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A Bayesian hierarchical approach to account for left-censored and missing radiation doses prone to classical measurement error when analyzing lung cancer mortality due to γ -ray exposure in the French cohort of uranium miners

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Abstract Epidemiological data on cohorts of occupationally exposed uranium miners are currently used to assess health risks associated with chronic exposure to low doses of ionizing radiation. Nevertheless, exposure uncertainty is ubiquitous and questions the validity of statistical inference in these cohorts. This paper highlights the flexibility and relevance of the Bayesian hierarchical approach to account for both missing and left-censored (i.e. only known to be lower than a fixed detection limit) radiation doses that are prone to measurement error, when estimating radiation-related risks. Up to the authors' knowledge, this is the first time these three sources of uncertainty are dealt with simultaneously in radiation epidemiology. To illustrate the issue, this paper focuses on the specific problem of accounting for these three sources of uncertainty when estimating the association between occupational exposure to low levels of γ -radiation and lung cancer mortality in the post-55 sub-cohort of French uranium miners. The impact of these three sources of dose uncertainty is of marginal importance when estimating the risk of death by lung cancer among French uranium miners. The corrected Excess Hazard Ratio (EHR) is 0.81 per 100 mSv (95% credible interval: [0.28; 1.75]). Interestingly, even if the 95% credible interval of the corrected EHR is wider than the uncorrected one, a statistically significant positive association remains between γ -ray exposure and the risk of death by lung cancer, after accounting for dose uncertainty. Sensitivity analyses show that the results obtained are robust to different assumptions. Because of its flexible and modular nature, the Bayesian hierarchical models proposed in this work could be easily extended to account for high proportions of missing and left-censored dose values or exposure data, prone to more complex patterns of measurement error.

Keywords: Measurement errors, Censored data, Bayesian inference, Survival models, Lung Cancer, Gamma Radiation

Introduction

Epidemiological data on cohorts of occupationally exposed uranium miners are currently used to assess health risks associated with chronic exposure to low levels of ionizing radiation (IR) like internal exposure to radon and its decay products (Clement et al. 2010; Vacquier et al. 2011; Rage et al. 2015) or external exposure to γ -rays (Vacquier et al. 2011; Kreuzer et al. 2013; Rage et al. 2015). These cohorts generally provide valuable information about the individual exposure history of workers to one or several radiological sources but also about other potential risk factors that might modify the exposure-risk relationships of interest (Kreuzer et al. 2017). Similarly, other cohorts of nuclear workers have been set up to study the health effects of external IR exposure (Leuraud et al. 2015).

In any occupational cohort study, exposure uncertainty, which refers to a lack of knowledge about the “true” value of occupational exposures, is inevitably present. This uncertainty arises from different reasons, called sources of uncertainty, including, for example: exposure measurement errors, detection limit of measurement devices, and missing dose values. Exposure measurement error arises whenever an exposure cannot be measured accurately and only an imperfect surrogate exposure measurement is available. This latter source of uncertainty refers to the discrepancy between a surrogate exposure value (i.e., observed exposure value) and a true (and unknown) exposure value, regardless of the reasons for this discrepancy. Epidemiological studies on occupational cohorts are mainly characterized by complex patterns of exposure measurement error (Allodji et al. 2012; Hoffmann et al. 2017). First, the type and magnitude of error can change over time and space depending on the methods of exposure assessment. Moreover, methods of group-level exposure estimation (e.g., job-exposure matrix) may give rise to errors which are shared between workers belonging to the same group or shared within workers, i.e. errors that affect all exposure values received for several years by a same worker in the same way (Hoffmann et al. 2018). Additionally, in cohorts of uranium miners, exposure data may be censored. This is especially the case when exposure measurements are based on measuring devices, like radiation dosimeters, that cannot measure a radiation exposure which is lower than a fixed threshold, called detection limit (DL). In this context, exposure data are said to be deterministically left-censored: they can be either measured or only known to be lower than a given DL. The DL, which denotes the smallest exposure value that can be detected by a measuring device, mainly depends on the type of the device (Fournier 2017). In cohorts of uranium miners or nuclear

workers where exposure measurements were based on radiation dosimeters, the DL usually decreased over the calendar periods due to an improved technology of the measuring devices. It is important to note that left-censored exposure data may also be prone to measurement error. Indeed, a true exposure value slightly higher (resp. lower) than the DL can be wrongly reported as lower (resp. higher) than the DL due to measurement error. Finally, in cohorts of uranium miners or nuclear workers, exposure data can be missing. First, they can have been lost. Moreover, they can be missing because uranium miners were expatriated, which means that the miners worked in a mine abroad and, consequently, were potentially exposed to IR. In the case of French expatriated miners, dosimetry data were not always retrieved in France and miners have missing exposure data for the time of their expatriation. Additionally, exposure data can be missing if the miner was not exposed and so, did not wear his dosimeter. This could be the case when he was on sick leave for example. Finally, if the available exposure data is the cumulative exposure over a year, it is highly probable that a miner did not wear his dosimeter for a few days. The associated missing values can result in an underestimation of his cumulative exposure.

Exposure uncertainty questions the validity of statistical inference in occupational cohort studies in radiation epidemiology (Thomas et al. 1993; Kim et al. 2006; Physick et al. 2007). When it is not or only poorly accounted for, exposure measurement error may cause bias in health risk estimates, a distortion of the exposure-risk relationship and a loss of statistical power (Carroll 2005; Carroll et al. 2006). Actually, its exact consequences on statistical inference depend on the magnitude and the type of error (e.g., classical/Berkson, shared/unshared, differential/non differential, ...) but also on the type of disease model (e.g., Poisson regression, logistic regression, survival models, ...) (Stefanski et al. 1985; Flegal et al. 1991; Reeves et al. 1998; Heid et al. 2002; Richardson and Loomis 2004; Hoffmann et al. 2018). Despite its deleterious consequences and despite its ubiquity in observational research, exposure measurement error is only rarely accounted for in the estimation of risk coefficients in radiation epidemiology (Kreuzer et al. 2013; Leuraud et al. 2015; Rage et al. 2015; Zablotska et al. 2018). One of the main reasons why measurement error is often discussed, but rarely accounted for in radiation epidemiology, may be that dealing with complex patterns of occupational exposure uncertainty implies to use sophisticated statistical approaches for which no user-friendly software exists. In radiation epidemiology, a single imputation method is often used to replace left-censored exposure data by zero, the DL or half of the DL of the dosimeters used (Ron 1998; Gilbert et al. 2006; Laurent et al. 2016; Yoder et al. 2018). Even

if the DL is small, especially in the latest periods of exposure, this naive approach may cause both a substantial underestimation of the variability of exposure and a possible under or over estimation of the cumulative exposure received by a worker over time (Lubin et al. 2004; Xue et al. 2006), which is the main covariate of interest when modelling exposure-risk relationships in radiation epidemiology. Moreover, in cases where an association exists between cumulative exposure and a given risk, this approach may cause bias in risk estimates (Lubin et al. 2004; Xue et al. 2006).

