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Cancer and non-cancer mortality among French uranium cycle workers: The TRACY cohort

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ABSTRACT

Objectives: The health effects of internal contamination by radionuclides, and notably by uranium, are poorly characterized. New cohorts of uranium workers are needed to better examine these effects. This paper analyses for the first time the mortality profile of the French cohort of uranium cycle workers. It considers mortality from cancer and non-cancer causes.

Methods: The cohort includes workers employed at least 6 months between 1958 and 2006 in French companies involved in the production of nuclear fuel. Vital status and causes of death were collected from French national registries. Workers were followed-up from January 1, 1968 to December 31, 2008. Standardized mortality ratios (SMRs) were computed based on mortality rates for the French general population.

Results: The cohort includes 12649 workers (88% men). The average length of follow-up is 27 years and the mean age at the end of the study 60 years old. Large mortality deficits are observed for non-cancer causes of death such as non-cancer respiratory diseases (SMR=0.51 [0.41-0.63]) and circulatory diseases (SMR=0.68 [0.62-0.74]). A mortality deficit of lower magnitude is also observed for all cancers combined (SMR [95% confidence interval (CI)]: 0.76 [0.71–0.81]). Pleural mesothelioma is elevated (SMR=2.04 [1.19–3.27]).

Conclusion: A healthy worker effect is observed in this new cohort of workers involved in the uranium cycle. Collection of individual information on internal uranium exposure as well as other risk factors is underway, to allow for the investigation of uranium related risks.

Strengths and limitations of this study
• TRACY is a new cohort, one of the rare of uranium fuel cycle workers • Almost 13000 workers included from 1958 to 2006 • Only 1% of workers were lost to follow-up • Individual causes of death are only available since 1968 in France • Further work is ongoing to allow for the detailed investigation or uranium-related risk

INTRODUCTION

Ionizing radiation is an established carcinogen[1] and its effects on cancer risk are reasonably well understood and quantified, at least at high doses (>100 mGy) and dose rates (>5 $mGy.h^{-1}$).[2] By comparison, cancer risks associated with internal exposures resulting from the incorporation of radionuclides into the body are less well quantified.[3] This is a major issue for radiation protection since internal exposures are responsible for a large portion of population's collective effective dose due to exposure to naturally occurring radionuclides, such as radon, as well as medical diagnostic and occupational sources of internal exposures.[1] In addition, there is growing interest in health effects other than cancer following exposure to low doses of ionizing radiation (e.g.: diseases of the circulatory system[4]), notably following internal exposure.[5]

With the exception of studies on radon, relatively few recent epidemiological studies have directly quantified the health effects of internal contamination in populations chronically exposed to radionuclides.[6-9] As a result, the International Commission on Radiological Protection, which elaborates and periodically updates international radiation protection recommendations, had to estimate the risks of internal exposure to radioisotopes, such as uranium, by combining epidemiological evidence from external exposure situations with that from experimental studies on the biological effects of internal emitters.[10] It would be preferable to have direct epidemiological evidence regarding the effects of internal exposure to such radionuclides. There is therefore the need for further studies of populations exposed to internal emitters, to help assess the adequacy of current radiation protection standards with respect to internal exposure.[5]

Cohorts of workers involved in the uranium fuel cycle are of interest to study the risks associated with internal contamination to uranium because many workers were regularly

monitored for internal exposure via bioassay analyses.[5] However, few such cohorts have been set up.[11-17] A recent review concluded that studies based on these cohorts so far do not provide reliable evidence on the potential health risks associated with uranium exposure, notably because of insufficient statistical power.[18] Pooling existing large cohorts of uranium workers and setting up new ones is clearly needed to improve the knowledge of the health effects of uranium exposure.[19]

France has operated a complete nuclear fuel production cycle since the 1960's. The French cohort of workers employed in the nuclear fuel production cycle (TRACY, for TRAvailleurs du CYcle) was set up to assess the risk of cancer and non-cancer mortality related to internal exposure to uranium. Pilot studies were successfully conducted in specific subsets of this large cohort.[20 21] The reconstitution of exposure data in the entire TRACY cohort is underway.

The aim of the current investigation was to describe mortality among the uranium workers in this new large cohort, by comparison with the general population.

MATERIAL AND METHODS

Study design

TRACY is a retrospective cohort designed to study the mortality of workers involved in the French uranium fuel cycle. As will be detailed below, occupational data was collected from 2009 to 2013 and cover period 1958 to 2006, whereas mortality data cover a period spanning from 1968 to 2008.

Study population

The companies included in this study cover different steps of the nuclear fuel production cycle in France (Figure 1): purification of concentrated natural uranium, conversion to uranium hexafluoride, enrichment by gaseous diffusion, fuel manufacturing and other activities such as storage (depleted and reprocessed uranium) and decontamination (waste and effluents). Companies involved in uranium mining and milling are not included, nor are companies that are end users of the nuclear fuel (e.g., electricity production). The companies included and their respective main activities are presented in Appendix Table 1. TRACY is complementary to the French uranium miners cohort[22] and to the French nuclear workers cohort designed to study the association between external chronic exposure to radiation and mortality,[23] whereas the main focus of TRACY is internal contamination by uranium.

Workers included in the cohort had to be employed at least 6 months, as members of the permanent staff of selected companies between 1958 and 2006. Personal identifiers and work histories were provided by the administrative departments of each company, either on paper or electronic files. The files were computerized whenever needed, validated and merged. Transfers from one company to another were taken into account to avoid duplicate counts and accurately reconstruct complete individual work histories.

The date of start of employment was defined as the earliest one if several periods of employment were recorded. The date of end of employment, whatever the reason (retirement, resignation, dismissal, job transfer to a company not included in the study), was identified from the last recorded period of employment. For workers still employed on December 31st, 2006, the end of employment was set to that date.

Follow up, vital status and causes of death

For each worker, follow-up of vital status began on the most recent date among the following: date of initial employment plus 6 months, or January 1st, 1968. The lower bound

of the follow-up period had to be set to that date since the national registry which provides cause of death information in France (CépiDC-Inserm) can deliver no individual data before 1968. Among the cohort members who began working before 1968, 53 had died or would have been lost to follow-up before 1968 and could not be included in the mortality study. The date of end of follow-up was defined as the earliest among the following ones: date of death, last information date (for workers lost to follow-up) and December 31st, 2008. Workers' vital status, and the date of death for workers who died, were obtained by file-matching with the National Vital Status Registry (Répertoire National d'Identication des Personnes Physiques). Causes of death coded according to the International Classication of Diseases (ICD, version 8 for period 1968–1978, version 9 for 1979–1999 and version 10 for period 2000–2008, see Appendix Table 2) were obtained by file-matching with the French national mortality registry (CépiDC-Inserm).

Statistical analysis

Mortality rates were compared with those in the French general population (also obtained from CépiDC-Inserm) by computing standardized mortality ratios (SMRs), therefore controlling for potential confounders: sex, age (categorized as follows: 15–19, 20-24,…, 80-84, ≥85) and calendar period (categorized as follows: 1968-1972, 1973-1977,…, 1998-2002, 2003-2008) as classically done for such analyses.[24] Confidence intervals (95% CIs) were calculated using the Poisson exact method.[25] This was done for specific causes of death (e.g.: cancer of specific organs or tissues) or broader groupings of causes (e.g.: all cancers, all circulatory diseases, cancers sites potentially associated with smoking).[26] Appendix Table 2 provides the definition and corresponding ICD codes of all causes of death considered. For the primary analysis, SMRs were computed for men and women grouped together. Results were reported only for causes of death with at least 5 cases observed across the whole cohort.

Supplementary analyses were conducted for broad groupings of causes of death (all causes, cancer and non-cancer diseases) to examine the evolution of SMRs according to time since hire (categorized as follows: <25 years, 25-39, ≥40), time since end of employment (categorized as follows: <10 years, 10-19, ≥20), total duration of employment (categorized as follows: <10 years, 10-24, ≥25) and attained age (categorized as follows: <50, 50-65, ≥66).[27] Further analyses were conducted to estimate SMRs among men and women separately.

All analyses were conducted using the SAS software, version 9.2 (Cary, North Carolina, USA).

The protocol of this study was validated by the French Data Protection Authority (CNIL), agreement n° DR-2012-611.

RESULTS

The inclusion process (summarized in Appendix Figure 1) started from a base of 21143 potentially eligible workers. After removal of duplicates and exclusion of workers who did not match the eligibility criteria, 12713 workers were confirmed to be eligible and included in the study. After further exclusion of one worker with identifiers not sufficient to match with national files (place of birth unknown) and of workers either dead or who would have been lost to follow-up before 1968, the mortality analysis was performed on 12649 workers.

The main characteristics of the cohort are presented in Table 1. Among the 12649 workers included, 88% were males. The cohort cumulated 342258 person-years of observation. The mean duration of follow-up was 27 years. The mean age at the end of the study was 60 years old. The mean age at hire was 30 years old and it was 49.3 years old at the end of employment. The mean duration of employment was 19 years. At the end of the follow-up,

82% of workers were still alive, 17% were deceased and 1% was lost to follow-up. Underlying cause of death was identified for 99% of the 2130 deaths recorded.

SMRs are presented in Table 2 for the whole cohort. A substantial mortality deficit is observed for all-cause mortality compared to expectation based on French national rates (SMR 0.65; 95% CI 0.62–0.68; n=2130).

There was a substantial deficit in mortality for most major categories of non-malignant diseases. All non-cancer mortality was in 42% deficit (SMR 0.58; 95% CI 0.55–0.62, n=1012). There were substantial deficits in deaths due to non-malignant respiratory diseases (SMR 0.51; 95% CI 0.41–0.63, n=88), circulatory diseases (SMR 0.68; 95% CI 0.62–0.74, n=539), non-malignant renal diseases (SMR 0.66; 95% CI 0.39–1.06, n=17), and external causes of death including suicides and accidents (SMR 0.54; 95% CI 0.46–0.62, n=186).

For deaths due to all malignant diseases grouped together, there was also a deficit in the entire cohort although less pronounced than for most non-malignant categories of cause of death. Overall, cancer mortality was in 24% deficit (SMR 0.76; 95% CI 0.71–0.81, n=912). However, a two-fold excess was observed for pleural mesothelioma (SMR 2.04; 95% CI 1.19–3.27; n= 17) and non-significant excesses were observed for other cancers: pancreas (SMR 1.05 ; 95% CI; 0.79–1.38, n=53), skin melanoma (SMR 1.60; 95% CI 0.90–2.64, n=15), breast (all observed cases being among women, see Appendix Table 4; SMR 1.53 ; 95% CI 0.94–2.37; n=20), brain and central nervous system (SMR 1.36; 95% CI 0,93–1,91, n=32), lymphocytic (SMR 1.38; 95% CI 0.71–2.42, n=12) and myeloid (SMR 1.06; 95% CI 0.59–1.74, n=15) leukemia and multiple myeloma (SMR 1.29; 95% CI 0.77–2.05, n=18). In contrast, there was a substantial deficit in deaths due to smoking-related cancers (SMR 0.68; 95% CI 0.62-0.75, n=495).

SMRs for cancer and non-cancer diseases tended to increase with time since hire, with time since end of employment and with attained age (Table 3). Twenty years after the end of employment, the risk of cancer mortality is not significantly different from that in the general population, whereas it remains significantly lower for non-cancer diseases. No clear trend was observed according to the duration of employment for mortality from all causes and from non-cancer diseases. However there was evidence of a decreasing trend along with duration of employment for cancer mortality. For all broad groupings of causes of death, the lowest SMRs were observed in workers with the longest duration of employment (Table 3).

Significant deficits in all-cause and non-cancer mortality were observed for both genders (see Appendix Tables 3 and 4). In men, a significant deficit in mortality from all cancers was also observed and results were overall comparable to those in the entire cohort. In women, non-significant excesses of cancer mortality were observed. However, confidence intervals were very wide due to the lower number of women (and therefore, of deaths observed in these women) in the cohort (see Appendix Table 4).

DISCUSSION

This is the first mortality study conducted in this new cohort of uranium cycle workers, which is one of the largest of its kind. A healthy worker effect (HWE) is observed. It is especially strong for major groups of non-cancer diseases, including circulatory and non-cancer respiratory diseases. For all cancers grouped together, a healthy worker effect is also observed overall, but is less marked than for non-cancer diseases. No deficit in cancer mortality is observed in workers with more than 20 years of employment or in women. A significant excess of malignant pleural mesothelioma is observed, and non-significant excesses are observed for a few other specific cancer sites.

