 1.6	0.99
Multiple myeloma (C88.2, C88.7, C88.9, C90)	5	0.84	0.27 to 1.9	0.92
Circulatory diseases (I00-I99)	281	0.79	0.70 to 0.89	<0.001
Ischaemic heart diseases (I20-I25)	95	0.72	0.58 to 0.88	<0.001
Cerebrovascular diseases (I60-I69)	71	0.93	0.73 to 1.2	0.59
Hypertension (I10-I15)	5	0.41	0.13 to 0.9	0.04
Respiratory diseases (J00-J99)	49	0.64	0.47 to 0.84	0.01
Chronic obstructive lung disease (J40-J44, J47)	18	0.66	0.39 to 1.04	0.08
Digestive diseases (K00-K93)	25	0.26	0.17 to 0.38	<0.001
External causes (V01-Y89)	77	0.53	0.42 to 0.66	<0.001
Unknown causes (R96-R99)	11	0.31	0.16 to 0.56	<0.001

*Two-tailed p value.
†Includes one case of chronic lymphocytic leukaemia (CLL).
CNS, central nervous system; ICD, International Classification of Diseases; SMR, standardised mortality ratio.

(SMR=0.79, 95% CI 0.70 to 0.89) and deaths due to external causes (SMR=0.53, 95% CI 0.42 to 0.66; table 2).

Within-cohort exposure–response analyses

Associations between cumulative exposures to rapidly soluble uranium compounds and external γ-radiation, and mortality outcomes are presented in table 3 and in table 4. Exposure to natural soluble uranium compounds was not significantly associated with any cause of mortality, and a monotonic decreasing trend from low exposed to highly exposed was observed for lung and lymphohaematopoietic cancers. A highly imprecise positive trend across exposure to natural soluble uranium compounds (RR=0.85, 95% CI 0.56 to 1.3, low exposed vs never exposed; RR=0.98, 95% CI 0.71 to 1.3, moderately exposed vs never exposed; RR=1.2, 95% CI 0.85 to 1.6, highly exposed vs never exposed) was observed for circulatory diseases (table 3). A positive non-significant association was found between external γ-radiation dose and mortality due to circulatory (ERR/100 mGy=0.38, 95% CI <0 to 2.3) and ischaemic heart diseases (ERR/100 mGy=0.91, 95% CI <0 to 5.1; table 4). Additional adjustments for non-radiological occupational hazards (TCE, heat and noise) did not substantially change RR, ERR or improve the model fit (data not shown). Cause-specific RRs associated with exposures to enriched and depleted uranium were of comparable magnitude (table 5). Associations of mortality with non-radiological hazards are presented in online supplementary table S2.

DISCUSSION

In our study, we analysed mortality in a national cohort of French uranium enrichment workers exposed to soluble uranium compounds, external γ-radiation and other non-radiological occupational hazards. Overall, this workforce exhibits a favourable mortality pattern (healthy worker effect), with the exception of a significantly elevated mortality risk for pleural cancer. We did not find an association between exposure to soluble uranium compounds and external γ-radiation and cause-specific mortality. There was an imprecise trend of

Table 3 Summary of within-cohort Poisson regression models for exposure–response between exposure to natural soluble uranium compounds lagged by 5 years and selected causes of death in the French cohort of uranium enrichment workers (n=4688)

	Natural soluble uranium compound exposure categories			
Outcome	**Unexposed**	**Low**	**Medium**	**High**
Solid cancers				
Cases	118	67	112	109
RR (95% CI)	ref.	1.1 (0.83 to 1.5)	1.02 (0.78 to 1.3)	1.03 (0.79 to 1.3)
Lung cancer				
Cases	30	20	27	23
RR (95% CI)	ref.	1.2 (0.64 to 2.05)	0.92 (0.54 to 1.6)	0.74 (0.42 to 1.3)
Lymphohaematopoietic cancers				
Cases	7	5	9	7
RR (95% CI)	ref.	1.7 (0.48 to 5.5)	1.4 (0.52 to 3.9)	1.08 (0.37 to 3.3)
Circulatory diseases				
Cases	87	35	74	85
RR (95% CI)	ref.	0.85 (0.56 to 1.3)	0.98 (0.71 to 1.3)	1.2 (0.85 to 1.6)
Ischaemic heart diseases				
Cases	32	16	21	26
RR (95% CI)	ref.	1.1 (0.58 to 2.01)	0.71 (0.39 to 1.2)	0.91 (0.53 to 1.5)
Cerebrovascular diseases				
Cases	23	6	22	20
RR (95% CI)	ref.	0.55 (0.19 to 1.3)	1.2 (0.66 to 2.3)	1.07 (0.6 to 1.9)

All models are stratified by sex, attained age, calendar period, socioeconomic status at hire and subcohort.
RR, relative risk.

increased risk of mortality due to circulatory diseases across increasing exposure to natural soluble uranium compounds.