Up to the authors' knowledge, the issue of missing and left-censored exposure data prone to measurement error has never been dealt with simultaneously in radiation epidemiology. The censoring process, measurement error and missing exposure are generally accounted for separately. Xue et al. (2006) studied the impact of classical measurement errors and left censored radiation exposure data due to DL on all-cause death risk estimates. Using a Cox model, they found that, when there is a true association between exposure and risk, the risk estimate is biased towards zero and the statistical power decreases as the magnitude of measurement error and the proportion of censored exposure data increase. However, when there is no association between exposure and risk, the risk estimate is unbiased neither by measurement error nor by censoring whatever the level of measurement error and the proportion of censored exposure data are. Hoffmann et al. (2017) proposed a Bayesian hierarchical approach to account for exposure measurement error when estimating the risk of lung cancer associated with occupational radon exposure in the French cohort of uranium miners (Vacquier et al. 2008; Rage et al. 2015). They illustrated that the Bayesian hierarchical approach is arguably a very flexible approach to deal with complex patterns of measurement error and multiple sources of uncertainty in occupational cohort studies in radiation epidemiology. Nevertheless, they considered zero and missing exposure data recorded in the database as the true mark of no exposure to radon.

In this paper, three Bayesian hierarchical models are described, to account for both missing and left-censored exposure data prone to classical measurement error when estimating health risks. It is assumed that the censoring indicators may be wrong due to exposure measurement error. Thanks to its well-known flexibility, using a Bayesian hierarchical approach made it possible to describe several sources of exposure uncertainty (i.e., missing exposures, left-censored exposures and measurement errors) and to estimate jointly all unknown quantities, including risk estimates and “true” exposures, in a unique model.

To illustrate the point, this paper focuses on the specific problem of accounting for the three above sources of uncertainty when estimating the association between occupational exposure to low levels of γ -radiation and lung cancer mortality in the French cohort of uranium miners. This association was previously estimated in Rage et al. (2015) by fitting a Poisson regression model without accounting for the measurement errors related to occupational γ -ray exposure (Allodji 2011). Moreover, all the zeros and missing personal dose equivalents due to external γ -ray exposure recorded in the database were considered by default as true zeros. An Excess Relative Risk of 0.74 per 100 mSv (95% CI: 0.23-1.73) was estimated when using the internal sub-cohort of non-exposed miners as a reference. A further aim of the present study was then to test the robustness of this result when accounting for these different sources of uncertainty. Note that external γ -ray exposures were recorded individually in the database, with personal dose equivalents. That's why, we will talk about dose uncertainty hereafter, instead of exposure uncertainty, even if this work can be more generally applied to exposure data.

Materials and methods

Study population

The study population is a sub-cohort of the French cohort of uranium miners. The characteristics, sources of data and methods of data collection (e.g., vital status, causes of death, ...) of this retrospective occupational cohort were described previously (Rage et al. 2015). Briefly, the last update included 5,086 males who were employed as uranium miners for at least one year in the CEA-COGEMA group between 1946 and 1990 and who were followed from 1946 to December 31, 2007.

The routine recording of external γ -ray exposures by individual dosimeters only began in 1956 in the French mines, following the introduction of radiation protection measures like the introduction of forced ventilation. In this paper, the study population is thus restricted to the so-called post-55 sub-cohort which includes 3,377 miners from the original cohort who were first employed after December 31, 1955. At the end of follow-up, 94 miners had died of lung cancer. An age limitation of 85 years for follow-up is fixed due to the imprecision in determining the exact cause of death in those occurring after the 85th birthday (Bouvier-Colle et al. 1990). Main characteristics of the post-55 sub-cohort are shown in Table 1 (Rage et al. 2015).

Table 1 Main characteristics of the post-55 French sub-cohort of uranium miners

No. of miners	3,377
Age at entry into study, mean [min,max]	28.3 [16.9, 57.7]
Duration of work in years, mean [min,max]	16.7 [1.0, 40.9]
Duration of follow-up in years, mean [min,max]	32.8 [0.1, 51.0]
Vital status, n (%)	
Alive < 85 years old	2,412 (71.4)
Alive $\geq$ 85 years old	74 (2.2)
Death from lung cancer	94 (2.8)
Death from another cause	777 (23.0)
Lost to follow-up	20 (0.6)
External γ -ray exposure *	
Exposed miners, n (%)	3,240 (95.9)
Duration of exposure (in years), mean [min,max]	13.2 [1.0, 36.0]
Cumulative exposure (in mSv), mean [min,max]	54.9 [0.2, 470.1]

* Results only on measured γ -ray exposures

γ -ray dose measurements

Personal dose equivalents (simply called “doses” hereafter) due to external γ -ray exposure were recorded individually using two different types of personal dosimeters, depending on the calendar period: personal film badge dosimeters (CEA PS1 type) from 1956 to 1985 and personal thermoluminescence dosimeters (TLDs) integrated to the Individual System of Integrated Dosimetry (ISID) from 1986 onwards. The DL of TLDs and film badge dosimeters were extracted from Allodji (2011). The DL of TLDs was 0.55 mSv and the DL of film badge dosimeters was 2.2 mSv. Owing to technological progress, the TLDs were then more accurate than film badge dosimeters. Moreover, it is reasonable to assume that the variance of measurement error was lower after 1986 given that the personal dosimeters were changed in 1986 and provided more precise γ -ray dose measurements. The annual individual dose values, expressed in mSv, were computerized from paper archives for the entire study period for the purpose of the epidemiological study.

Fig. 1 displays the boxplot of annual personal dose equivalents from γ -ray exposure for the years 1956-2007, for exposed miners of the post-55 sub-cohort. The annual means of exposed miners increased between 1956 and 1961 and decreased between 1961 and 2007. Moreover, the distribution of γ -ray doses strongly shrank from 1986 meaning that the variance of γ -ray doses strongly decreased from this year on. This may be due to changes in personal dosimeters making γ -ray dose values more precise from 1986 onwards, due to the use of personal TLDs.

Zero and missing γ -ray dose measurements

In the post-55 sub-cohort of French uranium miners, 7.60% of γ -ray dose values are recorded as zero values while 2.94% of these values are recorded as missing values. Nevertheless, some of these zero and missing values can reasonably be assumed to be strictly positive, even if potentially close to zero. This can be seen as a specific type of measurement error that was created during the import process of the dose values to the database. In this context, a first step of correction of this measurement error consisted in classifying these zero and missing γ -ray doses in: a) true zeros; b) γ -ray doses that were so close to zero that the dosimeter could not measure them (reported as false zeros or missing values in the database); typically, this corresponds to dose values that were strictly positive but smaller than the DL of the dosimeter used; c) γ -ray doses that were strictly positive, without any restriction. During their occupational activity, miners were simultaneously exposed to radon gas (and its short-lived progeny), external γ -rays and long-lived radionuclides (LLR) of uranium ore dust (Vacquier et al. 2011). To make relevant assumptions about zero and missing γ -ray exposures in the post-55 sub-cohort of French uranium miners, the radiological co-exposure of miners as well as their job position and exposure history were used. Table 2 summarizes the assumptions made regarding zero and missing γ -ray doses in the post-55 French sub-cohort of uranium miners. It also indicates the relative frequency (expressed in percentage) of γ -ray doses in each category. In the following paragraphs, the different assumptions regarding zero and missing γ -ray doses are justified, according to the available information. These assumptions will be used in the Bayesian hierarchical models described thereafter.