Mortality profile

The HWE is often observed in occupational cohorts, including nuclear worker cohorts.[23 24 27] It partly results from the selection of healthier people at hiring (referred to as the "healthy hire effect",[27] which tends to shrink with time since hire), and from other selection effects making the healthiest individuals more likely to be retained in the workforce than individuals with poorer health (referred to as the "healthy survivor effect"[27] and reflected by the fact that workers with the longest duration of employment exhibit the lowest SMRs). The regular health surveillance provided by occupational medicine services, but also other factors such as work-related physical activity are also suspected to contribute to the healthy survivor effect. As time since the end of employment goes by, the mortality profile of workers tend to reach that of the general population. These patterns were observed in the TRACY cohort, in agreement with previous literature.[23 24 27] Methods have been proposed to calculate adjusted SMRs as a complement to the traditional SMR that may facilitate interpretation of findings in spite of comparability issues due to the HWE; a recent example of such an approach draws on methods developed for the use of negative control outcomes for bias reduction.[28] Such methods have not been applied in the current paper however, since it is difficult to define a relevant negative control outcome for a population of workers exposed to uranium. In spite of the aforementioned limitations resulting from the HWE, comparisons of mortality profiles of occupational cohorts with those of general populations have been considered to be a useful approach, and therefore have been widely used, in occupational epidemiology.[17 24 29 30]

Importantly, the observed HWE does not mean that no case attributable to uranium or to other sources of radiation occurred in the TRACY cohort. The present analysis provides a simple but informative picture of the general level of risk in this cohort of workers of the uranium fuel cycle, through a comparison with the general population. The risk in the cohort is not only influenced by uranium and other radiation exposures but also by the levels of exposure to other risk factors. For instance, the SMR for the grouping of cancers sites that

may be caused by smoking[26] is low in the TRACY cohort. This suggests a lower level of exposure to smoking in this cohort than in the general population.

Conversely, we observed an excess of pleural mesothelioma. This observation is echoed by similar findings from most other nuclear worker cohort studies.[31] An excess risk was also observed in the French cohort of nuclear workers, designed to study the effects of external radiation exposure (based on 36 deaths),[32] but it has to be noted that these two results are not independent due to partial overlap of the two cohorts, concerning workers from AREVA NC and CEA Pierrelatte plant (10 deaths in common). Evidence for an association between exposure to ionizing radiation and pleural mesothelioma is weak however,[31] and to the best of our knowledge no association between uranium exposure and mesothelioma has ever been reported. By contrast, asbestos exposure is a strong risk factor for this disease, and has been known to occur in companies included in TRACY,[33] as well as in other companies in which some workers were employed before joining the nuclear fuel industry. This might contribute to the excess of malignant pleural mesothelioma observed in this cohort.

Non-significant excesses were observed for a few cancer sites in TRACY. For pancreas cancer, non-significantly positive SMRs were also observed in several other cohorts of uranium workers (including uranium millers)[13 16 34 35] but not in all.[14 17 29 30 36]

For all leukemias grouped together, patterns are not consistent across cohorts either. A proper comparison by leukemia subtypes is hampered by the inhomogeneous sets of subtypes for which results were reported in available studies. However, non-significant excesses of multiple myeloma[16 34 37] or myeloma[30] were reported in most cohorts which evaluated this outcome.

Non-significant excesses of cancers of the brain and central nervous system were reported in most cohorts of uranium workers.[13 30 34-36 38] Although no single study detected a significant

excess of brain cancer, the consistent pattern of non-significant excesses across cohorts for this outcome deserves further investigation. Animal studies have shown that brain is a target organ for uranium effects,[39] although to the best of our knowledge no animal study specifically focused on brain or central nervous system cancers.

Only one other cohort of uranium fuel cycle workers reported a non-significant excess of melanoma so far.[13] Only two studies reported non-significant excesses of breast cancer[13 17] and in one of them, the excess was only observed in women monitored for internal contamination.[17]

Strengths and limitations

The TRACY cohort has major strengths, such as its large size and excellent quality of follow-up. It is one of the rare cohorts of uranium fuel cycle workers in the world. However, the present study also has some limitations. No individual data on causes of death was available before 1968 due to late startup of the French mortality registry. This limitation applies to all epidemiological studies in France. Uranium related activities began as early as 1959 in some companies included in TRACY. However the gap in temporal overlap before year 1968 could not hamper the detection of potential excess of diseases occurring after a long latency time following occupational exposure (e.g. solid cancers are usually considered to occur after 10 or more years following radiation exposure). Similarly, the fact that occupational data have not been collected after year 2006 yet, although the mortality analysis covered period 1968-2008, is unlikely to generate a substantial impact on the analysis of diseases with long latency times. However, the possible impact of the aforementioned lacks of temporal overlap is less clear for diseases with shorter latency times such as leukemia.

The criteria for inclusion into the TRACY cohort guarantees that all permanent staff workers potentially exposed to uranium as part of the upstream steps of the French nuclear

fuel cycle (except miners and millers) are included. However, it is clear that some workers not exposed to uranium are also included in the cohort. Having these workers in the cohort will be useful to constitute an internal reference group, when associations between uranium exposure and mortality will be studied. However, further work is still needed (especially, a detailed reconstruction of bioassay record histories) before being able to separate all workers exposed from those non-exposed to uranium in the entire TRACY cohort. Complex changes in industrial processes combined with changes in individual job histories make it a long-term task.

The reconstruction of the multiple exposures of the workers in the TRACY cohort represents a necessary effort to assess risks according to different levels of exposure to uranium, while taking into account other sources of radiation and other potential risk factors. Uranium exposure is being reconstructed by a dual approach combining individual monitoring data[40] and specific job-exposure matrices.[33] Job Exposure Matrices also document exposures to potential confounders such as chemical agents and physical stressors (e.g.: heat and noise). This detailed exposure reconstruction will allow us to distinguish the different steps of the uranium fuel cycle (conversion, enrichment, fuel manufacturing) and better characterize the physicochemical characteristics of the different uranium compounds (in term of solubility and isotopy) to which workers were exposed. Additional information on risk factors such as tobacco smoking and various clinical parameters (body mass index, blood pressure, lipid profile etc.) is being collected from the occupational health services,[41] which will allow controlling for their potential confounding effects in future analyses.

The statistical power available to study rare or specific diseases (ex: specific cancer sites) remains limited in TRACY, but also in other cohorts of nuclear fuel cycle workers, unless large excesses actually occur (as was observed in TRACY for pleural mesothelioma). Extended follow-up and pooled analyses of these cohorts are needed to produce more

statistically precise estimates, which will allow drawing more robust conclusions on possible excess for these diseases and their association with uranium exposure. A pooling of TRACY with other cohorts of uranium workers and miners in Europe is planned, according to harmonized methodologies defined as part of the European project CURE.[19] In the future, this approach could be extended to other cohorts outside Europe.

CONCLUSION

This first mortality study of the TRACY cohort of French uranium cycle workers has shown a substantial mortality deficit for all broad groupings of causes of death and most of the pathologies studied. However a significant excess of malignant pleural mesothelioma was also observed and non-significant excesses were observed for a few specific cancer sites. To go further in the investigation of uranium related risks in this new cohort, collection of individual information on internal uranium exposure as well as other risk factors is underway.

Finally, through the pooling of TRACY with other cohorts of uranium workers, the TRACY cohort will help improving the knowledge of the health effects of uranium exposure and more generally of internal contaminations by radionuclides, in support of radiation protection research and practice.

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Competing Interests

Ana-Paula Serond and Pierre Laroche have been employed by AREVA. They provided access to data sources needed for the construction of the database and role in launching and supporting the study. They had no influence on decisions concerning analysis of the results. Other authors have no conflict of interest to disclose.

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Authors' contributions

Eric Samson launched the study, obtained the permissions, collected necessary data, ensured the data management, the analysis and wrote the first draft of the article.

Irwin Piot gathered the vital status and causes of deaths from the national French registries, helped for the data-management of the cohort and prepared the programs for the mortality analysis.

Dominique Laurier and Olivier Laurent contributed to the design of the study, the interpretation of the results and supervised the writing of the article.

Sergey Zhivin and David B. Richardson brought substantial contributions to the analysis of the data and the improvement of the article particularly for the discussion section, tables and figures.

Pierre Laroche and Ana-Paula Serond managed relationships with the AREVA plants and provided access to data sources needed for the construction of the database.

Data sharing

The agreement obtained from the French Data Protection Authority (CNIL) to launch this study is not allowing us to share data.

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Figure 1 – Simplified diagram describing the French uranium fuel cycle

Table 1. Description of the TRACY cohort

	Men		Women		All	
	Number	**%**	**Number**	**%**	**Number**	**%**
All workers	11122	87.9%	1527	12.1%	12649	100%
Person-years	303606	88.7%	38652	11.3%	342248	100%
Vital status on December 31, 2008						
Alive	8992	80.9%	1386	90.8%	10378	82.1%
Still employed	3937	35.4%	620	40,6%	4557	36.0%
Deceased	2028	18.2%	102	6.7%	2130	16.8%
With identified causes	2009	99.1%	102	100%	2111	16.7%
Lost to follow-up	102	0.9%	39	2.5%	141	1.1%
	Median	**Mean**	**Median**	**Mean**	**Median**	**Mean**
Year of birth	1943	1945	1949	1951	1944	1946
Age at death	67.8	66.4	60.9	62.2	67.5	66.2
Age at hiring	28.1	30.5	26.4	28.9	27.9	30.3
Age at end of employment (All)	53.8	49.8	47.5	45.5	53.1	49.3
Still employed	49.0	47.5	47.3	46.0	48.7	47.3
Not employed anymore	56.9	51.1	48.4	45.1	56.7	50.4
Duration of employment in years	19.9	19.4	14.3	16.6	19.3	19.0
Age at beginning of follow-up	31.2	33.2	29.0	31.1	31.0	32.9
Age at end of follow-up	61.1	60.5	56.3	56.5	60.6	60.0
Duration of follow-up in years	28.3	27.3	25.5	25.3	27.9	27.1

Table 2. Standardized mortality ratios (SMRs) in the TRACY cohort (1968-2008)*.

Cause of death	Observed number of deaths	SMR	95% confidence interval
All causes	2130	0.65	[0.62 - 0.68]
Non-cancers diseases	1012	0.58	[0.55 - 0.62]
Non-malignant tumors of central nervous system and sense organs	10	0.77	[0.37 - 1.42]
Endocrine, nutritional and metabolic diseases	47	0.67	[0.49 - 0.89]
Diseases of the blood and blood-forming organs	7	0.63	[0.25 - 1.30]
Cirrhosis, psychosis and other diseases due to alcohol	48	0.27	[0.20 - 0.35]
Non-tumoral diseases of central nervous system and sense organs	68	0.83	[0.64 - 1.05]
Diseases of the circulatory system	539	0.68	[0.62 - 0.74]
Hypertensive diseases	15	0.56	[0.31 - 0.93]
Ischemic heart diseases	211	0.71	[0.62 - 0.81]
Cerebrovascular diseases	130	0.75	[0.63 - 0.90]
Other and unspecified disorders of the circulatory system	183	0.61	[0.52 - 0.71]
Respiratory diseases	88	0.51	[0.41 - 0.63]
Diseases of the digestive system (other than cirrhosis)	48	0.58	[0.43 - 0.77]
Diseases of the genito-urinary system	23	0.70	[0.44 - 1.05]
Renal diseases	17	0.66	[0.39 - 1.06]
Diseases of the skin	5	1.14	[0.37 - 2.67]
Diseases of the musculoskeletal system and connective tissue	8	0.74	[0.32 - 1.46]
Other non-cancers diseases	121	0.43	[0.35 - 0.51]
All cancers	912	0.76	[0.71 - 0.81]
Smoking related cancers	495	0.68	[0.62 - 0.75]
Mouth	13	0.46	[0.25 - 0.79]
Pharynx	28	0.57	[0.38 - 0.82]
Esophagus	33	0.52	[0.36 - 0.73]
Stomach	29	0.64	[0.43 - 0.92]
Liver	31	0.65	[0.44 - 0.92]
Pancreas	53	1.05	[0.79 - 1.38]
Nasal cavity, sinus and middle ear	5	0.24	[0.08 - 0.57]
Larynx	20	0.49	[0.30 - 0.75]
Lung	217	0.73	[0.64 - 0.83]
Bladder	26	0.69	[0.45 - 1.01]
Kidney	24	0.84	[0.54 - 1.24]
Non-smoking related cancers	358	0.87	[0.79 - 0.97]
Colon	60	0.78	[0.60 - 1.01]
Rectum	26	0.87	[0.57 - 1.28]

Cause of death	Observed number of deaths	SMR	95% confidence interval
Gallbladder and bile ducts	7	0.98	[0.39 - 2.01]
Pleura	17	2.04	[1.19 - 3.27]
Melanoma	15	1.60	[0.90 - 2.64]
Breast	20	1.32	[0.81 - 2.04]
Prostate	71	0.94	[0.74 - 1.19]
Brain and central nervous system	32	1.36	[0.93 - 1.91]
Other non-smoking related cancers	106	0.69	[0.57 - 0.84]
Haematological and lymphatic malignancies	74	0.96	[0.75 - 1.20]
Leukaemia	33	1.00	[0.69 - 1.40]
Lymphocytic leukaemia	12	1.38	[0.71 - 2.42]
Chronical Lymphocytic leukaemia	8	1.28	[0.55 - 2.52]
Myeloid leukaemia	15	1.06	[0.59 - 1.74]
Acute myeloid leukaemia	10	1.22	[0.58 - 2.24]
Other leukaemia	6	0.59	[0.22 - 1.28]
Multiple myeloma	18	1.29	[0.77 - 2.05]
Non-Hodgkin's lymphoma	23	0.86	[0.55 - 1.30]
External causes	186	0.54	[0.46 - 0.62]
Suicides	77	0.66	[0.52 - 0.82]
Accidents	98	0.47	[0.39 - 0.58]
Other external causes	11	0.49	[0.24 - 0.87]

* For causes of deaths with at least 5 cases observed

Table 3. Standardized mortality ratios (SMRs) and 95% confidence interval in the TRACY cohort (1968-2008), by time since hire, time since end of employment, duration of employment and age reached, for broad groupings of causes of death.