Study strengths and limitations

A unique strength of our study is exposure reconstruction of both radiological and non-radiological (chemical and physical) occupational hazards and distinguishing isotopic forms of soluble uranium compounds (natural, enriched and depleted). Together with ionising radiation, uranium enrichment workers are known to be exposed to numerous non-radiological hazards.[9 17 26] While these chemical and physical hazards are present in nuclear fuel cycle activities, they are rarely considered in epidemiological studies. Also, partly owing to historical and regulatory reasons, employers and employees in the French nuclear industry might have been more concerned with radiation protection compared to other non-radiological hazards.[27] Although exposure data were collected on more than 20 hazards, we only considered those three non-radiological risk

Table 4 Summary of within-cohort Poisson regression models for exposure–response between exposure to external γ-radiation lagged by 5 years and selected causes of death in the French cohort of uranium enrichment workers (n=4688)

	External γ-radiation dose exposure categories					
Outcome	**Unexposed**	**0.01–0.12 mGy**	**0.13–0.8 mGy**	**0.9–10 mGy**	**>10 mGy**	**ERR/100 mGy (95% CI)**
Solid cancers						
Cases	270	4	77	33	22	0.16 (<0 to 0.75)*
RR (95% CI)	ref.	1.8 (0.55 to 4.3)	1.3 (0.98 to 1.6)	0.87 (0.59 to 1.2)	0.96 (0.59 to 1.5)	
Lung cancer						
Cases	75	0	17	4	4	−0.43 (<0 to 0.41)*
RR (95% CI)	ref.	NE	0.97 (0.10 to 1.6)	0.35 (0.11 to 0.85)	0.6 (0.19 to 1.6)	
Lymphohaematopoietic cancers						
Cases	13	0	7	8	0	−0.42 (<0 to 1.5)*
RR (95% CI)	ref.	NE	2.3 (0.84 to 5.7)	4.2 (1.6 to 10.4)	NE	
Circulatory diseases						
Cases	185	2	41	36	17	0.38 (<0 to 2.3)*
RR (95% CI)	ref.	1.7 (0.28 to 5.5)	1.02 (0.71 to 1.4)	1.5 (0.99 to 2.09)	1.3 (0.76 to 2.1)	
Ischaemic heart diseases						
Cases	64	0	11	13	7	0.91 (<0 to 5.1)*
RR (95% CI)	ref.	NE	0.8 (0.39 to 1.5)	1.6 (0.81 to 2.8)	1.5 (0.62 to 3.2)	
Cerebrovascular diseases						
Cases	50	2	11	6	2	−0.36 (<0 to 1.6)*
RR (95% CI)	ref.	6.4 (0.97 to 24.3)	0.99 (0.48 to 1.7)	0.9 (0.33 to 1.9)	0.59 (0.10 to 1.9)	

All models are stratified by sex, attained age, calendar period, socioeconomic status at hire and subcohort.
*Lower CI bound could not be estimated as it is on the boundary of the parameter space (−1/max dose).
ERR, excess relative risk; NE, not estimated; RR, relative risk.

Table 5 Summary of within-cohort Poisson regression models for exposure–response between exposures to enriched and depleted uranium lagged by 5 years, and selected causes of death in the Eurodif subcohort of the French cohort of uranium enrichment workers (n=1986)