The specific situation of radiological co-exposure of uranium miners was used to differentiate true zeros (i.e., no true exposure to external γ -rays) and false zeros. On the one hand, any zero γ -ray dose that was associated to zero exposure to radon and LLR in the database was

assumed to be a true zero. On the other hand, any zero γ -ray dose that was associated to strictly positive exposure values to radon or LLR in the database was assumed to be a false zero, which represents the most frequent category (4.85%) in Table 2. Each false zero was assumed to be strictly positive but smaller than the DL of the dosimeter used.

Regarding missing γ -ray doses, two situations were distinguished depending on the availability of information about radiological co-exposures to radon and LLR. If information on the radiological co-exposure of a given uranium miner was available, the following assumptions were made:

- a) missing γ -ray doses were assumed to be equal to zero when the exposures to radon and LLR were equal to zeros;
- b) missing γ -ray doses were assumed to be equal to zero when the exposure to radon (resp. LLR) was missing and the exposure to LLR (resp. radon) was equal to zero;
- c) missing γ -ray doses were assumed to be strictly positive measured values but lower than the DL when the exposures to radon or LLR were strictly positive. Indeed, in this case, the associated values of radon and LLR co-exposures were mainly lower than the first quartile of their respective distribution suggesting low values of γ -ray exposures. More elaborate assumptions could have been made using the correlation between the three radiological sources but, given that this category only concerned 0.45% of γ -ray dose values, this simple assumption was used.

If information on the radiological co-exposure of a given uranium miner was not available at a given time t (i.e., the annual exposures to radon, LLR and γ -ray were all missing at time t) but the annual exposure to γ -rays of this miner was strictly positive for at least one year before t and one year after t , then the job position indicated in the administrative files of this uranium miner was used to distinguish three situations and the following assumptions were made:

- a) If the miner's job position at time t was recorded as "regular", his missing γ -ray dose value at time t was assumed to be a strictly positive value but lower than the DL. Indeed, in this case, it was assumed to be unlikely that a miner in a "regular" job position and who was at least one time exposed to γ -rays before year t or after year t was not exposed (i.e., γ -ray dose truly equal to zero) at time t . Moreover, given that the three co-exposures were missing, the most probable reason is that the three co-

exposures that were measured by different devices were all lower than the respective DL of these devices.

- b) If the miner's job position at time t was recorded as "expatriate", the individual was assumed to have been exposed as a uranium miner in a foreign mine and his missing γ -ray dose value at time t was assumed to be strictly positive but not necessarily lower than the DL since the exposure conditions to γ -rays are unknown in foreign mines. It was simply assumed that the exposure conditions were similar as in the post-55 sub-cohort of French uranium miners. This means that the missing γ -ray dose values for miners who were expatriated were assumed to follow the same probability distribution (with same parameters) as the one used to describe the strictly positive γ -ray dose values in the post-55 sub-cohort of French uranium miners. There was then no restriction to the exposure range.

- c) If the miner's job position indicates that the miner was not working in a mine for a while (for example, "military service", "medical leave" or "fired"), his γ -ray dose was reasonably assumed to be a true zero. Note that if the situation of radiological co-exposure of a given uranium miner was not available at a given time t and his annual exposure to γ -rays was never strictly positive before and after t then it was simply assumed that the miner was not exposed to γ -rays at time t .

Table 2 Summary of assumptions about zero and missing γ -ray dose values made for the post-55 sub-cohort of French uranium miners.

γ -ray dose value recorded	Co-exposure measurement	Miner's job position	Assumptions regarding γ -ray dose value	Relative frequency of γ -ray dose values (in %)
0	Radon=0 and LLR=0	Regular	= 0	2.75%
	Radon>0 or LLR>0	Regular	< DL**	4.85%
NA*	Radon=0 and LLR=0	Regular	=0	0.50%
	Radon=NA* and LLR=0			
	Radon=0 and LLR=NA*			
	Radon>0 or LLR>0	Regular	<DL**	0.45%
	Radon=NA* and LLR=NA*	Regular	<DL**	1.41%
		Expatriate	>0	0.30%
		Other***	=0	0.28%

* missing dose value

** denotes the detection limit of the dosimeter

*** denotes any miner's job position that is different from "Regular position" or "Expatriate". "Military service", "medical leave" or "fired" are non-exhaustive examples of other miner's job positions.

Model formulation

Several Bayesian hierarchical models are proposed here to account for left-censored and missing dose values prone to measurement error when modelling the association between external γ -ray exposure and lung cancer mortality in the post-55 sub-cohort of French uranium miners.

Strongly inspired by the Bayesian hierarchical model that was proposed to estimate a corrected risk of death by lung cancer due to radon exposure in the French cohort of uranium miners (Hoffmann et al. 2017), these models are composed of three sub-models :

- The disease sub-model: this model relates the outcome of interest of each miner to his true cumulative and occupational γ -ray dose;
- The measurement sub-model: this model describes the association between the true (and unknown) annual γ -ray dose and the measured annual γ -ray dose;
- The exposure sub-model: this model describes the probability distribution of the true (and unknown) annual γ -ray dose in the post-55 sub-cohort.

Following Hoffmann et al. (2017), it is assumed that the measurement error related to γ -ray exposure is non-differential in the post-55 sub-cohort of French uranium miners. Thus, the disease sub-model, measurement sub-model and exposure sub-model are linked via conditional independence assumptions (Richardson et al. 1993).

Disease sub-model

Let T_i be the age (in days) at death by lung cancer of miner i , $i \in \{1, 2, \dots, n\}$ where n is the total number of miners. Let C_i be the right-censored age defined as the earliest age of miner i among age at death by a cause other than lung cancer; age on December 31, 2007; age in days corresponding to his 85th birthday and age until loss to follow-up. For each miner i , the observed outcome of interest can therefore be represented by the non-negative continuous variable $Y_i = \min(T_i, C_i)$ and the binary variable δ_i , where $\delta_i = 1$ if $T_i \leq C_i$ (i.e., miner i died of lung cancer at age $Y_i = T_i$) and $\delta_i = 0$ if $T_i > C_i$ (i.e., miner i “would have died of lung cancer” after age C_i).

Let $X_i^{cum}(t-5)$ be the true and unknown cumulative occupational γ -ray dose of miner i at age t , lagged by five years. Indeed, a latency period of five years between a received exposure and

its potential impact on lung cancer mortality is assumed (Langholz et al. 1999; Rage et al. 2015).

It is proposed to describe the relationship between the cumulative occupational γ -ray doses and the age at death by lung cancer of miner i with a survival sub-model defined by the following instantaneous hazard rate function:

$$h_i(t; \beta) = h_0(t)(1 + EHR_i(t; \beta)) \quad (1)$$

where $EHR_i(t; \beta)$ is the excess hazard ratio (EHR) of death by lung cancer potentially associated to γ -ray exposure for miner i at age t .