Time since hire			
Cause of death	Less than 25 years	25 to 39 years	40 years or more
All causes	0.54 [0.50 - 0.58]	0.70 [0.66 - 0.75]	0.73 [0.66 - 0.79]
All cancers	0.64 [0.57 - 0.73]	0.82 [0.74 - 0.89]	0.82 [0.71 - 0.93]
Non-cancer diseases	0.46 [0.41 - 0.52]	0.63 [0.57 - 0.69]	0.67 [0.59 - 0.75]
Time since end of employment			
Cause of death	Less than 10 years	10 to 19 years	20 years or more
All causes	0.56 [0.52 - 0.59]	0.74 [0.68 - 0.80]	0.76 [0.70 - 0.82]
All cancers	0.68 [0.62 - 0.75]	0.81 [0.71 - 0.92]	0.90 [0.79 - 1.02]
Non-cancer diseases	0.46 [0.41 - 0.51]	0.69 [0.61 - 0.77]	0.69 [0.62 - 0.77]
Duration of employment			
Cause of death	Less than 10 years	10 to 24 years	25 years or more
All causes	0.66 [0.61 - 0.72]	0.67 [0.63 - 0.71]	0.60 [0.55 - 0.66]
All cancers	0.82 [0.72 - 0.93]	0.78 [0.70 - 0.85]	0.69 [0.61 - 0.78]
Non-cancer diseases	0.57 [0.50 - 0.65]	0.61 [0.56 - 0.66]	0.52 [0.46 - 0.60]
Attained age			
Cause of death	Less than 50 years old	50 to 65 years old	66 years old or more
All causes	0.50 [0.44 - 0.56]	0.56 [0.52 - 0.61]	0.77 [0.72 - 0.81]
All cancers	0.60 [0.48 - 0.75]	0.70 [0.63 - 0.77]	0.86 [0.78 - 0.94]
Non-cancer diseases	0.39 [0.32 - 0.48]	0.46 [0.40 - 0.52]	0.71 [0.65 - 0.76]

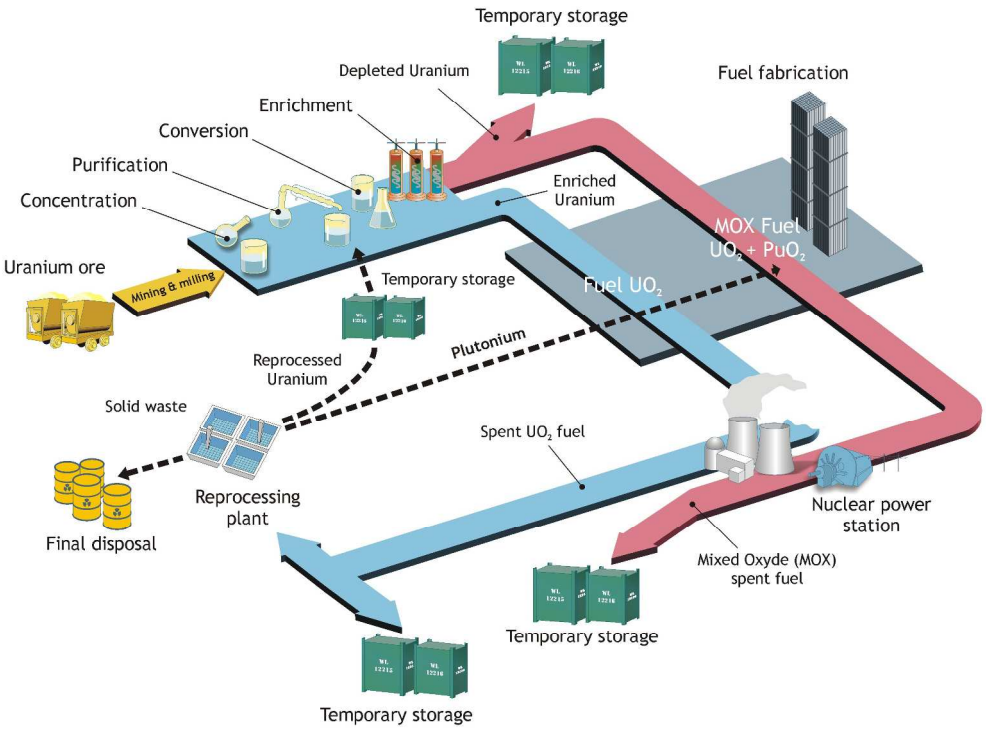

Figure 1 – Simplified diagram describing the French uranium fuel cycle
265x196mm (300 x 300 DPI)

Supplementary Material

Cancer and non-cancer mortality among French uranium cycle workers: The TRACY cohort

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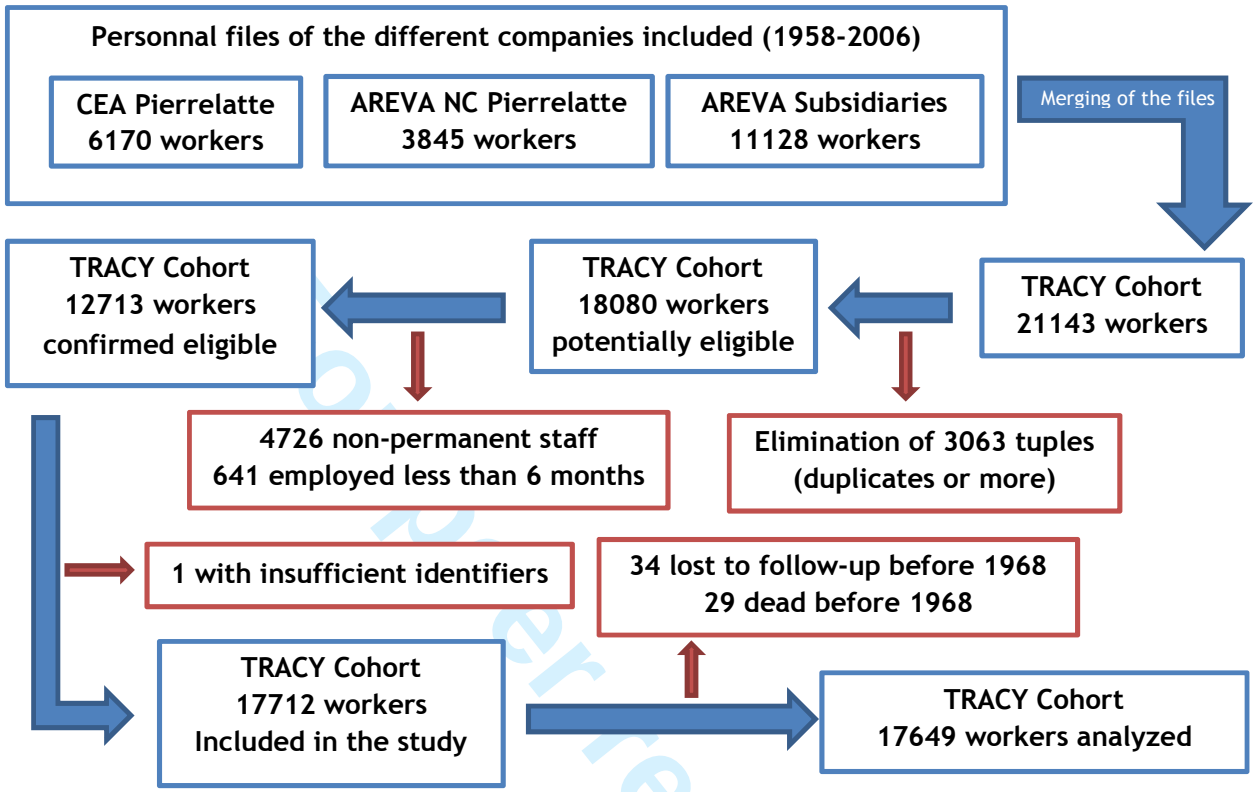
Appendix Figure 1 – Selection of workers for the mortality analysis



Appendix Table 1. Description of companies included in the TRACY cohort

Company	Year of beginning of operations	Plant location	Main activities
COMURHEX*	1959	Malvesi	Purification of uranium concentrates (from 75% to 99.5% of natural uranium). Conversion of yellow cake to uranium tetrafluoride (UF_4). Manufacturing of uranium-metal fuel until 1972 for the natural uranium gas-cooled reactors (UNGG).
COMURHEX*	1960	Pierrelatte	Conversion to uranium hexafluoride (UF_6) of the UF_4 from Malvesi or of reprocessed uranium from La Hague reprocessing plant.
CEA	1960	Pierrelatte	Until 1976, uranium enrichment by gaseous diffusion, mainly for military purposes. After 1976, research activities in the field of enrichment (mainly by laser).
AREVA NC	1976	Pierrelatte	Continued the CEA enrichment activity for military purposes until 1996 and until 1979 for the civil industry (commissioning of the EURODIF plant). In the early 1980s, processing of depleted uranium from EURODIF and reprocessed uranium from La Hague (processing into U_3O_8, uranium stable form for storage). Also preparation of depleted uranium for MOX fuel production (mix of natural depleted uranium and plutonium from reprocessed fuel).
EURODIF*	1978	Pierrelatte	Natural uranium enrichment by gaseous diffusion for the civil nuclear industry.
SOCATRI*	1975	Pierrelatte	Surface treatment for the EURODIF plant construction. Recovery and purification of waste and effluents from the Pierrelatte plant and from different amenities (hospital, research labs) of the area.
FBFC*	1976	Romans sur Isère	Fuel manufacturing (enriched UO_2 pellets) from natural and reprocessed enriched uranium. Preparation of assemblies.
FBFC*	1984	Pierrelatte	Fuel manufacturing (enriched UO_2 pellets) from natural uranium until 1998. Manufacturing the support grids and control clusters for the assemblies.
CERCA*	1960	Romans sur Isère	Production of fuel for research reactors (low-enriched to highly-enriched uranium up to 93.5%)
MELOX*	1994	Marcoule	MOX Fuel manufacturing.

* AREVA subsidiaries

Appendix Table 2. Causes of death studied and corresponding international classification of diseases (ICD) codes.

Cause of death	ICD version 8 (1968–1978)	ICD version 9 (1979–1999)	ICD version 10 (2000–2008)
All causes	1 to E999	1 to E999	A00 to Y89
Non-cancers diseases	210 to 796	210 to 999	D00 to U90
Non-malignant tumors of central nervous system and sense organs	225 + 238	225 + 239.6	D32 + D33 + D43.0 to D43.2
Endocrine, nutritional and metabolic diseases	240 to 279	240 to 278	E00 to E90
Diseases of the blood and blood-forming organs	280 to 289	279 to 289	D50 to D89
Cirrhosis, psychosis and other diseases due to alcohol	291 + 303 + 571	291 + 303 + 571	F10 + K70 + K73 + K74
Non-tumoral diseases of central nervous system and sense organs	320 to 389	320 to 389	G00 to H95
Diseases of the circulatory system	**390 to 458**	**390 to 459**	**I00 to I99**
Hypertensive diseases	400 to 404	401 to 405	I10 to I13 + I15
Ischaemic heart diseases	410 to 414	410 to 414	I20 to I25
Cerebrovascular diseases	430 to 438	430 to 438	I60 to I69
Respiratory diseases	460 to 519	460 to 519	J00 to J99
Diseases of the digestive system (other than cirrhosis)	520 to 577 - 571	520 to 579 - 571	K00 to K93 - K70 - K73 - K74
Diseases of the genitourinary system	580 to 629 + 792	580 to 629	N00 to N99
Renal diseases	580 to 593	580 to 593	N00 to N29
Diseases of the skin	680 to 709	680 to 709	L00 to L99
Diseases of the musculoskeletal system and connective tissue	710 to 738	710 to 739	M00 to M99
All cancers	140 to 207	140 to 208	C00 to C97
Smoking related cancers	140 to 151 + 155 + 157 + 160 to 162 + 180 + 188 + 189 + 205	140 to 151 + 155 - 155.2 + 157 + 160 to 162 + 180 + 188 + 189 + 205	C00 to C16 + C22 - C22.9 + C25 + C30 to C34 + C53 + C64 to C68 + C92
Mouth	140 to 145	140 to 145	C00 to C08
Pharynx	146 to 149	146 to 149	C09 to C14

Cause of death	ICD version 8 (1968–1978)	ICD version 9 (1979–1999)	ICD version 10 (2000–2008)
Oesophagus	150	150	C15
Stomac	151	151	C16
Liver	155	155 - 155.2	C22 - C22.9
Pancreas	157	157	C25
Nasal cavity, sinus and middle ear	160	160	C30 + C31
Larynx	161	161	C32
Lung	162	162	C33 + C34
Bladder	188	188	C67
Kidney	189	189	C64 to C66 + C68
Non-smoking related cancers	152 to 159 - 155 - 157 + 163 to 199 - 180 - 188 - 189	152 to 159 - 155 + 155.2 - 157 + 163 to 199 - 180 - 188 - 189	C17 to C29 - C22 + C22.9 - C25 + C35 to C63 - C53 + C69 to C80 + C97
Colon	153	153 + 159.0	C18 + C26.0
Rectum	154	154	C19 to C21
Gallbladder and bile ducts	156	156	C23 + C24
Pleura	163.0	163	C38.4 + C45.0
Melanoma	172	172	C43
Breast	174	174 + 175	C50
Prostate	185	185	C61
Brain and central nervous system	191 + 192	191 + 192	C70 to C72
Haematological and lymphatic malignancies	200 to 207	200 to 208	C81 to C96
Leukaemia	204 to 207	204 to 208	C91 to C95
Lymphocytic leukaemia	204	204	C91
Chronical Lymphocytic leukaemia	204.1	204.1	C91.1 + C91.4
Myeloid leukaemia	205	205	C92
Acute myeloid leukaemia	205.0	205.0	C92.0
Other leukaemia	206 to 207	206 to 208	C93 to C95
Multiple myeloma	203	203	C90 + C88

Cause of death	ICD version 8 (1968–1978)	ICD version 9 (1979–1999)	ICD version 10 (2000–2008)
Non-Hodgkin's lymphoma	200 + 202	200 + 202	C82 to C85 + C96
External causes	E800 to E999	E800 to E999	V01 to V89 + V90 to X84
Suicides	E950 to E959	E950 to E959	X60 to X84
Accidents	E800 to E929 + E940 + E942	E800 to E928	V01 to X59

Appendix Table 3. Standardized mortality ratios (SMRs) in the TRACY cohort (1968-2008) among men *.