	Exposure categories			
Outcome	**Unexposed**	**Low**	**Medium**	**High**
Solid cancers				
Enriched uranium				
Cases	37	8	19	21
RR (95% CI)	ref.	0.59 (0.25 to 1.2)	1.3 (0.69 to 2.2)	0.82 (0.47 to 1.4)
Depleted uranium				
Cases	38	3	19	25
RR (95% CI)	ref.	0.30 (0.10-0.84)	1.4 (0.77 to 2.4)	1.07 (0.63 to 1.8)
Lung cancer				
Enriched uranium				
Cases	10	1	7	5
RR (95% CI)	ref.	0.25 (0.10 to 1.3)	1.8 (0.64 to 4.6)	0.69 (0.21 to 1.9)
Depleted uranium				
Cases	10	0	4	9
RR (95% CI)	ref.	NE	1.2 (0.33 to 3.7)	1.5 (0.61 to 3.9)
Circulatory diseases				
Enriched uranium				
Cases	19	7	8	11
RR (95% CI)	ref.	0.91 (0.29 to 2.9)	0.96 (0.32 to 2.9)	0.84 (0.28 to 2.8)
Depleted uranium				
Cases	23	3	7	12
RR (95% CI)	ref.	0.37 (0.10 to 1.2)	0.64 (0.23 to 1.7)	0.84 (0.32 to 2.3)

All models are stratified by sex, attained age, calendar period, and socio-economic status at hire
CI, confidence intervals; NE, not estimated; RR, relative risk.

factors (TCE, heat and noise) that raise concerns among occupational physicians and workers and that are most prevalent at French uranium enrichment plants. We did not consider other established carcinogens (eg, chromium and asbestos), because of the limited number of exposed workers. For example, TCE, as a chlorinated solvent, is a known carcinogen of group 1 according to the International Agency for Research on Cancer (IARC).[23] This exposure was not statistically significantly associated with excess lung and lymphohaematopoietic cancer as observed in our previous study.[9] Finally, models were not adjusted for non-radiological exposures, because their simultaneous inclusion in the models produced unstable risk estimates.

Uranium enrichment in France started in the beginning of the 1960s, which is late compared to the USA where the first uranium enrichment facilities were opened during the Manhattan Project in the 1940s. Hence, the proportion of workers alive at the end of follow-up is still high and the statistical power of our study will be improved by continuing the follow-up, as well as by conducting combined analyses with similar cohorts of nuclear fuel cycle workers. Most medical files, radiological bioassays and industrial hygiene data are hard copy and not adapted for immediate use in large-scale epidemiological studies. Even though the use of a JEM can cause non-differential misclassification of exposure, its use is particularly advantageous in this situation. The JEM exposure score used in this study was calculated individually as a product of frequency, intensity and duration of exposure, allowing for quantitative exposure–response analyses in the absence of internal uranium doses. In the short term, the lack of information on potential lifestyle confounders may be overcome by conducting nested case–control studies.[28] After the available bioassay data have been collected for this cohort, internal dose estimation will be possible. The harmonised approach developed in the European Commission-funded Concerted Uranium Research in Europe (CURE) project for the computation of internal doses in European cohorts of uranium workers will be used for that purpose.[29] Use of the JEM to assign solubility and isotopic composition of uranium compounds will improve the accuracy of internal dosimetry.[30] Therefore, a major limitation of our study is the absence of individual uranium dose estimates.

Excluding an unknown number of construction workers employed by subcontractor companies that may have been highly exposed to ionising radiation during maintenance and construction work from this study may have affected the strength of the tested associations. As in other studies,[31 32] the obstacles to including this workforce are the difficulty of locating payroll rosters and the impracticality of collecting occupational health monitoring files due to the frequent structural changes of subcontractor companies.

In addition, other limitations of our study are its limited statistical power and the lack of information on smoking and other lifestyle factors.

Comparison with the general population

Nuclear workers are subject to selection at the time of hiring on the basis of initial health status, and regular surveillance by occupational health services, which leads to selection of healthy workers. Decreased mortality in comparison with the general population—or healthy worker effect (HWE)—is common in occupational studies. As in other occupational cohorts,[33] an HWE was evident in our study for many causes of death (including cancer and circulatory diseases), indicative of selection bias. An excess risk typically becomes apparent when workers are exposed to an occupational hazard associated with a high risk of disease. Although it was possible to find by chance