As commonly assumed when modelling the association between solid cancer mortality and exposure to γ -rays (Vacquier et al. 2011; Rage et al. 2015), a linear structure in cumulative dose is assumed, with no effect modification:

$$EHR_i(t; \beta) = \beta X_i^{cum}(t - 5) \quad (2)$$

Thus, β is the unknown risk coefficient of interest, subject to the constraint $\beta X_i^{cum}(t-5) > -1 \forall t \forall i$ to ensure the positivity of $h_i(t; \beta)$. Finally, $h_0(t)$ corresponds to the instantaneous baseline hazard rate of death by lung cancer at age t for an unexposed miner.

The baseline hazard rate $h_0(t)$ is assumed to be piecewise constant and given by:

$$h_0(t) = \lambda_j \quad \forall t \in (s_{j-1}, s_j] \quad (3)$$

with cut-points of the time axis fixed at: $s_0=0$, $s_1=40$, $s_2=55$, $s_3=70$ and $s_4=85$ years old. Thus, four age intervals are considered for which the values of the baseline hazard λ_j are assumed to be constant. In the following, $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ denotes the vector of unknown baseline hazard parameters.

Measurement sub-model

This sub-model describes the association between a true γ -ray dose and a γ -ray dose prone to measurement error. The latter can be either a strictly positive measured dose or the unknown dose that would have been measured if non-missing or non-censored. Here, it is assumed that missing exposure data are missing at random, meaning that their absence could be

compensated by strictly positive γ -ray doses and other relevant covariates like calendar period, localization of the mine, job type....

All the γ -ray doses assumed to be zero according to Table 2 are assumed to be true zeros in the following. Consequently, they are assumed not to be prone to measurement error and, consequently, they are not included in the following measurement sub-model. Additionally, some missing γ -ray doses and all those assumed to be lower than the DL are treated as latent random variables (with restrictions detailed in Table 2) whose uncertainty is described by the same probability distribution (i.e., with the same parameters) as the one used to describe the strictly positive γ -ray doses measured at a given time, for the exposed miners of the post-55 sub-cohort.

Let $X_i(t)$ be the true γ -ray dose of miner i at time t . Let $Z_i(t)$ be either the strictly positive measured γ -ray dose of miner i at time t (if higher than the DL) or the unknown γ -ray dose that would have been measured for miner i if non-missing at time t or if the personal dosimeter did not have a DL at time t (denoted with $DL(t)$ hereafter). $Z_i(t)$ is assumed to be prone to measurement error. Moreover, $X_i(t)$ and $Z_i(t)$ are treated as latent variables, except when $Z_i(t)$ corresponds to a strictly positive measured γ -ray dose. If $Z_i(t)$ is not measured, it is assumed to follow a specific probability distribution (described in the following) and, additionally, to be smaller than $DL(t)$ if it is left-censored. Note that, here, the censoring process is deterministic since $DL(t)$ is fixed at each time t : $DL(t)=2.2$ mSv for t between 1956 and 1985, and $DL(t)=0.55$ mSv for t between 1986 and 2007. The outcome of interest of the measurement sub-model is defined by $(W_i(t), \delta_{it}^W)$ where $W_i(t)=\max(Z_i(t), DL(t))$ and δ_{it}^W indicates whether $Z_i(t)$ exceeds the DL or not (i.e., $\delta_{it}^W = 1$ if $Z_i(t) \geq DL(t)$ and $\delta_{it}^W = 0$ if $Z_i(t) < DL(t)$). If the miner's job position is recorded as "regular" with an assumed exposure smaller than DL (see Table 2), then it is assumed that $W_i(t)=DL(t)$ and $\delta_{it}^W=0$. If the miner's job position is recorded as "expatriate" (see Table 2), then it is assumed that $W_i(t)=\max(Z_i(t), DL(t))$ and $\delta_{it}^W=0$ or 1.

Given that γ -ray dose values are based on personal dosimeters during the whole exposure period (1956-2007) in the post-55 sub-cohort of French uranium miners, a classical error is naturally assumed for γ -ray doses in order to reflect the lack of precision of personal dosimeters. A shared measurement error occurs when the discrepancy between true and observed exposures depends on error components that affect similarly several miners or

several exposure times of a same miner. In the specific context of personal dosimetry, there is no reason to assume a shared error component in the measurement sub-model, for the whole exposure period.

Consistent with much of the literature suggesting that a multiplicative measurement error sub-model may be more realistic than an additive one in occupational epidemiology in general (Armstrong 1998), a lognormal and multiplicative error structure is postulated. Nevertheless, given that γ -ray doses were measured with film badge dosimeters between 1956 and 1985 and then with TLDs between 1986 and 2007, the variance of measurement error changed over time. Therefore, the following classical measurement error sub-model is assumed:

$$Z_i(t) = X_i(t)U_i(t) \quad (4)$$

The measurement error terms $U_i(t)$ are supposed to be independent from each other and to follow a lognormal distribution with a geometric mean of $-\sigma^2_{U,q(t)}/2$ and a geometric variance of $\sigma^2_{U,q(t)}$:

$$U_i(t) \sim \text{LogN}\left(-\frac{\sigma^2_{U,q(t)}}{2}, \sigma^2_{U,q(t)}\right) \quad (5)$$

where $q(t)$ equals 1 for exposure period 1956-1985 and 2 for exposure period 1986-2007.

Assuming a lognormal distribution implies that $E(U_i(t))=1$ for all i and for all t and thus, that $E(Z_i(t)|X_i(t))=X_i(t)$. $Z_i(t)$ is thus an unbiased estimate of the true dose $X_i(t)$. Note that, since $Z_i(t)$ is prone to classical measurement error, $X_i(t)$ might be greater than $DL(t)$ even if $Z_i(t) < DL(t)$.

Due to the lack of validation data to estimate the true variance of the measurement error, the geometric standard deviation of the lognormal error terms $U_i(t)$ was extracted from Allodji (2011) for each calendar period of interest: $\sigma_{U,1}=0.245$ between 1956 and 1985 and $\sigma_{U,2} = 0.16$ between 1986 and 2007. To estimate these values, Allodji (2011) first listed several potential reasons for the existence of measurement error in γ -ray doses in the post-55 sub-cohort: accuracy of measurement devices for the medical, radiological and environmental radiation fields, loss of record keeping, and issues in data transcription. Then, the impact of these reasons on the global measurement error was estimated from the studies published by Brady et al. (1985) and Gilbert et al. (1996).

Exposure sub-model

The correction of classical measurement error requires the specification of the probability distribution for the true latent γ -ray dose $X_i(t)$. As occupational exposures are often assumed to follow a lognormal distribution (Steenland et al. 2015), and following Allodji (2011), a lognormal distribution is assumed:

$$\log(X_i(t)) \sim N(\mu_{x,i}(t), \sigma_{x,i}^2(t)) \quad (6)$$

where $\mu_{x,i}(t)$ and $\sigma_{x,i}(t)$ denote the expected value and the standard deviation of the log-transformed true γ -ray dose of miner i at time t .