Cause of death	Observed number of deaths	SMR	95% confidence interval
All causes	2028	0.64	[0.61 - 0.67]
Non-cancers diseases	979	0.58	[0.55 - 0.62]
Non-malignant tumors of central nervous system and sense organs	8	0.66	[0.28 - 1.30]
Endocrine, nutritional and metabolic diseases	46	0.69	[0.50 - 0.92]
Diseases of the blood and blood-forming organs	7	0.67	[0.27 - 1.37]
Cirrhosis, psychosis and other diseases due to alcohol	47	0.27	[0.20 - 0.36]
Non-tumoral diseases of central nervous system and sense organs	68	0.88	[0.68 - 1.11]
Diseases of the circulatory system	523	0.68	[0.62 - 0.74]
Hypertensive diseases	15	0.59	[0.33 - 0.98]
Ischemic heart diseases	207	0.71	[0.62 - 0.81]
Cerebrovascular diseases	123	0.75	[0.62 - 0.89]
Other and unspecified disorders of the circulatory system	178	0.62	[0.53 - 0.71]
Respiratory diseases	85	0.51	[0.41 - 0.63]
Diseases of the digestive system (other than cirrhosis)	44	0.56	[0.40 - 0.75]
Diseases of the genito-urinary system	23	0.73	[0.46 - 1.10]
Renal diseases	17	0.69	[0.40 - 1.11]
Diseases of the skin	5	1.22	[0.40 - 2.85]
Diseases of the musculoskeletal system and connective tissue	7	0.70	[0.28 - 1.45]
Other non-cancers diseases	116	0.43	[0.35 - 0.51]
All cancers	853	0.74	[0.70 - 0.80]
Smoking related cancers	478	0.67	[0.61 - 0.74]
Mouth	13	0.46	[0.25 - 0.80]
Pharynx	27	0.55	[0.36 - 0.80]
Esophagus	32	0.51	[0.35 - 0.72]
Stomach	27	0.61	[0.40 - 0.89]
Liver	30	0.64	[0.43 - 0.91]
Pancreas	50	1.04	[0.78 - 1.38]
Nasal cavity, sinus and middle ear	5	0.25	[0.08 - 0.58]
Larynx	19	0.47	[0.28 - 0.73]
Lung	212	0.72	[0.63 - 0.83]
Bladder	26	0.70	[0.46 - 1.02]
Kidney	23	0.83	[0.53 - 1.24]
Non-smoking related cancers	320	0.85	[0.76 - 0.95]
Colon	55	0.76	[0.57 - 0.99]

Cause of death	Observed number of deaths	SMR	95% confidence interval
Rectum	26	0.92	[0.60 - 1.34]
Gallbladder and bile ducts	7	1.06	[0.43 - 2.19]
Pleura	16	1.97	[1.13 - 3.20]
Melanoma	12	1.38	[0.71 - 2.41]
Prostate	71	0.94	[0.74 - 1.19]
Brain and central nervous system	30	1.36	[0.92 - 1.94]
Other non-smoking related cancers	102	0.70	[0.57 - 0.85]
Haematological and lymphatic malignancies	69	0.94	[0.73 - 1.19]
Leukaemia	31	0.99	[0.67 - 1.41]
Lymphocytic leukaemia	12	1.44	[0.75 - 2.52]
Chronical Lymphocytic leukaemia	8	1.32	[0.57 - 2.61]
Myeloid leukaemia	14	1.05	[0.57 - 1.76]
Acute myeloid leukaemia	10	1.30	[0.62 - 2.39]
Other leukaemia	5	0.52	[0.17 - 1.21]
Multiple myeloma	17	1.30	[0.76 - 2.08]
Non-Hodgkin's lymphoma	21	0.83	[0.51 - 1.28]
External causes	176	0.53	[0.45 - 0.61]
Suicides	73	0.65	[0.51 - 0.82]
Accidents	93	0.47	[0.38 - 0.57]
Other external causes	10	0.46	[0.22 - 0.85]

* For causes of deaths with at least 5 cases observed among men

APPENDIX Table 4. Standardized mortality ratios (SMRs) in the TRACY cohort (1968-2008) among women *.

Cause of death	Observed number of deaths	SMR	95% confidence interval
All causes	102	0.77	[0.63 - 0.94]
Non-cancers diseases	33	0.49	[0.34 - 0.69]
Diseases of the circulatory system	16	0.60	[0.35 - 0.98]
Cerebrovascular diseases	7	0.92	[0.37 - 1.90]
Other and unspecified disorders of the circulatory system	5	0.45	[0.15 - 1.05]
Other non-cancers diseases	5	0.39	[0.13 - 0.91]
All cancers	59	1.14	[0.87 - 1.48]
Smoking related cancers	17	1.16	[0.68 - 1.87]
Lung	5	1.09	[0.35 - 2.54]
Non-smoking related cancers	38	1.13	[0.80 - 1.55]
Colon	5	1.28	[0.42 - 3.00]
Breast	20	1.53	[0.94 - 2.37]
Haematological and lymphatic malignancies	5	1.17	[0.38 - 2.73]
External causes	10	0.74	[0.36 - 1.37]
Accidents	5	0.67	[0.22 - 1.56]

* For causes of deaths with at least 5 cases observed among women

TRACY Cohort - STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	/
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) If applicable, explain how loss to follow-up was addressed	7-8
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	Supplementary file p2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	/
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Cancer and non-cancer mortality among French uranium cycle workers: The TRACY cohort

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ABSTRACT

Objectives: The health effects of internal contamination by radionuclides, and notably by uranium, are poorly characterized. New cohorts of uranium workers are needed to better examine these effects. This paper analyses for the first time the mortality profile of the French cohort of uranium cycle workers. It considers mortality from cancer and non-cancer causes.

Methods: The cohort includes workers employed at least 6 months between 1958 and 2006 in French companies involved in the production of nuclear fuel. Vital status and causes of death were collected from French national registries. Workers were followed-up from January 1, 1968 to December 31, 2008. Standardized mortality ratios (SMRs) were computed based on mortality rates for the French general population.

Results: The cohort includes 12649 workers (88% men). The average length of follow-up is 27 years and the mean age at the end of the study 60 years old. Large mortality deficits are observed for non-cancer causes of death such as non-cancer respiratory diseases (SMR=0.51 [0.41-0.63]) and circulatory diseases (SMR=0.68 [0.62-0.74]). A mortality deficit of lower magnitude is also observed for all cancers combined (SMR [95% confidence interval (CI)]: 0.76 [0.71–0.81]). Pleural mesothelioma is elevated (SMR=2.04 [1.19–3.27]).

Conclusion: A healthy worker effect is observed in this new cohort of workers involved in the uranium cycle. Collection of individual information on internal uranium exposure as well as other risk factors is underway, to allow for the investigation of uranium related risks.

Strengths and limitations of this study
• TRACY is a new cohort, one of the rare of uranium fuel cycle workers • Almost 13000 workers included from 1958 to 2006 • Only 1% of workers were lost to follow-up • Individual causes of death are only available since 1968 in France Further work is ongoing to allow for the detailed investigation of uranium-related risk

INTRODUCTION

Ionizing radiation is an established carcinogen[1] and its effects on cancer risk are reasonably well understood and quantified, at least at high doses (>100 mGy) and dose rates (>5 $mGy.h^{-1}$).[2] By comparison, cancer risks associated with internal exposures resulting from the incorporation of radionuclides into the body are less well quantified.[3] This is a major issue for radiation protection since internal exposures are responsible for a large portion of population's collective effective dose due to exposure to naturally occurring radionuclides, such as radon, as well as medical diagnostic and occupational sources of internal exposures.[1] In addition, there is growing interest in health effects other than cancer following exposure to low doses of ionizing radiation (e.g.: diseases of the circulatory system[4]), notably following internal exposure.[5]

With the exception of studies on radon, relatively few recent epidemiological studies have directly quantified the health effects of internal contamination in populations chronically exposed to radionuclides.[6-9] As a result, the International Commission on Radiological Protection, which elaborates and periodically updates international radiation protection recommendations, had to estimate the radiation-related risks of internal exposure to radioisotopes, such as uranium, by combining epidemiological evidence from external exposure situations with that from experimental studies on the biological effects of internal emitters.[10] It would be preferable to have direct epidemiological evidence regarding the effects of internal exposure to such radionuclides. There is therefore the need for further studies of populations exposed to internal emitters, to help assess the adequacy of current radiation protection standards with respect to internal exposure.[5]

In addition to its radiological toxicity, uranium may exhibit chemical toxicity, as a heavy metal. This chemical toxicity was demonstrated on kidney and brain,[11] and might possibly

extend to other organs. Therefore, even if models used to predict radiation-induced health effects from uranium exposure proved strictly adequate, additional data would be needed to characterize the total (i.e.: radiological *plus* chemical) health effects of uranium exposure in humans. This further justifies the need to directly quantify these effects in exposed populations.

Cohorts of workers involved in the uranium fuel cycle are of interest to study the risks associated with internal contamination to uranium because many workers were regularly monitored for internal exposure via bioassay analyses.[5] However, few such cohorts have been set up.[12-18] A recent review concluded that studies based on these cohorts so far do not provide reliable evidence on the potential health risks associated with uranium exposure, notably because of insufficient statistical power.[19] Pooling existing large cohorts of uranium workers and setting up new ones is clearly needed to improve the knowledge of the health effects of uranium exposure.[20]

France has operated a complete nuclear fuel production cycle since the 1960's. The French cohort of workers employed in the nuclear fuel production cycle (TRACY, for TRAvailleurs du CYcle) was set up to assess the risk of cancer and non-cancer mortality related to internal exposure to uranium. Pilot studies were successfully conducted in specific subsets of this large cohort.[21 22] The reconstitution of exposure data in the entire TRACY cohort is underway.

The aim of the current investigation was to describe mortality among the uranium workers in this new large cohort, by comparison with the general population.

MATERIAL AND METHODS

Study design

TRACY is a retrospective cohort designed to study the mortality of workers involved in the French uranium fuel cycle. As will be detailed below, occupational data was collected from 2009 to 2013 and cover period 1958 to 2006, whereas mortality data cover a period spanning from 1968 to 2008.

Study population

The companies included in this study cover different steps of the nuclear fuel production cycle in France (Figure 1): purification of concentrated natural uranium, conversion to uranium hexafluoride, enrichment by gaseous diffusion, fuel manufacturing and other activities such as storage (depleted and reprocessed uranium) and decontamination (waste and effluents). Companies involved in uranium mining and milling are not included, nor are companies that are end users of the nuclear fuel (e.g., electricity production). The companies included and their respective main activities are presented in Appendix Table 1. TRACY is complementary to the French uranium miners cohort[23] and to the French nuclear workers cohort designed to study the association between external chronic exposure to radiation and mortality,[24] whereas the main focus of TRACY is internal contamination by uranium. The overlaps between TRACY and the French cohorts of uranium miners and nuclear workers are of 158 and 5057 subjects, respectively.

Workers included in the cohort had to be employed at least 6 months, as members of the permanent staff of selected companies between 1958 and 2006. Personal identifiers and work histories were provided by the administrative departments of each company, either on paper or electronic files. The files were computerized whenever needed, validated and merged. Transfers from one company to another were taken into account to avoid duplicate counts and accurately reconstruct time spent in the different companies included in the TRACY cohort

where workers were employed. The detailed characterization of workplaces and job titles is a long-term task for this large cohort and is still underway.

The date of start of employment was defined as the earliest one if several periods of employment were recorded. The date of end of employment, whatever the reason (retirement, resignation, dismissal, job transfer to a company not included in the study), was identified from the last recorded period of employment. For workers still employed on December 31st, 2006, the end of employment was set to that date.

Follow up, vital status and causes of death

For each worker, follow-up of vital status began on the most recent date among the following: date of initial employment plus 6 months, or January 1st, 1968. The lower bound of the follow-up period had to be set to that date since the national registry which provides cause of death information in France (CépiDC-Inserm) can deliver no individual data before 1968. Among the cohort members who began working before 1968, 53 had died or would have been lost to follow-up before 1968 and could not be included in the mortality study. The date of end of follow-up was defined as the earliest among the following ones: date of death, last information date (for workers lost to follow-up) and December 31st, 2008. Workers' vital status, and the date of death for workers who died, were obtained by from the National Vital Status Registry (Répertoire National d'Identication des Personnes Physiques) by file-matching on name, surnames, gender, date and place of birth. To avoid erroneous linkages, only workers with one possible match with the registry were considered as identified. Causes of death coded according to the International Classication of Diseases (ICD, version 8 for period 1968–1978, version 9 for 1979–1999 and version 10 for period 2000–2008, see Appendix Table 2) and corresponding labels were obtained by file-matching on gender, date

and place of birth, and date and place of death with the French national mortality registry (CépiDC-Inserm). In case of multiple matches, no causes could be obtained for these workers.