a significant association in the SMR analysis due to the large number of tests performed, the significant result for pleural cancer might be linked with previous exposure to asbestos. The magnitude of latency for pleural mesothelioma is 40–50 years after first asbestos exposure, depending on the occupation and the intensity of exposure.[34] This increased pleural cancer mortality (mostly represented by pleural mesothelioma) is a common finding in studies of nuclear workers exposed to low-level radiation, and a critical role of unmeasured confounding by asbestos has been emphasised.[35] The excess for pleural cancer, albeit based on nine cases, may be a true finding due to the fact that many French nuclear workers started their career at naval shipyards where exposure to asbestos and external γ-radiation was quite substantial. Exposure to asbestos at uranium enrichment plants was of lower magnitude (P. Collomb, personal communication). Nine workers who died from pleural cancer in our study had a higher mean γ-radiation dose (13.3 mGy), compared to the cohort average (2.81 mGy) and started their employment in uranium enrichment at the age of 37.6 years, on average. Thus, the increased mortality due to pleural cancer may be attributed to exposures received before the work in uranium enrichment. Continuing monitoring of mortality due to pleural cancer is necessary in this study; however, detailed exposure–response analyses are not feasible at this stage due to the limited number of cases.

Associations with soluble uranium and external γ-radiation

An absence of significant associations between exposure to soluble uranium compounds and cause-specific mortality is noticeable. This may be due to a low influence of rapidly soluble UF_6 on studied causes of mortality. In fact, the products of the UF_6 hydrolysis (HF, UO_2F_2) dissolve in the upper airways by forming solid UO_2F_2 aggregates and not entering deeply into the lungs. Knowledge gained from several accidental exposures of UF_6 has shown that 73% of the uranium was excreted during the first 24 h.[36] Thus, the acute toxic effects of HF (skin damages and lung oedema) may prevail over the long-term health effects of UO_2F_2.

An increase in mortality due to lymphohaematopoietic cancer was reported in a recent study of the US Paducah gaseous diffusion plant workers.[12] This may be explained by the use of reprocessed uranium at this plant, which may have been contaminated with other radionuclides such as ^{99}Tc, ^{237}Np and ^{239}Pu,[12] having a shorter half-life period. In addition, as recently suggested by one case of accidental exposure to UF_6, its biokinetics may be modified by the lung oedema and lead to prolonged material retention in the lungs and lymphatic nodes.[37] While leukaemias are known to originate in haematopoietic stem cells of the red bone marrow, some lymphomas (non-Hodgkin's lymphoma and Hodgkin's disease) originate in the mature lymphoid cells situated in the lymphatic nodes.[38 39] In our study, an additional analysis excluding 246 workers with potential exposure to insoluble uranium compounds did not produce different risk estimates for lymphohaematopoietic cancer (results not shown).

The only suggestive non-significant trend across exposure categories of exposure to soluble uranium compounds was noted for circulatory diseases. A recent review of toxic effects of chronic uranium ingestion in animals has reported heterogeneous tissue sensitivity to uranium.[40] It seems that toxic effects of uranium exposure are not directly correlated with the amount of uranium accumulated in an organ.[40] While the studies reviewed by Dublineau *et al*[40] were not focused on cancer or circulatory diseases, there are numerous mechanistic theories of the relationship between circulatory diseases and low-dose radiation, such as induction of atherosclerosis, microvascular damage to the heart, kidney and lung and direct damage to the heart.[41] Owing to the lack of statistical significance of our observations and the lack of radiobiological studies on the effect of chronic uranium inhalation on the circulatory system, our findings should be considered very cautiously. A positive but non-significant association was also observed between circulatory diseases and external γ-radiation, which was comparable with other studies of French nuclear workers.[42 43]

Differences in the magnitude of mortality risks associated with exposures to natural, enriched and depleted uranium were indistinguishable in our study. Natural, enriched and depleted uranium share the same chemical toxicity, but the radiological toxicity of these three types of isotope mixtures varies, from lowest for depleted, intermediate for natural and highest for enriched uranium. Although enriched uranium, having strong α-emission potential, is more likely to produce double-strand breaks in DNA, a recent study showed that depleted uranium caused the same kind of DNA damage in bronchoalveolar cells of rats.[44] It should be noted, however, that an analysis stratified by the isotopic form of soluble uranium compounds was only possible within the Eurodif subcohort. This subcohort is the youngest of three subcohorts included in this study, with only 9% of workers having died at the end of follow-up. In time, it will therefore be necessary to include more workers exposed to enriched and depleted uranium to allow for more powerful analyses. At this stage, the most appropriate risk estimates of soluble uranium compounds are those obtained in the analysis of the total cohort of French uranium enrichment workers presented in this paper.