For the sake of parsimony, different modelling assumptions are made on the structure of $\mu_{x,i}(t)$ and $\sigma_{x,i}(t)$, in order to avoid having as many unknown parameters as the total number of years of exposure for all the exposed uranium miners of the post-55 sub-cohort of French uranium miners. These assumptions also allow taking advantage of the information brought by all the miners over time, depending on the calendar period or the type of mine.

Previous statistical analyses (results not shown) showed that the geometric standard deviation $\sigma_{x,i}(t)$ can reasonably be assumed to be constant over time and for all miners. Therefore, in the following, it is assumed that $\sigma_{x,i}(t) = \sigma_x$ for all i and all t .

To allow the expected value of the log-transformed true γ -ray dose $\mu_{x,i}(t)$ to vary over time, three sub-models are proposed. The first exposure sub-model, noted M_1 , assumed $\mu_{x,i}(t)$ to be the same piecewise-constant function over time for all miners:

$$\mu_{x,i}(t) = \mu_{x,p(t)} \quad \forall i \forall t \quad (7)$$

where the variable $p(t)$ takes values in $\{1,2,3,4,5\}$ corresponding to five exposure periods of approximately ten years and accounting for the change in personal dosimeters that occurred in 1986: 1956-1965, 1966-1975, 1976-1985, 1986-1995 and 1996-2007. Therefore, $\mu_x = (\mu_{x,1}, \mu_{x,2}, \mu_{x,3}, \mu_{x,4}, \mu_{x,5})$ is the vector of unknown expected values of the log-transformed true doses for the five exposure periods. The vector of six unknown parameters of the sub-model M_1 is then given by (μ_x, σ_x) .

The second exposure sub-model, referred to as M_2 , is a hierarchical model that describes the uncertainty on parameters $\mu_{x,i}(t)$ through a normal distribution with the mean to be defined as

a linear function over time with an unknown slope a and intercept b . This linear function is assumed to be the same for all miners:

$$\mu_{x,i}(t) \sim N(a \cdot f(t) + b, \sigma_\mu^2), \text{ where } f(t)=t-1956 \quad (8)$$

The parameter b can be interpreted as the expected value of the log-transformed true γ -ray dose in 1956 in the post-55 sub-cohort of French uranium miners. For the sake of parsimony, the standard deviation σ_μ of the expected value of the log-transformed true γ -ray dose is assumed to be constant over time. The vector of four unknown parameters of the sub-model M_2 is $(a, b, \sigma_x, \sigma_\mu)$.

Finally, it is also supposed that the temporal trend of log-transformed true γ -ray doses is different in underground mines and in open-pit ones. The third exposure sub-model, referred to as M_3 and which is also a hierarchical model, accounts for this assumption:

$$\begin{aligned} \mu_{x,i}(t) &= \mu_{x,m_i(t)}(t) \text{ with} \\ \mu_{x,J}(t) &\sim N(a_J \cdot f(t) + b_J, \sigma_\mu^2) \text{ and} \\ \mu_{x,F}(t) &\sim N(a_F \cdot f(t) + b_F, \sigma_\mu^2) \end{aligned} \quad (9)$$

Where $m_i(t) = \{F, J\}$ is the type of mine where the miner i worked at time t .

Here, the sub-model depends on the miner through the type of mine, as the type of mine is time and miner specific. In this sub-model, the slope and the intercept of the linear temporal trend depend on the type of mine. When information on the type of mine $m_i(t)$ is missing for miner i at time t (percentage of missing values in the post-55 sub-cohort = 11%), a Bernoulli probability distribution is assigned to the variable $m_i(t)$. Its parameter is p_F which denotes the unknown probability for a miner to work in an underground mine. F and J correspond to an underground mine and an open-pit mine, respectively. The vector of seven unknown parameters of the sub-model M_3 is $(a_J, a_F, b_J, b_F, \sigma_x, \sigma_\mu, p_F)$.

Prior choice and Bayesian inference

Fig. 2 shows the directed acyclic graph for the full hierarchical model combining the disease sub-model, the measurement sub-model and the exposure sub-model M_3 . To fit the three

hierarchical sub-models under the Bayesian paradigm, prior distributions must be assigned to all the unknown parameters, which are assumed to be independent.

The prior for the risk coefficient β is a vague prior in the form of a centered normal distribution with large variance (10^6). The prior is not left truncated but the positivity of the instantaneous hazard $h_i(t)$ is guaranteed during the inferential process, when computing the sub-model likelihood. Following Hoffmann et al. (2017), an informative gamma prior is assigned with shape parameter 23.66 and scale parameter $4.90 \cdot 10^8$ for the baseline hazard rate λ_1 (corresponding to the age interval $[0; 40]$) and flat uniform distributions between 0 and 100 for the baseline hazard rates λ_2 , λ_3 and λ_4 . Actually, since only one miner died of lung cancer before the age of 40 in the post-55 sub-cohort, the information contained in the data about λ_1 is very poor, making a reliable estimation of this parameter impossible from data. Consequently, it would have been hazardous to estimate the baseline hazard rate λ_1 from a flat uniform prior distribution and this justified assigning an informative prior to this parameter. The hyperparameters of the gamma prior distribution for λ_1 were derived from external data on the French national mortality rates by lung cancer between 1968 and 2005 (Hoffmann et al. 2017).

Finally, the prior distributions for the parameters of the three exposure sub-models are inspired from non-informative Jeffreys prior distributions (Jeffreys 1998). They are indicated in Table 3. The goal is here to formalize the absence of knowledge about the distribution of the log-transformed true γ -ray doses in the post-55 sub-cohort of French uranium miners and to use prior probability distributions that are invariant by reparametrization.

Table 3 Jeffreys prior probability distributions for the parameters of the three exposure sub-models

Exposure sub-model	Parameters	Prior distribution (up to a constant)
M_1	$\mu_{x,1}, \mu_{x,2}, \mu_{x,3}, \mu_{x,4}, \mu_{x,5}$	I
	$\tau_x(^*)$	$1/\tau_x$
M_2	a, b	I
	τ_x	$1/\tau_x$
	$\tau_\mu(^{**})$	$1/\tau_\mu$
M_3	a_J, b_J, a_F, b_F	I
	τ_x	$1/\tau_x$
	τ_μ	$1/\tau_\mu$
	p_F	$Beta(1/2, 1/2)$

(*) $\tau_x = 1/\sigma_x^2$; τ_x is called the precision parameter

(**) $\tau_\mu = 1/\sigma_\mu^2$; τ_μ is called the precision parameter

A Markov Chain Monte Carlo (MCMC) algorithm was implemented in the programming language Python (for more details see: <https://www.python.org/doc/>) to sample from the joint posterior distribution of the unknown parameters and latent variables of each hierarchical model, combining the disease sub-model, the measurement sub-model and one of the three exposure sub-models. A Metropolis-within-Gibbs algorithm (Roberts et al. 2009) was adopted to conduct the Bayesian inference, as full conditional distributions were analytically intractable except for the parameters of the exposure sub-model. In the adaptive phase of Metropolis-Hastings steps, the variance of each proposal distribution was calibrated to target an acceptance rate of 40% for single parameters and 20% for vectors (Roberts et al. 2009), in order to improve the efficiency and the convergence of the algorithm. Parameters and latent variables were independently updated. Three chains with different initial values were run. After 100 cycles of 100 iterations for the adaptive phase, the first 10,000 iterations were discarded as burn-in phase, and 55,000 additional iterations were run for each model. To decrease intra-chains autocorrelation, the sample was thinned storing only every 30 iterations. The posterior samples included then 5,500 values. Trace plots of the Markov chains and the

Gelman Rubin statistics (Gelman et al. 1992) were used to check that there were no convergence issues (results not shown). Finally, the Monte-Carlo (MC) error (Gilks et al. (1995)) of the risk coefficient β was computed and showed that the size of the posterior samples was large enough to provide accurate estimates of β (results not shown).