Statistical analysis

Mortality rates were compared with those in the French general population (also obtained from CépiDC-Inserm) by computing standardized mortality ratios (SMRs), therefore controlling for potential confounders: sex, age (categorized as follows: 15–19, 20-24,…, 80-84, ≥85) and calendar period (categorized as follows: 1968-1972, 1973-1977,…, 1998-2002, 2003-2008) as classically done for such analyses.[25] Confidence intervals (95% CIs) were calculated using the Poisson exact method.[26] This was done for specific causes of death (e.g.: cancer of specific organs or tissues) or broader groupings of causes (e.g.: all cancers, all circulatory diseases, cancers sites potentially associated with smoking).[27] Appendix Table 2 provides the definition and corresponding ICD codes of all causes of death considered. For the primary analysis, SMRs were computed for men and women grouped together. The "All causes" group included workers with non-identified causes of death. Results were reported only for causes of death with at least 5 cases observed across the whole cohort.

Supplementary analyses were conducted for broad groupings of causes of death (all causes, cancers, diseases of the circulatory system and respiratory diseases) to examine the evolution of SMRs according to time since hire (categorized as follows: <25 years, 25-39, ≥40), time since end of employment (categorized as follows: <10 years, 10-19, ≥20), total duration of employment (categorized as follows: <10 years, 10-24, ≥25) and attained age (categorized as follows: <50, 50-65, ≥66).[28] Further analyses were conducted to estimate SMRs among men and women separately. We also conducted supplementary analyses according to groupings of companies involved in the three main steps of the uranium cycle (conversion, enrichment by gaseous diffusion and manufacturing of oxide fuel), in two ways. First, we considered

workers involved in only one grouping of companies covering a specific step (therefore not allowing for overlap between population subgroups, by excluding workers who got involved during their careers in several groupings of companies covering different steps) and second, considering workers involved in at least one of these grouping of companies (therefore allowing for overlap between the population groupings analyzed). For conversion, we considered workers employed by Comurhex (Malvési and Pierrelatte plants). For enrichment, we considered a specific sub cohort extract from the TRACY cohort with workers involved in both military and civil enrichment.[29] Workers employed by FBFC (Romans sur Isère and Pierrelatte plants) constituted the oxide fuel manufacturing grouping.

All analyses were conducted using the SAS software, version 9.2 (Cary, North Carolina, USA).

The protocol of this study was validated by the French Data Protection Authority (CNIL), agreement n° DR-2012-611.

RESULTS

The inclusion process (summarized in Appendix Figure 1) started from a base of 21143 potentially eligible workers. After removal of duplicates (3063 tuples) and exclusion of workers who did not match the eligibility criteria, 12713 workers were confirmed to be eligible and included in the study. After further exclusion of one worker with identifiers not sufficient to match with national files (place of birth unknown) and of workers either dead or who would have been lost to follow-up before 1968, the mortality analysis was performed on 12649 workers.

Workers excluded were permanent status workers who cumulated less than 6 months of employment (N=641), trainees (N=2561), short-term workers (N=2036) and others special

contracts (military service, scientific advisor, N=129). Excluded workers cumulated an average duration of work of 0.50 years. Contractors were not mentioned in the employee personnel files and therefore could not be considered.

The main characteristics of the cohort are presented in Table 1. Among the 12649 workers included, 88% were males. The cohort cumulated 342258 person-years of observation. The mean duration of follow-up was 27 years. The mean age at the end of the study was 60 years old. The mean age at hire was 30 years old and it was 49.3 years old at the end of employment. The mean duration of employment was 19 years. At the end of the follow-up, 82% of workers were still alive, 17% were deceased and 1% was lost to follow-up. Underlying cause of death was identified for 99% of the 2130 deaths recorded.

SMRs are presented in Table 2 for the whole cohort. A substantial mortality deficit was observed for all-cause mortality compared to expectation based on French national rates (SMR 0.65; 95% CI 0.62–0.68; n=2130).

There was a substantial deficit in mortality for most major categories of non-malignant diseases. All non-cancer mortality was in 42% deficit (SMR 0.58; 95% CI 0.55–0.62, n=1012). There were substantial deficits in deaths due to non-malignant respiratory diseases (SMR 0.51; 95% CI 0.41–0.63, n=88), circulatory diseases (SMR 0.68; 95% CI 0.62–0.74, n=540), non-malignant renal diseases (SMR 0.66; 95% CI 0.39–1.06, n=17), and external causes of death including suicides and accidents (SMR 0.54; 95% CI 0.46–0.62, n=186).

For deaths due to all malignant diseases grouped together, there was also a deficit in the entire cohort although less pronounced than for most non-malignant categories of cause of death. Overall, cancer mortality was in 24% deficit (SMR 0.76; 95% CI 0.71–0.81, n=912). However, a two-fold excess was observed for pleural mesothelioma (SMR 2.04; 95% CI 1.19–3.27; n= 17) and non-significant excesses were observed for other cancers: pancreas

(SMR 1.05 ; 95% CI; 0.79–1.38, n=53), skin melanoma (SMR 1.60; 95% CI 0.90–2.64, n=15), breast (all observed cases being among women, see Appendix Table 3; SMR 1.53 ; 95% CI 0.94–2.37; n=20), brain and central nervous system (SMR 1.36; 95% CI 0,93–1,91, n=32), lymphocytic (SMR 1.38; 95% CI 0.71–2.42, n=12) and myeloid (SMR 1.06; 95% CI 0.59–1.74, n=15) leukemia and multiple myeloma (SMR 1.29; 95% CI 0.77–2.05, n=18). In contrast, there was a substantial deficit in deaths due to smoking-related cancers (SMR 0.68; 95% CI 0.62-0.75, n=495).

SMRs for cancer diseases tended to increase with time since hire, with time since end of employment and with attained age (Table 3). Twenty years after the end of employment, the risk of cancer mortality is not significantly different from that in the general population, whereas it remains significantly lower for circulatory and respiratory diseases. No clear trend was observed according to the duration of employment for mortality from all causes and from circulatory diseases. However there was evidence of a decreasing trend along with duration of employment for mortality from cancer and respiratory diseases. For all broad groupings of causes of death, the lowest SMRs were observed in workers with the longest duration of employment (Table 3).

Significant deficits in all-cause and non-cancer mortality were observed for both genders (see Appendix Tables 3 and 4). In women, non-significant excesses of cancer mortality were observed. However, confidence intervals were very wide due to the lower number of women (and therefore, of deaths observed in these women) in the cohort (see Appendix Table 3). In men, a significant deficit in mortality from all cancers was also observed and results were overall comparable to those in the entire cohort (see Appendix Table 4).

For all groupings of causes of death considered, we observed no difference in mortality patterns according to groupings of companies involved in the main three steps of the cycle, regardless of the way the groupings were defined (see Appendix Table 5).

DISCUSSION

This is the first mortality study conducted in this new cohort of uranium cycle workers, which is one of the largest of its kind. A healthy worker effect (HWE) is observed. It is especially strong for major groups of non-cancer diseases, including circulatory and non-cancer respiratory diseases. For all cancers grouped together, a healthy worker effect is also observed overall, but is less marked than for non-cancer diseases. No deficit in cancer mortality is observed in workers 20 years or more after the end of employment or in women. A significant excess of malignant pleural mesothelioma is observed, and non-significant excesses are observed for a few other specific cancer sites.

Mortality profile

The HWE is often observed in occupational cohorts, including nuclear worker cohorts.[24 25 28] It partly results from the selection of healthier people at hiring (referred to as the "healthy hire effect",[28] which tends to shrink with time since hire), and from other selection effects making the healthiest individuals more likely to be retained in the workforce than individuals with poorer health (referred to as the "healthy survivor effect"[28] and reflected by the fact that workers with the longest duration of employment exhibit the lowest SMRs). The regular health surveillance provided by occupational medicine services, but also other factors such as work-related physical activity are also suspected to contribute to the healthy survivor effect. As time since the end of employment goes by, the mortality profile of workers tend to reach that of the general population. These patterns were observed in the TRACY cohort, in agreement with previous literature.[24 25 28] Methods have been proposed to calculate adjusted

SMRs as a complement to the traditional SMR that may facilitate interpretation of findings in spite of comparability issues due to the HWE; a recent example of such an approach draws on methods developed for the use of negative control outcomes for bias reduction.[30] Such methods have not been applied in the current paper however, since it is difficult to define a relevant negative control outcome for a population of workers exposed to uranium. In spite of the aforementioned limitations resulting from the HWE, comparisons of mortality profiles of occupational cohorts with those of general populations have been considered to be a useful approach, and therefore have been widely used, in occupational epidemiology.[18 25 31 32]

Importantly, the observed HWE does not mean that no case attributable to uranium or to other sources of radiation occurred in the TRACY cohort. The present analysis provides a simple but informative picture of the general level of risk in this cohort of workers of the uranium fuel cycle, through a comparison with the general population. The risk in the cohort is not only influenced by uranium and other radiation exposures but also by the levels of exposure to other risk factors. For instance, the SMR for the grouping of cancers sites that may be caused by smoking[27] is low in the TRACY cohort. This suggests a lower level of exposure to smoking in this cohort than in the general population.

Conversely, we observed an excess of pleural mesothelioma. We acknowledge that the diagnosis and ascertainment of mesothelioma on death certificates has been problematic until at least the early 1990's.[33] This limitation applied both to the TRACY cohort and to the comparison group, the French general population.[34] The ascertainment of mesothelioma improved with the introduction of ICD10,[35] which was used since year 2000 for French death certificates. Excesses of pleural mesothelioma were also reported in most other nuclear worker cohort studies.[36] An excess risk was also observed in the French cohort of nuclear workers, designed to study the effects of external radiation exposure (based on 36 deaths),[37] but it has to be noted that these two results are not independent due to partial overlap of the

two cohorts, concerning workers from AREVA NC and CEA Pierrelatte plant (10 deaths in common, among 5057 workers included in both cohorts). Evidence for an association between exposure to ionizing radiation and pleural mesothelioma is weak however,[36] and to the best of our knowledge no association between uranium exposure and mesothelioma has ever been reported. By contrast, asbestos exposure is a strong risk factor for this disease, and has been known to occur in companies included in TRACY,[38] as well as in other companies in which some workers were employed before joining the nuclear fuel industry. This might contribute to the excess of malignant pleural mesothelioma observed in this cohort.

Non-significant excesses were observed for a few cancer sites in TRACY. For pancreas cancer, non-significantly positive SMRs were also observed in several other cohorts of uranium workers (including uranium millers)[14 17 39 40] but not in all[15 18 31 32 41] (see Appendix Table 6).

For all leukemias grouped together, patterns are not consistent across cohorts either. A proper comparison by leukemia subtypes is hampered by the inhomogeneous sets of subtypes for which results were reported in available studies. However, non-significant excesses of multiple myeloma[17 39 42] or myeloma[32] were reported in most cohorts which evaluated this outcome (see Appendix Table 6).

Non-significant excesses of cancers of the brain and central nervous system were reported in most cohorts of uranium workers.[14 32 39-41 43] Although no single study detected a significant excess of brain cancer, the consistent pattern of non-significant excesses across cohorts for this outcome deserves further investigation (see Appendix Table 6). Animal studies have shown that brain is a target organ for uranium effects,[44-46] although to the best of our knowledge no animal study specifically focused on brain or central nervous system cancers.

Only one other cohort of uranium fuel cycle workers reported a non-significant excess of skin cancer so far.[14] Only three studies reported non-significant excesses of breast cancer[14 15 18] and in two of them, the excess was only observed in women monitored for internal contamination.[15 18]

Strengths and limitations

The TRACY cohort has major strengths, such as its large size and excellent quality of follow-up. It is one of the rare cohorts of uranium fuel cycle workers in the world. However, the present study also has some limitations. No individual data on causes of death was available before 1968 due to late startup of the French mortality registry. This limitation applies to all epidemiological studies in France. Uranium related activities began as early as 1959 in some companies included in TRACY. However the gap in temporal overlap before year 1968 could not hamper the detection of potential excess of diseases occurring after a long latency time following occupational exposure (e.g. solid cancers are usually considered to occur after 10 or more years following radiation exposure). Similarly, the fact that occupational data have not been collected after year 2006 yet, although the mortality analysis covered period 1968-2008, is unlikely to generate a substantial impact on the analysis of diseases with long latency times. However, the possible impact of the aforementioned lacks of temporal overlap is less clear for diseases with shorter latency times such as leukemia. In addition, although the use of mortality data is very informative, it does not allow capturing the full range of possible health effects of uranium exposure, for instance cognitive, reproductive effects or kidney damage.[11] More generally, it does not capture adequately the incidence of diseases which are rarely fatal.