CONCLUSION

In summary, the first mortality analysis of the cohort of French uranium enrichment workers has not shown affirmative associations between exposure to soluble uranium compounds and cause-specific mortality. The findings obtained in this study should be revisited after continuing follow-up of this cohort, carrying out further analyses using individual-level internal uranium doses, and ultimately combining the data with those of similar cohorts of nuclear fuel cycle workers to increase statistical power. Opportunities to conduct such analyses in Europe were recently demonstrated by the European Commission-funded CURE project.[29]

Acknowledgements The authors would like to thank Dr Eve Bourgkard from the Institut national de recherche et de sécurité pour la prévention des accidents du travail et des maladies professionnelles (INRS) for her help in the use of national mortality statistics, Dr Pascale Scanff and Dr Hervé Roy from the Institut de Radioprotection et de Sûreté Nucléaire (IRSN) for providing access to external dosimetry data, and Dr Estelle Rage, Dr Klervi Leuraud, Ms Lucy Fournier and Professor Dale Preston for their help in using EPICURE software. Finally, the authors thank Professor David Richardson for his critical review of the manuscript and helpful suggestions.

Contributors SZ designed the study, conducted statistical analyses and had the lead role in writing the manuscript. DL, IGC, LBZ, ES, OL and JG participated in developing the study analytical strategy and in revising the manuscript. PC helped in the acquisition of occupational records.

Funding This research was funded by a research grant from the 'Health, Environment, and Toxicology' scientific programme of the Région Île-de-France. This article was prepared within the framework of the CURE project, supported by the EU FP7 DoReMi Network of Excellence (grant agreement: 249689). The construction of the TRACY U cohort was partly supported by AREVA in the framework of a bilateral IRSN-AREVA research agreement. The views of the authors do not necessarily reflect the views of the funding agencies.

Competing interests PC was employed by AREVA and had no control over the study design or statistical analysis.