Competing exposure sub-models were compared via the Watanabe-Akaike, also called Widely Applicable Information Criterion (Watanabe 2010). WAIC quantifies the predictive accuracy of a fitted model to data while accounting for its effective number of parameters to adjust for overfitting. WAIC is based on the log-transformed pointwise posterior predictive distribution of the outcomes of interest that can be approximated by simulations from the posterior sample derived from the MCMC algorithm. A smaller WAIC value indicates a better predictive accuracy for a given model.

Results

Sensitivity to the exposure sub-model

As described earlier, three different exposure sub-models were implemented to describe the uncertainty of the true latent γ -ray doses in the post-55 sub-cohort. The posterior medians of the excess hazard ratio (EHR) per 100 mSv and the associated 95% credible intervals (95% CI) as well as the DIC and the WAIC values for the different exposure sub-models are given in Table 4.

Table 4 Posterior medians and 95% credible intervals (CI) of the excess hazard ratio (EHR) (per 100 mSv) for lung cancer mortality in the post-55 sub-cohort of French uranium miners, assuming three different exposure sub-models. Watanabe-Akaike Information Criterion (WAIC) and Deviance Information Criterion (DIC) for the three exposure sub-models

Exposure submodel	EHR per 100 mSv	WAIC	DIC
M_1	0.82 [0.29; 1.71]	2462.0	2461.8
M_2	0.81 [0.30; 1.75]	2461.9	2461.7
M_3	0.81 [0.28; 1.75]	2461.7	2461.5

In general, there are no substantial differences between the risk estimates, 95% CI, DIC and WAIC values for the three exposure sub-models. This shows that the risk estimates are robust to the exposure sub-model choice. Given that the sub-model M_3 provides more information than the other sub-models on the temporal trend of log-transformed true γ -ray doses according to the type of mine and the smallest estimated geometric standard deviation σ_x of the true latent γ -ray doses, in the following focus will be placed on this sub-model. Results of the Bayesian hierarchical models based on the exposure sub-models M_1 and M_2 are provided in the supplementary materials.

Results for the hierarchical model with exposure sub-model M_3

Table 5 gives the posterior medians and 95% CI of the EHR (per 100 mSv) for lung cancer mortality, the baseline hazards and the parameters of the full hierarchical model based on the exposure sub-model M_3 (see Fig. 2).

Table 5 Posterior medians and 95% credible intervals (CI) of the parameters of the full hierarchical model combining the disease sub-model, the measurement sub-model and the exposure sub-model M_3 . EHR – excess hazard ratio.

Parameter	Posterior median	95% CI
EHR per 100 mSv	0.81	[0.28 ; 1.75]
$\lambda_1 (10^{-6})$	0.05	[0.03 ; 0.07]
$\lambda_2 (10^{-6})$	0.78	[0.45 ; 1.27]
$\lambda_3 (10^{-6})$	4.24	[2.72 ; 6.22]
$\lambda_4 (10^{-6})$	7.33	[4.18; 11.88]
<i>a</i>		
Open-pit (J)	-0.025	[-0.034 ; -0.016]
Underground (F)	-0.047	[-0.054 ; -0.039]
<i>b</i>		
Open-pit (J)	-1.59	[-1.81 ; -1.37]
Underground (F)	-0.05	[-0.26 ; 0.16]
<i>p</i>		
Underground (F)	0.67	[0.66 ; 0.68]
σ_μ	0.33	[0.27 ; 0.45]
σ_x	0.93	[0.90 ; 0.96]

The corrected risk coefficient for death by lung cancer associated with cumulative γ -ray doses in the post-55 French sub-cohort of uranium miners was estimated to be 0.81 per 100 mSv (95% CI: [0.28; 1.75]). Therefore, after accounting for γ -ray dose uncertainty, there is still a statistically significant positive association between γ -ray doses and the risk of death by lung cancer in the post-55 sub-cohort. The slope parameters a_J and a_F defining the temporal trend of the log-transformed γ -ray doses are significantly negative for both types of mine. This confirms that the expected value of the log-transformed true γ -ray dose decreased over time in the French uranium mines (Fig. 1). This downward trend is stronger in underground mines than in open-pit ones, as displayed in Fig. 3. As expected, the intercept parameter b_F that

denotes the expected log-transformed true γ -ray dose in 1956 is higher for the underground mines than the intercept parameter b_I for the open-pit mines. Interestingly, Fig. 3 also shows that, from 1996, there is no significant difference between the annual expected true γ -ray dose in underground mines and in open-pit mines. This does not mean that the levels of γ -ray exposure were the same in underground and open-pit mines, but rather that the number of exposed miners was too low from 1996 to highlight any significant difference, should it exist. Indeed, French uranium mines closed shortly after this date.

Sensitivity to the detection limit of dosimeters

Given that the values fixed for the DL of the dosimeters might also be uncertain, the robustness of the estimated EHR to these values was also tested. For this, the Bayesian hierarchical model including exposure sub-model M_3 was fitted after considering two alternative scenarios. First, the previously defined DLs were increased by 50% (3.3 mSv before 1986 and 0.825 mSv after 1986). To do this, any dose value between the original DL and the increased DL was assumed to be left-censored. In other words, $Z_i(t)$ – that was observed with the original DL – was assumed to be unknown but smaller than the DL(t), and was also assumed to follow the lognormal distribution given by Eq. (4). The posterior median of the EHR was then estimated to be 0.80 per 100 mSv with a 95% CI of [0.28; 1.73]. Second, the previously defined DLs were increased by 75% (3.85 mSv before 1986 and 0.9625 mSv after 1986). The posterior median of the EHR was then estimated to be 0.83 per 100 mSv with a 95%CI of [0.29; 1.75]. Therefore, it is observed that increasing the value of the DL does not substantially change the risk estimates.