The criteria for inclusion into the TRACY cohort guarantees that all permanent staff workers potentially exposed to uranium as part of the upstream steps of the French nuclear

fuel cycle (except miners and millers) are included. However, it is clear that some workers not exposed to uranium are also included in the cohort. Having these workers in the cohort will be useful to constitute an internal reference group, when associations between uranium exposure and mortality will be studied. However, further work is still needed (especially, a detailed reconstruction of bioassay record histories) before being able to separate all workers exposed from those non-exposed to uranium in the entire TRACY cohort. Complex changes in industrial processes combined with changes in individual job histories make it a long-term task.

However, as a preliminary approach we explored the hypothesis of different health effects according to different parts of the uranium cycle, by conducting a first analysis by groupings of companies involved in the three main steps of the uranium cycle (conversion, enrichment and fuel manufacturing). We failed to demonstrate potential differences, possibly because of the lack of statistical power and of the inclusion of non-exposed workers in each group.

Perspectives

The reconstruction of the multiple exposures of the workers in the TRACY cohort represents a necessary effort to assess risks according to different levels of exposure to uranium, while taking into account other sources of radiation (external exposure to X and gamma rays, and internal contamination with radionuclides such as for instance uranium decay products, plutonium and tritium) and other potential risk factors, including CMR (Carcinogenic, Mutagenic or Toxic to Reproduction) chemicals, heat, noise and shift work . Uranium exposure is being reconstructed by a dual approach combining individual monitoring data[47] and specific job-exposure matrices.[38] Job Exposure Matrices allow estimating exposures not covered by any individual monitoring and document uranium compounds present at each job.. This detailed exposure reconstruction will allow us to distinguish more

finely the different steps of the uranium fuel cycle and therefore better characterize the physicochemical characteristics of the different uranium compounds (in term of solubility and isotopy) to which workers were exposed.

The calculation of uranium concentrations in the target organs of uranium (e.g.: lungs, kidneys, bones and brain among others) but also of resulting absorbed radiation doses to these same organs, will help disentangling chemical from radiation effects of uranium exposure. This specific investigation will be possible since separate populations of workers have been exposed to uranium of different isotopic compositions, which show contrasted specific activity (e.g.: 0.33 µCi/g for depleted uranium, 0.68 µCi/g for natural uranium and up to 50 µCi/g for enriched uranium). Since depleted uranium has a very low specific activity, an estimate of the relationship between depleted uranium concentrations in organs and health risks will almost purely assess the potential chemical toxicity of uranium. Beside this, workers exposed to a same level of uranium concentration in organs will receive different internal radiation dose from this nuclide, depending on whether they were exposed to depleted, natural or enriched uranium (again, because of their varying specific activities). Comparing risks in workers exposed to uranium of different isotopic compositions will therefore provide an opportunity to isolate and quantify the radiological component of uranium toxicity. Last, information on risk factors such as tobacco smoking and various clinical parameters (body mass index, blood pressure, lipid profile etc.) is being collected from the occupational health services,[48] which will allow controlling for their potential confounding effects in future analyses.

The TRACY cohort is still young, with an average age of 60 and only 17% of workers deceased at the end of follow-up. The statistical power available to study rare or specific diseases (ex: specific cancer sites) remains limited in this cohort, but also in other cohorts of nuclear fuel cycle workers, unless large excesses actually occur (as was observed in TRACY

for pleural mesothelioma). Extended follow-up and pooled analyses of these cohorts, including TRACY, are needed to produce more statistically precise estimates, which will allow drawing more robust conclusions on possible excess for these diseases and their association with uranium exposure. A pooling of TRACY with other cohorts of uranium workers and miners in Europe is planned, according to harmonized methodologies defined as part of the European project CURE.[20] In the future, this approach could be extended to other cohorts outside Europe.

CONCLUSION

This first mortality study of the TRACY cohort of French uranium cycle workers has shown a substantial mortality deficit for all broad groupings of causes of death and most of the pathologies studied. However a significant excess of malignant pleural mesothelioma was also observed and non-significant excesses were observed for a few specific cancer sites. To go further in the investigation of uranium related risks in this new cohort, collection of individual information on internal uranium exposure as well as other risk factors is underway.

Finally, through the pooling of TRACY with other cohorts of uranium workers, the TRACY cohort will help improving the knowledge of the health effects of uranium exposure and more generally of internal contaminations by radionuclides, in support of radiation protection research and practice.

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Competing Interests

Ana-Paula Serond and Pierre Laroche have been employed by AREVA. They provided access to data sources needed for the construction of the database and role in launching and supporting the study. They had no influence on decisions concerning analysis of the results. Other authors have no conflict of interest to disclose.

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Authors' contributions

Eric Samson launched the study, obtained the permissions, collected necessary data, ensured the data management, the analysis and wrote the first draft of the article.

Irwin Piot gathered the vital status and causes of deaths from the national French registries, helped for the data-management of the cohort and prepared the programs for the mortality analysis.

Dominique Laurier and Olivier Laurent contributed to the design of the study and the interpretation of the results. Olivier Laurent supervised the writing of the article.

Sergey Zhivin and David B. Richardson brought substantial contributions to the analysis of the data and the improvement of the article particularly for the discussion section, tables and figures.

Pierre Laroche and Ana-Paula Serond managed relationships with the AREVA plants and provided access to data sources needed for the construction of the database.

Data sharing

No additional data available.

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Figure 1 – Simplified diagram describing the French uranium fuel cycle

Table 1. Description of the TRACY cohort

	Men		Women		All	
	Number	**%**	**Number**	**%**	**Number**	**%**
All workers	11122	87.9%	1527	12.1%	12649	100%
Person-years	303606	88.7%	38652	11.3%	342258	100%
Vital status on December 31, 2008						
Alive	8992	80.9%	1386	90.8%	10378	82.1%
Still employed	3937	35.4%	620	40,6%	4557	36.0%
Deceased	2028	18.2%	102	6.7%	2130	16.8%
With identified causes	2009	99.1%	102	100%	2111	16.7%
Lost to follow-up	102	0.9%	39	2.5%	141	1.1%
	Median	**Mean**	**Median**	**Mean**	**Median**	**Mean**
Year of birth	1943	1945	1949	1951	1944	1946
Age at death	67.8	66.4	60.9	62.2	67.5	66.2
Age at hiring	28.1	30.5	26.4	28.9	27.9	30.3
Age at end of employment (All)	53.8	49.8	47.5	45.5	53.1	49.3
Still employed	49.0	47.5	47.3	46.0	48.7	47.3
Not employed anymore	56.9	51.1	48.4	45.1	56.7	50.4
Duration of employment in years	19.9	19.4	14.3	16.6	19.3	19.0
Age at beginning of follow-up	31.2	33.2	29.0	31.1	31.0	32.9
Age at end of follow-up	61.1	60.5	56.3	56.5	60.6	60.0
Duration of follow-up in years	28.3	27.3	25.5	25.3	27.9	27.1

Table 2. Standardized mortality ratios (SMRs) in the TRACY cohort (1968-2008)*.

Cause of death	Observed number of deaths	SMR	95% confidence interval
All causes	2130	0.65	[0.62 - 0.68]
Non-cancers diseases	1013	0.58	[0.55 - 0.62]
Diseases of the circulatory system	540	0.68	[0.62 - 0.74]
Hypertensive diseases	15	0.56	[0.31 - 0.93]
Ischemic heart diseases	212	0.71	[0.62 - 0.81]
Cerebrovascular diseases	130	0.75	[0.63 - 0.90]
Other and unspecified disorders of the circulatory system	183	0.61	[0.52 - 0.71]
Respiratory diseases	88	0.51	[0.41 - 0.63]
Diseases of the digestive system (other than cirrhosis)	48	0.58	[0.43 - 0.77]
Diseases of the genito-urinary system	23	0.70	[0.44 - 1.05]
Renal diseases	17	0.66	[0.39 - 1.06]
Other non-cancers diseases			
Non-malignant tumors of central nervous system and sense organs	10	0.77	[0.37 - 1.42]
Endocrine, nutritional and metabolic diseases	47	0.67	[0.49 - 0.89]
Diseases of the blood and blood-forming organs	7	0.63	[0.25 - 1.30]
Cirrhosis, psychosis and other diseases due to alcohol	48	0.27	[0.20 - 0.35]
Non-tumoral diseases of central nervous system and sense organs	68	0.83	[0.64 - 1.05]
Diseases of the skin	5	1.14	[0.37 - 2.67]
Diseases of the musculoskeletal system and connective tissue	8	0.74	[0.32 - 1.46]
Other	121	0.43	[0.35 - 0.51]
All cancers	912	0.76	[0.71 - 0.81]
Smoking related cancers	495	0.68	[0.62 - 0.75]
Mouth	13	0.46	[0.25 - 0.79]
Pharynx	28	0.57	[0.38 - 0.82]
Esophagus	33	0.52	[0.36 - 0.73]
Stomach	29	0.64	[0.43 - 0.92]
Liver	31	0.65	[0.44 - 0.92]
Pancreas	53	1.05	[0.79 - 1.38]
Nasal cavity, sinus and middle ear	5	0.24	[0.08 - 0.57]
Larynx	20	0.49	[0.30 - 0.75]
Lung	217	0.73	[0.64 - 0.83]
Bladder	26	0.69	[0.45 - 1.01]
Kidney	24	0.84	[0.54 - 1.24]
Non-smoking related cancers	358	0.87	[0.79 - 0.97]

Cause of death	Observed number of deaths	SMR	95% confidence interval
Colon	60	0.78	[0.60 - 1.01]
Rectum	26	0.87	[0.57 - 1.28]
Gallbladder and bile ducts	7	0.98	[0.39 - 2.01]
Pleura	17	2.04	[1.19 - 3.27]
Melanoma	15	1.60	[0.90 - 2.64]
Breast	20	1.32	[0.81 - 2.04]
Prostate	71	0.94	[0.74 - 1.19]
Brain and central nervous system	32	1.36	[0.93 - 1.91]
Other non-smoking related cancers	106	0.69	[0.57 - 0.84]
Haematological and lymphatic malignancies	74	0.96	[0.75 - 1.20]
Leukaemia	33	1.00	[0.69 - 1.40]
Lymphocytic leukaemia	12	1.38	[0.71 - 2.42]
Chronic lymphocytic leukaemia (CLL)	8	1.28	[0.55 - 2.52]
Myeloid leukaemia	15	1.06	[0.59 - 1.74]
Acute myeloid leukaemia	10	1.22	[0.58 - 2.24]
Other leukaemia	6	0.59	[0.22 - 1.28]
Leukaemia without CLL	25	0.93	[0.60 - 1.38]
Multiple myeloma	18	1.29	[0.77 - 2.05]
Non-Hodgkin's lymphoma	23	0.86	[0.55 - 1.30]
External causes	186	0.54	[0.46 - 0.62]
Suicides	77	0.66	[0.52 - 0.82]
Accidents	98	0.47	[0.39 - 0.58]
Other external causes	11	0.49	[0.24 - 0.87]

* For causes of deaths with at least 5 cases observed

Table 3. Standardized mortality ratios (SMRs) and 95% confidence interval in the TRACY cohort (1968-2008), by time since hire, time since end of employment, duration of employment and age reached, for broad groupings of causes of death.

Time since hire								
	Less than 25 years			25 to 39 years			40 years or more		
Cause of death	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval
All causes	633	0.54	[0.50 - 0.58]	967	0.70	[0.66 - 0.75]	530	0.73	[0.66 - 0.79]
All cancers	242	0.64	[0.57 - 0.73]	457	0.81	[0.74 - 0.89]	213	0.82	[0.71 - 0.93]
Circulatory diseases	160	0.67	[0.57 - 0.79]	235	0.66	[0.58 - 0.75]	145	0.71	[0.60 - 0.83]
Respiratory diseases	14	0.33	[0.18 - 0.55]	48	0.61	[0.45 - 0.81]	26	0.50	[0.33 - 0.73]
Time since end of employment									
	Less than 10 years			10 to 19 years			20 years or more		
Cause of death	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval
All causes	945	0.56	[0.52 - 0.59]	591	0.74	[0.68 - 0.80]	594	0.75	[0.70 - 0.82]
All cancers	430	0.68	[0.62 - 0.75]	243	0.81	[0.71 - 0.92]	239	0.89	[0.79 - 1.02]
Circulatory diseases	217	0.62	[0.54 - 0.71]	162	0.72	[0.61 - 0.84]	161	0.72	[0.61 - 0.84]
Respiratory diseases	16	0.25	[0.14 - 0.41]	39	0.75	[0.53 - 1.02]	33	0.58	[0.40 - 0.81]
Duration of employment									
	Less than 10 years			10 to 24 years			25 years or more		
Cause of death	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval
All causes	575	0.66	[0.61 - 0.71]	1073	0.67	[0.63 - 0.71]	482	0.60	[0.55 - 0.66]
All cancers	243	0.82	[0.72 - 0.93]	426	0.78	[0.70 - 0.85]	243	0.69	[0.61 - 0.78]
Circulatory diseases	126	0.66	[0.55 - 0.79]	314	0.73	[0.65 - 0.82]	100	0.56	[0.45 - 0.68]

Respiratory diseases	25	0.62	[0.40 - 0.92]	48	0.50	[0.37 - 0.67]	15	0.40	[0.22 - 0.66]