Ethics approval The study has been approved by the French Data Protection Authority (CNIL) (declaration No. DR-2012–611).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Guseva Canu I, Zhivin S, Garsi JP, *et al*. [Effects of chronic uranium internal exposure on mortality: results of a pilot study among French nuclear workers]. *Rev Epidemiol Sante Publique* 2014;62:339–50.
2 Azizova TV, Haylock RG, Moseeva MB, *et al*. Cerebrovascular diseases incidence and mortality in an extended Mayak Worker Cohort 1948–1982. *Radiat Res* 2014;182:529–44.
3 Boice JD Jr, Cohen SS, Mumma MT, *et al*. Mortality among mound workers exposed to polonium-210 and other sources of radiation, 1944–1979. *Radiat Res* 2014;181:208–28.
4 Silver SR, Bertke SJ, Hein MJ, *et al*. Mortality and ionising radiation exposures among workers employed at the Fernald Feed Materials Production Center (1951–1985). *Occup Environ Med* 2013;70:453–63.
5 Durbin PW. Actinides in animals and man. In: Morss LR, Edelstein N, Fuger J, Katz JJ, eds. *The chemistry of the actinide and transactinide elements*. Netherlands: Springer, 2010;3339–74.
6 ATSDR (Agency for Toxic Substances and Disease Registry). *Toxicological profile of uranium*. Atlanta: CDC, 2012.
7 Canu IG, Ellis ED, Tirmarche M. Cancer risk in nuclear workers occupationally exposed to uranium-emphasis on internal exposure. *Health Phys* 2008;94:1–17.
8 Zhivin S, Laurier D, Guseva Canu I. Health effects of occupational exposure to uranium: do physicochemical properties matter? *Int J Radiat Biol* 2014;90:1104–13.
9 Zhivin S, Laurier D, Caër-Lorho S, *et al*. Impact of chemical exposure on cancer mortality in a French cohort of uranium processing workers. *Am J Ind Med* 2013;56:1262–71.
10 Laurier D, Guseva Canu I, Baatout S, *et al*. DoReMi workshop on multidisciplinary approaches to evaluating cancer risks associated with low-dose internal contamination. *Radioprotection* 2012;47:119–48.
11 NCRP (National Council on Radiation Protection and Measurements). Exposure of the US population from occupational radiation. Report No. 151. Bethesda: NCRP, 1989.
12 Chan C, Hughes TS, Muldoon S, *et al*. Mortality patterns among Paducah Gaseous Diffusion Plant Workers. *J Occup Environ Med* 2010;52:725–32.
13 McGeoghegan D, Binks K. The mortality and cancer morbidity experience of workers at the Capenhurst uranium enrichment facility 1946–95. *J Radiol Prot* 2000;20:381–401.
14 NIOSH (National Institute of Occupational Safety and Health). Mortality patterns among uranium enrichment workers at the Portsmouth gaseous diffusion plant Piketon, Ohio. 2001. http://www.cdc.gov/niosh/oerp/pdfs/2001–133g5–2.pdf (accessed 4 May 2015).
15 Darolles C, Broggio D, Feugier A, *et al*. Different genotoxic profiles between depleted and enriched uranium. *Toxicol Lett* 2010;192:337–48.
16 Samson E, Piot I, Zhivin S, *et al*. 0184 Mortality profile of the French cohort of uranium processing workers. *Occup Environ Med* 2014;71:2014–102362.
17 Guseva Canu I, Faust S, Knieczak E, *et al*. Estimating historic exposures at the European Gaseous Diffusion plants. *Int J Hyg Environ Health* 2013;216:499–507.
18 Guseva Canu I, Molina G, Goldberg M, *et al*. [Development of a job exposure matrix for the epidemiological follow-up of workers in the French nuclear industry]. *Rev Epidemiol Sante Publique* 2008;56:21–9.
19 Guseva Canu I, Laurier D, Caër-Lorho S, *et al*. Characterisation of protracted low-level exposure to uranium in the workplace: a comparison of two approaches. *Int J Hyg Environ Health* 2010;213:270–7.
20 Guseva Canu I, Garsi JP, Caër-Lorho S, *et al*. Does uranium induce circulatory diseases? First results from a French cohort of uranium workers. *Occup Environ Med* 2012;69:404–9.
21 ICRP (International Commission on Radiological Protection). *Publication 66. Human respiratory tract model for radiological protection*. Oxford: Pergamon Press, 1994.
22 Feuardent J, Scanff P, Crescini D, *et al*. Occupational external exposure to ionising radiation in France (2005–2011). *Radiat Prot Dosimetry* 2013;157:610–18.
23 IARC (International Agency for Research on Cancer). *IARC monographs on the evaluation of carcinogenic risks to humans, trichloroethylene, tetrachloroethylene, and some other chlorinated agents*. Vol 106. Lyon: IARC, 2014.
24 Gan WQ, Davies HW, Demers PA. Exposure to occupational noise and cardiovascular disease in the United States: the National Health and Nutrition Examination Survey 1999–2004. *Occup Environ Med* 2011;68:183–90.
25 Breslow NE, Day NE. *Statistical methods in cancer research. The design and analysis of cohort studies*. Vol II. Lyon: IARC, 1987.
26 Yiin JH, Schubauer-Berigan MK, Silver SR, *et al*. Risk of lung cancer and leukemia from exposure to ionizing radiation and potential confounders among workers at the Portsmouth Naval Shipyard. *Radiat Res* 2005;163:603–13.
27 Guseva Canu I, Faust S, Canioni P, *et al*. Attitude towards personal protective equipment in the French nuclear fuel industry. *Arh Hig Rada Toksikol* 2013;64:99–107.
28 Garsi JP, Samson E, Chablais L, *et al*. Half-century archives of occupational medical data on French nuclear workers: a dusty warehouse or gold mine for epidemiological research? *Arh Hig Rada Toksikol* 2014;65:407–16.
29 Laurent O, Gomolka M, Haylock R, *et al*. Task 5.8 CURE final report. D5.17: Report for an integrated (biology-dosimetry-epidemiology) research project on occupational uranium exposure. 2015. http://www.doremi-noe.net/ (accessed 4 May 2015).
30 Etherington G, Birchall A, Puncher M, *et al*. Uncertainties in doses from intakes of radionuclides assessed from monitoring measurements. *Radiat Prot Dosimetry* 2006;121:40–51.
31 Guérin S, Richard G, Biau A, *et al*. Cancer mortality among French nuclear contract workers. *Am J Ind Med* 2009;52:916–25.
32 Silver SR, Robinson CF, Kinnes G, *et al*. National Institute for Occupational Safety and Health. Evaluation of data for DOE site remediation workers. 2000. http://www.cdc.gov/niosh/oerp/pdfs/2001–133g21.pdf (accessed 4 May 2015).
33 Checkoway H, Pearce N, Kriebel D. *Research methods in occupational epidemiology*. Oxford: Oxford University Press, 2004.
34 Bianchi C, Giarelli L, Grandi G, *et al*. Latency periods in asbestos-related mesothelioma of the pleura. *Eur J Cancer Prev* 1997;6:162–6.
35 Metz-Flamant C, Guseva Canu I, Laurier D. Malignant pleural mesothelioma risk among nuclear workers: a review. *J Radiol Prot* 2011;31:9–23.
36 Beau PG, Chalabreysse J. Knowledge gained from bioassay data on some metabolic and toxicological features of uranium hexafluoride and its degradation products. *Radiat Prot Dosimetry* 1989;26:107–12.
37 Avtandilashvili M, Puncher M, McComish SL, *et al*. US Transuranium and Uranium Registries case study on accidental exposure to uranium hexafluoride. *J Radiol Prot* 2015;35:129–51.
38 Harris NL, Stein H, Coupland SE, *et al*. New approaches to lymphoma diagnosis. *Hematology Am Soc Hematol Educ Program* 2001;1:194–220.
39 Greaves M. Molecular genetics, natural history and the demise of childhood leukaemia. *Eur J Cancer* 1999;35:1941–53.
40 Dublineau I, Souidi M, Gueguen Y, *et al*. Unexpected lack of deleterious effects of uranium on physiological systems following a chronic oral intake in adult rat. *Biomed Res Int* 2014;2014:181989.
41 AGIR (Advisory Group on Ionising Radiation). Circulatory Disease Risk. Report of the Independent Advisory Group on Ionising Radiation. London: HPA, 2010.
42 Laurent O, Metz-Flamant C, Rogel A, *et al*. Relationship between occupational exposure to ionizing radiation and mortality at the French electricity company, period 1961–2003. *Int Arch Occup Environ Health* 2010;83:935–44.
43 Metz-Flamant C, Laurent O, Samson E, *et al*. Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers. *Occup Environ Med* 2013;70:630–8.
44 Monleau M, De Méo M, Paquet F, *et al*. Genotoxic and inflammatory effects of depleted uranium particles inhaled by rats. *Toxicol Sci* 2006;89:287–95.