Impact of the different sources of γ -ray dose uncertainty on risk estimate

Finally, the disease sub-model was fitted without accounting for exposure measurement error and after replacing all left-censored and missing γ -ray dose values by zero. The uncorrected EHR of death by lung cancer due to occupational γ -ray exposure was then estimated to be 0.78 per 100 mSv with a 95% CI of [0.28; 1.64]. This result is similar to the uncorrected Excess Relative Risk estimated from a Poisson regression model which was 0.74 per 100 mSv with a 95% CI of [0.23; 1.73] (Rage et al. 2015). Given that the corrected EHR estimate is

0.81 per 100 mSv with a 95% CI of [0.28; 1.75], it is concluded that no substantial change of the estimated EHR per 100 mSv is observed when accounting for dose uncertainty. The associated 95% CI is larger when accounting for dose uncertainty but does not include zero meaning that the positive association between lung cancer mortality and γ -ray exposure remains statistically significant.

In order to distinguish the impact on risk estimate of both classical measurement errors and left-censored or missing dose values, a hierarchical model was fitted accounting for measurement error with exposure sub-model M_3 but after replacing all left-censored and missing exposure data by zero. In other words, classical measurement errors were accounted for but the existence of left-censored or missing exposure data was neglected. The EHR of death by lung cancer due to occupational γ -ray exposure was then estimated to be 0.80 per 100 mSv (95% CI: [0.29; 1.70]). Thus, when only accounting for classical measurement error, again no substantial change in the estimated EHR per 100 mSv was observed. Finally, a hierarchical model was fitted accounting for the existence of left-censored and missing dose values but neglecting the existence of classical measurement errors. The EHR of death by lung cancer due to occupational γ -ray exposure was then estimated to be 0.80 per 100 mSv (95% CI: [0.28; 1.75]). Again, when only accounting for left-censored and missing exposure data, no substantial change of the EHR per 100 mSv was observed. Nevertheless, the associated 95% CI is slightly wider when this source of uncertainty is accounted for by the model, as compared to the 95% CI obtained when only accounting for classical measurement error. In all cases, the 95% CI of the EHR per 100 mSv did not include 0 and, consequently, the positive association between lung cancer mortality and γ -ray exposure remained statistically significant. Fig. 4 displays the prior and posterior densities of the risk coefficient (i.e., β) for these different models.

Sensitivity to the assumptions regarding the magnitude of the measurement error

In order to test the robustness of the results to the geometric standard deviations fixed for the lognormal measurement error components (see subsection on measurement sub-model), the full Bayesian hierarchical model including exposure sub-model M_3 was fitted after increasing the corresponding standard deviations by 50% and 100%. When assuming an increase of 50%, the EHR per 100 mSv remained positive and statistically significant with a posterior

median equal to 0.86 per 100 mSv and a 95% CI of [0.33; 1.84]. When assuming an increase of 100%, the estimated posterior median of the EHR was 0.90 per 100 mSv with a 95% CI of [0.34, 1.89]. As expected, the results are sensitive to the magnitude of the measurement error. They also show that, in cases where this parameter is under-estimated (resp. over-estimated), the risk of death by lung cancer may be under-estimated (resp. over-estimated) as well, as its estimation uncertainty.

Discussion

In this work, three Bayesian hierarchical models based on different exposure sub-models were developed, fitted and compared, to explicitly account for missing and left-censored γ -ray dose measurements prone to classical measurement error, when estimating the risk of death by lung cancer, in the post-55 sub-cohort of French uranium miners. Advantage was taken of the flexibility of hierarchical modelling to simultaneously describe several sources of exposure uncertainty, i.e., classical measurement errors, the deterministic censoring process due to the detection limit of the dosimeters, and missing data. In contrast to classical functional approaches such as SIMEX (Cook et al. 1994) or regression-calibration (Stefanski et al. 1985), where several consecutive steps are used to impute left-censored and missing exposure data and to estimate true exposure and unknown risk parameters, fitting these hierarchical models under the Bayesian paradigm allowed for a simultaneous estimation - through a coherent and valid inferential framework - of risk parameters, true doses, and assumed doses (in case of false zeros or missing data). This implies that the estimation of uncertainty of each unknown quantity - which may be large and/or far from a Gaussian distribution - is accounted for when estimating other unknown quantities that depend on it. In this work, for instance, the estimation of uncertainty of the true latent γ -ray doses $X_i(t)$ is accounted for when estimating the EHR of death by lung cancer. Sampling from the joint posterior distribution of the assumed dose values (i.e., $Z_i(t)$) for false zeros and missing γ -ray dose values only) and the true doses (i.e. $X_i(t)$) was carried out through the MCMC algorithm. This allowed to explicitly account for the associated uncertainty when computing the cumulative dose of each miner. At this point, it is also important to note that the proposed Bayesian hierarchical models allowed taking advantage of all information available through the strictly positive and true zero γ -ray dose values at a given period and/or in a given type of mine (i.e., open-pit, underground) to learn about all the unknown strictly positive and potentially left-censored γ -ray dose values in

the same period and/or type of mine. Finally, another advantage of using Bayesian statistics was the possibility to assign an informative prior distribution for unknown parameters that were only poorly informed by the data, in order to improve their estimation. In the present study, this was particularly useful for the estimation of the baseline hazard of death by lung cancer for uranium miners younger than 40 years old (i.e. parameter λ_1) for which poor information was available in the post-55 sub-cohort of French uranium miners.

In this paper, emphasis was placed on the problem of accounting for three specific sources of dose uncertainty when estimating the association between occupational exposure to low levels of γ -radiation and lung cancer mortality in the post-55 sub-cohort of French uranium miners. Missing and left-censored γ -ray dose values prone to unshared classical measurement error were modelled on an individual level, using an excess hazard ratio (EHR) survival sub-model. Given the modelling assumptions, no substantial impact of the considered sources of dose uncertainty on the risk of death by lung cancer due to cumulative γ -ray exposure was found. Recently, Hoffmann et al. showed, through a simulation study, that the impact of unshared classical measurement error (multiplicative and log-normally distributed) on an EHR survival sub-model was very small for a geometric variance of the measurement error equal to 0.1 (Hoffmann et al. 2018). Yet here, and according to the previous work by Allodji (2011), it was assumed that the geometric variance of the measurement error was always smaller than 0.06 for the whole period of γ -ray exposure, which might explain why measurement error had no substantial impact on risk estimates. Additionally, the small proportion (about 7%) of left-censored and missing γ -ray exposures in the post-55 sub-cohort of French uranium miners explained why replacing all left-censored and missing γ -ray exposures by zero had no significant impact on risk estimates either. A sensitivity analysis showed that the results obtained are robust to an increase of the detection limit of the dosimeters by 75%. The corrected risk coefficient of death by lung cancer was estimated to be 0.81 per 100 mSv with a 95% CI of [0.28; 1.75]. This confirms the robustness of the risk estimate obtained from a survival EHR which does not account for measurement error and where all left-censored and missing γ -ray dose values were replaced by zero (EHR of 0.78 per 100 mSv with a 95% CI of [0.28; 1.64]). Even if the 95% credible interval of the EHR is wider after accounting for exposure uncertainty, a statistically significant positive association remained between γ -ray exposure and the risk of death by lung cancer. It was also shown that the results obtained are robust to the different assumptions made to describe the temporal trend of the expected true γ -ray doses.