Attained age

	Less than 50 years old			50 to 65 years old			66 years old or more		
Cause of death	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval
All causes	269	0.50	[0.44 - 0.56]	662	0.56	[0.52 - 0.61]	1199	0.77	[0.72 - 0.81]
All cancers	78	0.60	[0.48 - 0.75]	358	0.70	[0.63 - 0.77]	476	0.86	[0.78 - 0.94]
Circulatory diseases	52	0.67	[0.50 - 0.87]	147	0.59	[0.50 - 0.69]	341	0.73	[0.65 - 0.81]
Respiratory diseases	5	0.38	[0.12 - 0.88]	13	0.29	[0.16 - 0.50]	70	0.61	[0.48 - 0.77]

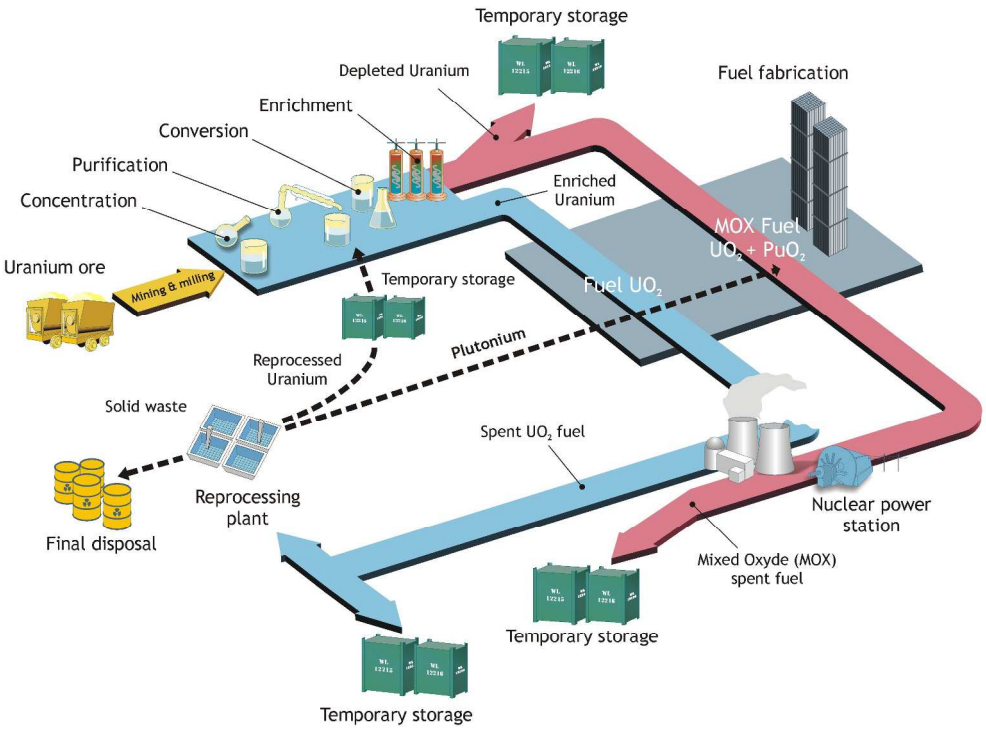

Figure 1 – Simplified diagram describing the French uranium fuel cycle
265x196mm (300 x 300 DPI)

Supplementary Material

Cancer and non-cancer mortality among French uranium cycle workers: The TRACY cohort

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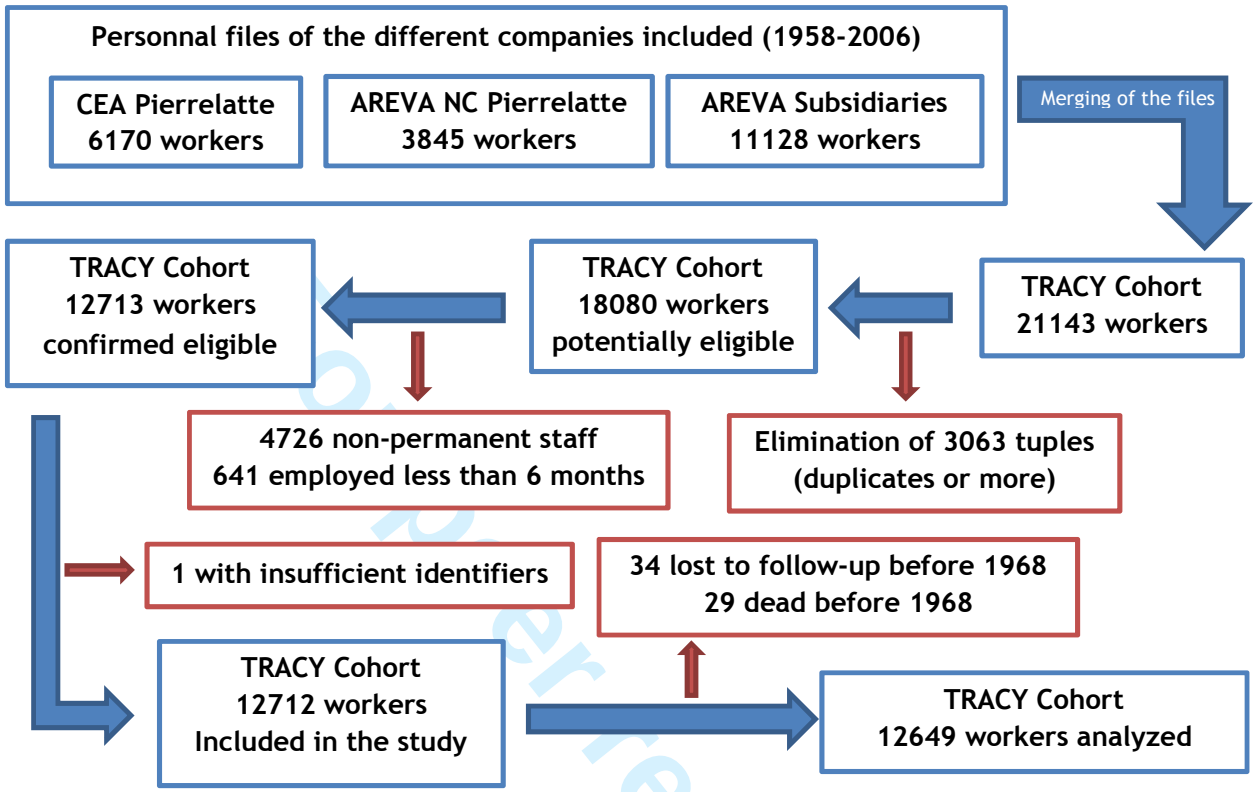
Appendix Figure 1 – Selection of workers for the mortality analysis



Appendix Table 1. Description of companies included in the TRACY cohort

Company	Year of beginning of operations	Plant location	Main activities	Person-Years In the TRACY cohort
COMURHEX*	1959	Malvesi	Purification of uranium concentrates (from 75% to 99.5% of natural uranium). Conversion of yellow cake to uranium tetrafluoride (UF_4). Manufacturing of uranium-metal fuel until 1972 for the natural uranium gas-cooled reactors (UNGG).	13954.17 (6%)
COMURHEX*	1960	Pierrelatte	Conversion to uranium hexafluoride (UF_6) of the UF_4 from Malvesi or of reprocessed uranium from La Hague reprocessing plant.	15138.48 (6%)
CEA	1960	Pierrelatte	Until 1976, uranium enrichment by gaseous diffusion, mainly for military purposes. After 1976, research activities in the field of enrichment (mainly by laser).	72255.99 (31%)
AREVA NC	1976	Pierrelatte	Continued the CEA enrichment activity for military purposes until 1996 and until 1979 for the civil industry (commissioning of the EURODIF plant). In the early 1980s, processing of depleted uranium from EURODIF and reprocessed uranium from La Hague (processing into U_3O_8, uranium stable form for storage). Also preparation of depleted uranium for MOX fuel production (mix of natural depleted uranium and plutonium from reprocessed fuel).	45962.78 (19%)
EURODIF*	1978	Pierrelatte	Natural uranium enrichment by gaseous diffusion for the civil nuclear industry.	34440.02 (15%)
SOCATRI*	1975	Pierrelatte	Surface treatment for the EURODIF plant construction. Recovery and purification of waste and effluents from the Pierrelatte plant and from different amenities (hospital, research labs) of the area.	8228.23 (3%)
FBFC*	1976	Romans sur Isère	Fuel manufacturing (enriched UO_2 pellets) from natural and reprocessed enriched uranium.	32592.34 (14%)
CERCA*	1960		Production of fuel for research reactors (low-enriched to highly-enriched uranium up to 93.5%) Preparation of assemblies.	
FBFC*	1984	Pierrelatte	Fuel manufacturing (enriched UO_2 pellets) from natural uranium until 1998. Manufacturing the support grids and control clusters for the assemblies.	5824.46 (2%)
MELOX*	1994	Marcoule	MOX Fuel manufacturing.	8357.85 (4%)

* AREVA subsidiaries

Appendix Table 2. Causes of death studied and corresponding international classification of diseases (ICD) codes.

Cause of death	ICD version 8 (1968–1978)	ICD version 9 (1979–1999)	ICD version 10 (2000–2008)
All causes	1 to E999	1 to E999	A00 to Y89
Non-cancers diseases	210 to 796	210 to 999	D00 to U90
Diseases of the circulatory system	**390 to 458**	**390 to 459**	**I00 to I99**
Hypertensive diseases	400 to 404	401 to 405	I10 to I13 + I15
Ischaemic heart diseases	410 to 414	410 to 414	I20 to I25
Cerebrovascular diseases	430 to 438	430 to 438	I60 to I69
Respiratory diseases	460 to 519	460 to 519	J00 to J99
Diseases of the digestive system (other than cirrhosis)	520 to 577 - 571	520 to 579 - 571	K00 to K93 - K70 - K73 - K74
Diseases of the genitourinary system	580 to 629 + 792	580 to 629	N00 to N99
Renal diseases	580 to 593	580 to 593	N00 to N29
Other non-cancers diseases			
Non-malignant tumors of central nervous system and sense organs	225 + 238	225 + 239.6	D32 + D33 + D43.0 to D43.2
Endocrine, nutritional and metabolic diseases	240 to 279	240 to 278	E00 to E90
Diseases of the blood and blood-forming organs	280 to 289	279 to 289	D50 to D89
Cirrhosis, psychosis and other diseases due to alcohol	291 + 303 + 571	291 + 303 + 571	F10 + K70 + K73 + K74
Non-tumoral diseases of central nervous system and sense organs	320 to 389	320 to 389	G00 to H95
Diseases of the skin	680 to 709	680 to 709	L00 to L99
Diseases of the musculoskeletal system and connective tissue	710 to 738	710 to 739	M00 to M99
All cancers	140 to 207	140 to 208	C00 to C97
Smoking related cancers	140 to 151 + 155 + 157 + 160 to 162 + 180 + 188 + 189 + 205	140 to 151 + 155 - 155.2 + 157 + 160 to 162 + 180 + 188 + 189 + 205	C00 to C16 + C22 - C22.9 + C25 + C30 to C34 + C53 + C64 to C68 + C92

Cause of death	ICD version 8 (1968–1978)	ICD version 9 (1979–1999)	ICD version 10 (2000–2008)
Mouth	140 to 145	140 to 145	C00 to C08
Pharynx	146 to 149	146 to 149	C09 to C14
Oesophagus	150	150	C15
Stomac	151	151	C16
Liver	155	155 - 155.2	C22 - C22.9
Pancreas	157	157	C25
Nasal cavity, sinus and middle ear	160	160	C30 + C31
Larynx	161	161	C32
Lung	162	162	C33 + C34
Bladder	188	188	C67
Kidney	189	189	C64 to C66 + C68
Non-smoking related cancers	152 to 159 - 155 - 157 + 163 to 199 - 180 - 188 - 189	152 to 159 - 155 + 155.2 - 157 + 163 to 199 - 180 - 188 - 189	C17 to C29 - C22 + C22.9 - C25 + C35 to C63 - C53 + C69 to C80 + C97
Colon	153	153 + 159.0	C18 + C26.0
Rectum	154	154	C19 to C21
Gallbladder and bile ducts	156	156	C23 + C24
Pleura	163.0	163	C38.4 + C45.0
Melanoma	172	172	C43
Breast	174	174 + 175	C50
Prostate	185	185	C61
Brain and central nervous system	191 + 192	191 + 192	C70 to C72
Haematological and lymphatic malignancies	200 to 207	200 to 208	C81 to C96
Leukaemia	204 to 207	204 to 208	C91 to C95
Lymphocytic leukaemia	204	204	C91
Chronic lymphocytic leukaemia (CLL)	204.1	204.1	C91.1 + C91.4
Myeloid leukaemia	205	205	C92
Acute myeloid leukaemia	205.0	205.0	C92.0

Cause of death	ICD version 8 (1968–1978)	ICD version 9 (1979–1999)	ICD version 10 (2000–2008)
Other leukaemia	206 to 207	206 to 208	C93 to C95
Leukaemia without CLL	200 to 207 – 204.1	200 to 208 – 204.1	C81 to C96 - C91.1 - C91.4
Multiple myeloma	203	203	C90 + C88
Non-Hodgkin's lymphoma	200 + 202	200 + 202	C82 to C85 + C96
External causes	E800 to E999	E800 to E999	V01 to V89 + V90 to X84
Suicides	E950 to E959	E950 to E959	X60 to X84
Accidents	E800 to E929 + E940 + E942	E800 to E928	V01 to X59

Appendix Table 3. Standardized mortality ratios (SMRs) in the TRACY cohort (1968-2008) among women[a].