Online supplementary table S1. History of uranium enrichment by gaseous diffusion technology in France

Facility	Operation years	Enrichment %
CEA pilot facility	1960-1964	NA
CEA/AREVA NC[*¶]		
low-grade enrichment	1964-1982	2
moderate-grade enrichment	1965-1984	7
high-grade enrichment	1966-1996	25
very high-grade enrichment	1967-1996	90
Eurodif[§]	1977-2008	3-5

[*]AREVA NC was operated by CEA until 1975.
[¶]Areva NC was formerly known as Cogema (Compagnie générale des matières nucléaires) before 2006.
[§]Eurodif was operated under an agreement between Germany, France, the Netherlands, and the UK. CEA, Commissariat à l'énergie atomique; Eurodif, European gaseous diffusion uranium enrichment consortium ; NA, not known.

Online supplementary table S2. Summary of within-cohort Poisson regression models for exposure-response between exposures to trichloroethylene, heat and noise lagged by five years, and selected causes of death in the French cohort of uranium enrichment workers (n = 4688)

			Exposure categories			
Outcome			**Unexposed**	**Low**	**Medium**	**High**[†]
		Cases	124	45	116	121
Solid cancers	TCE	RR (95%CI)	ref.	1.01 (0.70 to 1.4)	1.06 (0.82 to 1.4)	1.06 (0.82 to 1.4)
		Cases	34	11	25	30
Lung cancer	TCE	RR (95%CI)	ref.	0.75 (0.36 to 1.4)	0.80 (0.5 to 1.3)	0.85 (0.51 to 1.4)
		Cases	5	5	11	7
Lymphohematopoietic cancers	TCE	RR (95%CI)	ref.	3.05 (0.83 to 11.2	2.5 (0.91 to 8.2)	1.6 (0.49 to 5.4)
		Cases	44	25	156	56
	Heat	RR (95%CI)	ref.	1.3 (0.75 to 2.08)	1.03 (0.74 to 1.5)	0.95 (0.63 to 1.4)
		Cases	120			161
Circulatory diseases	Noise	RR (95%CI)	ref.			0.9 (0.7 to 1.2)
		Cases	14	8	52	21
	Heat	RR (95%CI)	ref.	1.5 (0.58 to 3.5)	1.05 (0.6 to 1.9)	1.08 (0.55 to 2.2)
		Cases	34			61
Ischemic heart diseases	Noise	RR (95%CI)	ref.			1.2 (0.72 to 1.9)
		Cases	11	6	45	9
	Heat	RR (95%CI)	ref.	1.3 (0.4 to 3.5)	1.23 (0.64 to 2.6)	0.70 (0.28 to 1.7)
		Cases	32			39
Cerebrovascular diseases	Noise	RR (95%CI)	ref.			0.88 (0.52 to 1.5)