The robustness of the results could also have been tested with other assumptions on the expected true dose such as non-linear trends or temporal correlations. However, the estimated risk of death by lung cancer associated to γ -ray exposure cannot, for now, be compared to other risk estimates in comparable populations. Indeed, up to our knowledge, this risk has not been calculated in other cohorts of uranium miners. An analysis of the health risks associated to γ -ray exposure is planned in the Pooled Uranium Miners Analysis (PUMA) (Rage et al. 2020), which will allow a comparison with our results.

Interestingly, the Bayesian hierarchical model based on the exposure sub-model M_3 allowed estimating a statistically significant decrease of the true log-transformed γ -ray doses over time in underground and open-pit mines, and showed that this downward trend was stronger in underground mines than in open-pit ones. This decreasing trend was also observed in the German Uranium Miners cohort (Kreuzer et al. 2013). This trend could be due to intensive mining operations that may have led to lower uranium concentration and thus a reduced level of γ -ray exposure, and to changes in radiation protection practice like a reduction in exposure time of uranium miners.

In this study, since there were no validation data available to estimate the magnitude of measurement error, the measurement error was fixed according to the calendar period following the work by Allodji (2011). Nevertheless, as expected, the risk estimate of death by lung cancer was sensitive to this parameter showing that a careful assessment of this crucial parameter must be made to ensure the validity of the risk estimate. Here, the corrected risk estimate of death by lung cancer (0.81 per 100 mSv with a 95% CI of [0.28; 1.75]) must be considered with prudence, assuming that the geometric standard deviation is 0.245 between 1956 and 1985 and 0.16 between 1986 and 2007 when considering a multiplicative error structure.

This study did not account for the tobacco consumption of miners, although smoking is known to be the most important cause of lung cancer. Unfortunately, the smoking status is only available for about 4% of the miners in the post-55 sub-cohort of French uranium miners. This major lack of information makes it very hazardous to adjust for smoking status when estimating the risk of death by lung cancer due to γ -ray exposure among this cohort. Moreover, previous analyses on the impact of smoking in occupational cohort studies of uranium miners suggested that smoking was not a source of confounding in these studies (Richardson et al. 2014; Keil et al. 2015). Additionally, analyses on sub-cohorts for which the

smoking history of workers was available observed a significant association between radon exposure and lung cancer mortality for both smokers and for non-smokers with an estimated risk coefficient that tended to be higher for non-smokers than for smokers (Tomasek 2002; Tirmarche et al. 2012; Kreuzer et al. 2017). Finally, case-control studies nested in the French cohort of uranium miners (Leuraud et al. 2007) and in two other European cohorts of uranium miners (Leuraud et al. 2011) found that, when adjusting for smoking, the effect of radon exposure on lung cancer risk persisted and the adjustment did not substantially alter the estimated risk coefficient associated with radon exposure.

Radon was classified as a pulmonary carcinogen in humans by the International Agency for Research on Cancer in 1988 (Cancer 1988), and is considered as the second cause of death by lung cancer after tobacco consumption (Samet 1989; Birchall et al. 2005). Given that radon and γ -ray exposure measurements are highly correlated in the French cohort of uranium miners (Pearson correlation coefficient = 0.90) (Vacquier et al. 2011) and given that radon is not included in the hierarchical models used here, due to multi-collinearity issues, the statistically significant positive association found between γ -ray exposure and the risk of death by lung cancer must be interpreted with caution. Indeed, the results obtained here could reflect either a real specific association between γ -ray exposure and lung cancer mortality or, more probably, a spurious association due to radon which acts as a confounding factor in this relationship.

Because of its flexible and modular nature, the Bayesian hierarchical models described in this paper could be easily extended to account for missing and left-censored dose values or more generally exposure data, prone to more complex patterns of measurement error, for which a substantial impact on risk estimates may be suspected. This should be particularly the case for exposure uncertainty that is shared between and/or within individuals (i.e., shared for several years of exposure for an individual) (Hoffmann et al. 2018). The possibility to include additional information on uncertain parameters like the standard deviation of the measurement error or exposure sub-model parameters could also help reducing uncertainty on risk coefficient estimates. Finally, to better highlight the potential impact on risk estimates of replacing missing and left-censored dose values or exposure data by zero, it would be very interesting to apply the Bayesian hierarchical models used here on cohorts of occupationally exposed uranium workers affected by a very high proportion of missing and left-censored dose values or exposure data.

Conclusion

This paper highlights the flexibility and relevance of the Bayesian hierarchical approach to account for both missing and left-censored radiological exposure data that are prone to measurement error, when estimating radiation-related risks. Up to the authors' knowledge, this is the first time these three sources of uncertainty are dealt with simultaneously in radiation epidemiology. Regarding the specific problem of estimating the risk of death by lung cancer due to external γ -rays exposure among French uranium miners, the impact of these three sources of uncertainty on the risk estimate is found to be of marginal importance (given the modelling assumptions). The corrected EHR is 0.81 per 100 mSv (95% credible interval: [0.28; 1.75]). Interestingly, this paper shows that, even if the 95% credible interval of the corrected EHR is wider than the uncorrected one, a statistically significant positive association remains between γ -ray exposure and the risk of death by lung cancer, after accounting for dose uncertainty. This could reflect either a real specific association or, more probably, a spurious association due to radon which acts as a confounding factor in this relationship. Finally, because of its flexible and modular nature, the Bayesian hierarchical models described in this paper could be easily extended to account for higher proportions of missing and left-censored exposure data than in the post-55 sub-cohort of French uranium miners and more complex patterns of measurement error, for which a substantial impact on risk estimates may be suspected. This should be particularly the case for exposure uncertainty that is shared between and/or within individuals.

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Figure captions

Fig 1 Boxplot of annual doses (i.e., personal dose equivalents) from γ -ray exposure (in mSv) for the years 1956-2007 in the post-55 French sub-cohort of uranium miners. Non-exposed uranium miners were excluded

Fig 2 Directed acyclic graph for the full hierarchical model based on the exposure sub-model M_3 . Circles indicate unknown quantities and rectangles indicate observed variables or fixed parameters. Single arrows indicate oriented probabilistic links between two quantities and double arrows indicate oriented deterministic links between two quantities.

Fig 3 Expected log-transformed true γ -ray exposures in underground mines (i.e., $\log(\mu_{x,F}(t))$) and open-pit mines (i.e., $\log(\mu_{x,J}(t))$) over time, in the post-55 sub-cohort of French uranium miners. The circles and triangles represent the posterior medians of $\log(\mu_{x,J}(t))$ and $\log(\mu_{x,F}(t))$, respectively, and the segments indicate the 95% credible intervals. Solid lines show $\log(\mathbf{a}_J \cdot \mathbf{f}(t) + \mathbf{b}_J)$ and $\log(\mathbf{a}_F \cdot \mathbf{f}(t) + \mathbf{b}_F)$ that are estimated from the posterior medians of $\mathbf{a}_J, \mathbf{a}_F, \mathbf{b}_J$ and $\mathbf{b}_F$.

Fig 4 Posterior densities of the EHR per 100 mSv of death by lung cancer due to occupational γ -ray exposure in the post-55 sub-cohort of French uranium miners, depending on the sources of exposure uncertainty that were accounted for

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