Cause of death	Observed number of deaths	SMR	95% confidence interval
All causes	102	0.77	[0.63 - 0.94]
Non-cancers diseases	33	0.49	[0.34 - 0.69]
Diseases of the circulatory system	16	0.60	[0.35 - 0.98]
Cerebrovascular diseases	7	0.92	[0.37 - 1.90]
Other and unspecified disorders of the circulatory system	5	0.45	[0.15 - 1.05]
Other non-cancers diseases	5	0.39	[0.13 - 0.91]
All cancers	59	1.14	[0.87 - 1.48]
Smoking related cancers	17	1.16	[0.68 - 1.87]
Lung	5	1.09	[0.35 - 2.54]
Non-smoking related cancers	38	1.13	[0.80 - 1.55]
Colon	5	1.28	[0.42 - 3.00]
Breast	20	1.53	[0.94 - 2.37]
Haematological and lymphatic malignancies	5	1.17	[0.38 - 2.73]
External causes	10	0.74	[0.36 - 1.37]
Accidents	5	0.67	[0.22 - 1.56]

a. For causes of deaths with at least 5 cases observed among women

Appendix Table 4. Standardized mortality ratios (SMRs) in the TRACY cohort (1968-2008) among men[a].

Cause of death	Observed number of deaths	SMR	95% confidence interval
All causes	2028	0.64	[0.61 - 0.67]
Non-cancers diseases	980	0.59	[0.55 - 0.62]
Diseases of the circulatory system	524	0.68	[0.62 - 0.74]
Hypertensive diseases	15	0.59	[0.33 - 0.98]
Ischemic heart diseases	208	0.71	[0.62 - 0.82]
Cerebrovascular diseases	123	0.75	[0.62 - 0.89]
Other and unspecified disorders of the circulatory system	178	0.62	[0.53 - 0.71]
Respiratory diseases	85	0.51	[0.41 - 0.63]
Diseases of the digestive system (other than cirrhosis)	44	0.56	[0.40 - 0.75]
Diseases of the genito-urinary system	23	0.73	[0.46 - 1.10]
Renal diseases	17	0.69	[0.40 - 1.11]
Diseases of the skin	5	1.22	[0.40 - 2.85]
Diseases of the musculoskeletal system and connective tissue	7	0.70	[0.28 - 1.45]
Other non-cancers diseases			
Non-malignant tumors of central nervous system and sense organs	8	0.66	[0.28 - 1.30]
Endocrine, nutritional and metabolic diseases	46	0.69	[0.50 - 0.92]
Diseases of the blood and blood-forming organs	7	0.67	[0.27 - 1.37]
Cirrhosis, psychosis and other diseases due to alcohol	47	0.27	[0.20 - 0.36]
Non-tumoral diseases of central nervous system and sense organs	68	0.88	[0.68 - 1.11]
Diseases of the skin	5	1.22	[0.40 - 2.85]
Diseases of the musculoskeletal system and connective tissue	7	0.70	[0.28 - 1.45]
Other	116	0.43	[0.35 - 0.51]
All cancers	853	0.74	[0.70 - 0.80]
Smoking related cancers	478	0.67	[0.61 - 0.74]
Mouth	13	0.46	[0.25 - 0.80]
Pharynx	27	0.55	[0.36 - 0.80]
Esophagus	32	0.51	[0.35 - 0.72]
Stomach	27	0.61	[0.40 - 0.89]
Liver	30	0.64	[0.43 - 0.91]
Pancreas	50	1.04	[0.78 - 1.38]
Nasal cavity, sinus and middle ear	5	0.25	[0.08 - 0.58]
Larynx	19	0.47	[0.28 - 0.73]

Cause of death	Observed number of deaths	SMR	95% confidence interval
Lung	212	0.72	[0.63 - 0.83]
Bladder	26	0.70	[0.46 - 1.02]
Kidney	23	0.83	[0.53 - 1.24]
Non-smoking related cancers	320	0.85	[0.76 - 0.95]
Colon	55	0.76	[0.57 - 0.99]
Rectum	26	0.92	[0.60 - 1.34]
Gallbladder and bile ducts	7	1.06	[0.43 - 2.19]
Pleura	16	1.97	[1.13 - 3.20]
Melanoma	12	1.38	[0.71 - 2.41]
Prostate	71	0.94	[0.74 - 1.19]
Brain and central nervous system	30	1.36	[0.92 - 1.94]
Other non-smoking related cancers	102	0.70	[0.57 - 0.85]
Haematological and lymphatic malignancies	69	0.94	[0.73 - 1.19]
Leukaemia	31	0.99	[0.67 - 1.41]
Lymphocytic leukaemia	12	1.44	[0.75 - 2.52]
Chronic lymphocytic leukaemia (CLL)	8	1.32	[0.57 - 2.61]
Myeloid leukaemia	14	1.05	[0.57 - 1.76]
Acute myeloid leukaemia	10	1.30	[0.62 - 2.39]
Other leukaemia	5	0.52	[0.17 - 1.21]
Leukaemia without CLL	23	0.91	[0.58 - 1.37]
Multiple myeloma	17	1.30	[0.76 - 2.08]
Non-Hodgkin's lymphoma	21	0.83	[0.51 - 1.28]
External causes	176	0.53	[0.45 - 0.61]
Suicides	73	0.65	[0.51 - 0.82]
Accidents	93	0.47	[0.38 - 0.57]
Other external causes	10	0.46	[0.22 - 0.85]

a. For causes of deaths with at least 5 cases observed among men

Appendix Table 5. Standardized mortality ratios (SMRs) in the TRACY cohort (1968-2008) according to groupings of companies involved in the three main steps of the uranium fuel cycle.

Workers involved in only one grouping of companies									
	Conversion [a] (N=1489)			Civil and military Enrichment [b] (N=3338)			Fuel UO_2 Manufacturing [c] (N=1952)		
Cause of death	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval
All causes	299	0.68	[0.61 - 0.77]	733	0.70	[0.65 - 0.75]	259	0.67	[0.59 - 0.76]
All cancers	117	0.76	[0.63 - 0.91]	321	0.83	[0.74 - 0.93]	114	0.81	[0.67 - 0.97]
Circulatory diseases	81	0.72	[0.57 - 0.90]	197	0.76	[0.66 - 0.87]	50	0.57	[0.42 - 0.75]
Respiratory diseases	14	0.56	[0.31 - 0.95]	38	0.67	[0.48 - 0.92]	12	0.65	[0.34 - 1.14]
Workers involved in at least one grouping of companies									
	Conversion [a] (N=1690)			Civil and military Enrichment [b] (N=4688)			Fuel UO_2 Manufacturing [c] (N=2116)		
Cause of death	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval	Observed Number of deaths	SMR	95% confidence interval
All causes	307	0.67	[0.60 - 0.75]	1010	0.69	[0.65 - 0.74]	264	0.65	[0.57 - 0.73]
All cancers	120	0.75	[0.62 - 0.90]	429	0.79	[0.72 - 0.87]	116	0.79	[0.65 - 0.94]
Circulatory diseases	81	0.70	[0.56 - 0.87]	281	0.79	[0.70 - 0.89]	50	0.54	[0.40 - 0.72]
Respiratory diseases	14	0.55	[0.30 - 0.92]	49	0.64	[0.47 - 0.84]	12	0.62	[0.32 - 1.09]

a. Workers employed by Comurhex (Malvési and Pierrelatte plants)

b. Workers employed by Eurodif, CEA and AREVA NC (formerly Cogema) on the Pierrelatte plant and involved in enrichment

c. Workers employed by FBFC (Romans and Pierrelatte plants)

Appendix Table 6. Comparison of standardized mortality ratios (and associated 95% confidence interval) observed in TRACY and in other studies of uranium workers, including millers, for selected causes of death.

Study	TRACY (present study)	Malinckrodt workers, USA (Dupree et al 2000)[39]	Fernald workers, USA (Silver et al 2013)[42]		Paducah plant workers, USA (Chan et al 2010)[17]	Rocketdyne workers, USA (Boice et al, 2011)[15]		Oak Ridge Y12 plant workers, USA (Loomis et al., 1996)[14]
Follow-up period	1968-2008	1942-1993	1951-2004		1940-2002	1948-2008		1947-1990
Workers included	12649 (males + females)	2514 (males)	3663 (males, hourly paid)	1818 (males, salaried)	6820 (males + females)	5801 (males + females)	2232 (males + females) with internal exposure (mostly to uranium)	8116 (males + females)
Cause of death								
Pancreas cancer	1.05 [0.79-1.38)	1.18 [0.67- 1.87]	1.20 [0.81-1.72]	1.03 [0.53-1.80]	1.10 [0.75-1.56]	0.84 [0.59-1.17]	0.92 [0.52-1.52]	1.36 [0.94-1.90]
Pleural cancer	2.04 [1.19-3.27]		1.89 [0.05-10.5]	no case		0.63 [0.08-2.29]	no case	
Skin melanoma	1.60 [0.90-2.64]					0.84 [0.43-1.46]	0.70 [0.19-1.78]	1.07 [0.54-1.92][a]
Breast cancer	1.32 [0.81-2.04]		1.63 [0.04-9.08]	no case		0.97 [0.42-1.91]	1.15 [0.14-4.14]	1.21 [0.60-2.17]
Brain and central nervous system cancers	1.36 [0.93-1.91]	1.57 [0.84-2.64]	1.47 [0.89-2.30]	0.63 [0.17-1.61]	1.00 [0.57-1.63]	1.12 [0.71-1.68]	1.10 [0.50-2.08]	1.29 [0.79-2.00]
Haematological and lymphatic malignancies	0.96 [0.75-1.20]		1.08 [0.81-1.42]	1.52 [1.06-2.12]	1.19 [0.85-1.61]			0.83 [0.59-1.13]
Leukemia	1.00 [0.69-1.40]	1.11 [0.57-1.89]	0.92 [0.54-1.48]	1.71 [0.95-2.81]	1.11 [0.71-1.65]	1.11 [0.76-1.56]	1.20 [0.66-2.01]	0.60 [0.30-1.07]
Chronic lymphocytic leukaemia	1.28 [0.55-2.52]					1.36 [0.59-2.68]	no case	
Multiple myeloma	1.29 [0.77-2.05]	1.30 [0.42-3.03]	1.44 [0.75-2.52]	1.82 [0.73-3.75]	1.02 [0.49-1.87]	0.71 [0.34-1.31]	0.92 [0.30-2.14]	
Non-Hodgkin's Lymphoma	0.86 [0.55-1.30]		0.97 [0.58-1.54]	1.33 [0.69-2.32]	1.43 [0.98-2.01]	1.01 [0.69-1.44]	0.92 [0.46-1.64]	

a. All skin cancers

Appendix Table 6 (continued). Comparison of standardized mortality ratios (and associated 95% confidence interval) observed in TRACY and in other studies of uranium workers, including millers, for selected causes of death.

Study	TRACY (present study)	BNFL workers, UK (Gillies et al., 2014)[18]		Colorado millers, USA (Pinkerton et al., 2004)[31]	German uranium millers (Kreuzer et al., 2015)[32]	Port Hope workers, Canada (Zablotska et al., 2013)[41]	Grants millers, USA (Boice et al. 2008)[40]
Follow-up period	1968-2008	1946-2005		1940-1998	1970-2008	1950-1999	1979-2005
Workers included	12649 (males + females)	64820 (males + females)	22675 (males + females) workers, UK with internal exposure, possibly to uranium	1484 (males)	4054 (males)	3000 (males + females)	718 millers who likely worked with uranium (males + females)
Cause of death							
Pancreas cancer	1.05 [0.79-1.38)	0.82 [0.71-0.94]	0.91 [0.71-1.14]	0.58 [0.21-1.27]	0.88 [0.49-1.27]	0.68 [0.33-1.26]	1.37 [0.37-3.49]
Pleural cancer	2.04 [1.19-3.27]	2.06 [1.64-2.55]	2.25 [1.55-3.16]				4.6 [0.12-25.6]
Skin melanoma	1.60 [0.90-2.64]	0.88 [0.64-1.18]	0.61 [0.29-1.12]				no case
Breast cancer	1.32 [0.81-2.04]	0.84 [0.69-1.00]	1.17 [0.51-2.31]				no case
Brain and central nervous system cancers	1.36 [0.93-1.91]	0.91 [0.76-1.07]	0.83 [0.60-1.12]		1.24 [0.56-1.91]	0.74 [0.24-1.73]	1.93 [0.40-5.63]
Haematological and lymphatic malignancies	0.96 [0.75-1.20]	0.91 [0.82-1.01]	1.01 [0.84-1.19]	1.22 [0.70-1.72][a]			0.69 [0.19-1.77]
Leukemia	1.00 [0.69-1.40]	0.91 [0.76-7.07]	0.98 [0.72-1.30]	0.66 [0.21-1.53]		0.63 [0.23-1.37]	1.35 [0.28-3.96]
Chronic lymphocytic leukaemia	1.28 [0.55-2.52]						
Multiple myeloma	1.29 [0.77-2.05]	0.95 [0.75-1.18]	0.94 [0.61-1.39]				
Non-Hodgkin's Lymphoma	0.86 [0.55-1.30]			1.44 [0.60-2.76]	0.88 [0.27-1.48]	0.81 [0.33-1.67]	

a. Re-estimated from source data

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(numbered according to main text)

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TRACY Cohort - STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	/
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) If applicable, explain how loss to follow-up was addressed	7-8
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	Supplementary file p2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	/
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.