All models are stratified by sex, attained age, calendar period, socio-economic status at hire, and subcohort

[†]High exposure category corresponds to ever-exposed category in case of noise exposure

CI, confidence intervals; RR, relative risk; TCE, trichloroethylene.

ABSTRACT

External γ-radiation exposure has been shown to be associated with mortality risk due to leukemia, solid cancer, and, possibly, circulatory diseases (CSD). By contrast, little information is available on health risks following the internal contamination, especially the inhalation of uranium compounds with respect to their physicochemical properties (PCP), such as solubility, isotopic composition and others.

The aim of this PhD thesis was to estimate mortality risk of cancer and non-cancer diseases in French nuclear fuel cycle workers and comprises three objectives: (1) evaluation of the impact of uranium on mortality through a critical literature review, (2) analysis of cancer and non-cancer mortality in a cohort of uranium enrichment workers, (3) analysis of the relationship between CSD mortality and internal uranium dose in AREVA NC Pierrelatte workers.

Existing epidemiological data on uranium PCP and associated health outcomes are scarce. Studies of nuclear fuel cycle workers by sub-groups within the specific stage of the cycle (e.g., uranium enrichment and fuel fabrication) are considered the most promising to shed light on the possible associations, given that such sub-groups present the advantage of a more homogenous uranium exposure.

To study the mortality risk associated with exposure to rapidly soluble uranium compounds, we set up a cohort of 4,688 uranium enrichment workers with follow-up between 1968 and 2008. Individual annual exposure to uranium, external γ-radiation, and other non-radiological hazards (trichloroethylene, heat, and noise) were reconstructed from job-exposure matrixes (JEM) and dosimetry records. Over the follow-up period, 131,161 person-years at risk were accrued and 21% of the subjects had die. Analysis of Standardized Mortality Ratios (SMR) showed a strong healthy worker effect (SMR all deaths 0.69, 95% confidence intervals (CI) 0.65 to 0.74; n=1,010). Exposures to uranium and external γ-radiation were not significantly associated with any cause of mortality in log-linear and linear excess relative risk models. A monotonic decreasing trend was observed for lung and lymphohematopoietic cancers across uranium exposure categories.

Previous analysis of a cohort of AREVA NC Pierrelatte uranium processing workers suggested that exposure to uranium may increase CSD mortality. A nested case-control study was set up to analyze the dose-response relationship and adjust for major CSD risk factors (smoking, blood pressure, body mass index, total cholesterol, and glycemia) collected from medical files. The study included 102 CSD cases and 416 controls matched on attained age, gender, birth cohort, and socio-professional status. Absorbed dose was calculated taking into account the solubility of uranium compounds extracted from the JEM. CSD risk was analyzed by conditional logistic regression. A positive but imprecise association was observed (excess odds ratio per mGy 0.2, 95% CI 0.004 to 0.5). None of the considered CSD risk factor confounded this association.

Compared to previous studies, our work provided important methodological improvements: consideration of specific uranium PCP, calculation of uranium organ doses, and adjustment on potential confounding factors (non-radiological exposures and CSD risk factors). The absence of association between exposure to rapidly soluble uranium compounds and mortality in the cohort of uranium enrichment workers may be indicative of the effective elimination of uranium from the human body. Analysis within the nested case-control study confirmed an association between uranium exposure and CSD mortality, not confounded by CSD risk factors. Our results should be confirmed in further studies. Future work should focus on uncertainties associated with internal uranium dose estimation, on nature of association with CSD mortality, and on temporal relationships between radiation and CSD risk factors.

Key words: uranium; epidemiology; cohort study; nested case-control study; internal dose estimation.