



Liu, H., Wakeford, R., Riddell, A., O'Hagan, J., MacGregor, D., Agius, R., Wilson, C., Peace, M., & de Vocht, F. (2016). A review of job-exposure matrix methodology for application to workers exposed to radiation from internally deposited plutonium or other radioactive materials. *Journal of Radiological Protection*, 36(1), R1-R22. [R1]. <https://doi.org/10.1088/0952-4746/36/1/R1>

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A review of job-exposure matrix methodology for application to workers exposed to radiation from internally deposited plutonium or other radioactive materials

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Received 11 September 2015, revised 26 October 2015

Accepted for publication 19 November 2015

Published 10 February 2016



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Abstract

Any potential health effects of radiation emitted from radionuclides deposited in the bodies of workers exposed to radioactive materials can be directly investigated through epidemiological studies. However, estimates of radionuclide exposure and consequent tissue-specific doses, particularly for early workers for whom monitoring was relatively crude but exposures tended to be highest, can be uncertain, limiting the accuracy of risk estimates. We review the use of job-exposure matrices (JEMs) in peer-reviewed epidemiological and exposure assessment studies of nuclear industry workers exposed to radioactive materials as a method for addressing gaps in exposure data, and discuss methodology and comparability between studies. We identified nine studies of nuclear worker cohorts in France, Russia, the USA and the UK that had incorporated JEMs in their exposure assessments. All



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these JEMs were study or cohort-specific, and although broadly comparable methodologies were used in their construction, this is insufficient to enable the transfer of any one JEM to another study. Moreover there was often inadequate detail on whether, or how, JEMs were validated. JEMs have become more detailed and more quantitative, and this trend may eventually enable better comparison across, and the pooling of, studies. We conclude that JEMs have been shown to be a valuable exposure assessment methodology for imputation of missing exposure data for nuclear worker cohorts with data not missing at random. The next step forward for direct comparison or pooled analysis of complete cohorts would be the use of transparent and transferable methods.

Keywords: plutonium, exposure assessment, occupational exposure, epidemiology, job-exposure matrix, JEM, nuclear power

(Some figures may appear in colour only in the online journal)

1. Introduction

The potential radiotoxicity of the long-lived alpha-particle-emitting isotopes of plutonium was recognised soon after its discovery [1]. Plutonium-239, with a half-life ($t_{1/2}$) of 24 100 years, is normally produced by the neutron bombardment of uranium-238 in a nuclear reactor, and is usually the isotope of principal interest [2]. The longer the uranium fuel is kept in a reactor (i.e. the higher the fuel 'burnup') the greater the proportions of other plutonium isotopes produced. Plutonium exposure may occur to workers engaged in plutonium production, nuclear fuel reprocessing, decommissioning and clean-up operations [3, 4] or to the general public as a result of atmospheric testing of nuclear weapons, nuclear accidents, or discharges and waste disposal from nuclear facilities [5].

Alpha-particle radiation is the main risk posed by exposure to plutonium, although low-energy x-rays and gamma-rays are also emitted during alpha-particle decay, as are neutrons from spontaneous fission [6]. Plutonium-241 ($t_{1/2} = 14$ years) emits beta-particles but decays to americium-241 ($t_{1/2} = 433$ years) which is also an alpha-particle emitter and can produce significant doses of radiation [6]. Since the alpha-particles emitted by plutonium possess high energies but only travel short distances (approximately 50 μm in tissue, i.e. the typical length of one adult human liver cell), the greatest concern regarding health effects of exposure is the biological damage that may occur once plutonium has been taken into the body via inhalation, ingestion or puncture wounds [7]. In most exposure scenarios, alpha-particle radiation from sources external to the body does not penetrate the topmost dead layer of skin and hence generally poses little health risk [8]. Once plutonium radioisotopes are taken into the body they can be retained for decades [9, 10]. Primary retention sites are the liver and skeleton, with the lung being important for inhalation exposures, which is the primary route for most occupational exposures [9, 10]. The long physical and biological half-lives of plutonium mean that exposed tissues accumulate doses of alpha-particle radiation over many years even if exposure was of short duration.

Evidence for increased cancer and non-cancer risks from plutonium exposures has been reported for workers at the Mayak Production Association in the Russian Federation [11–14]. Mayak was used to produce plutonium for nuclear weapons and exposures, in the early years of operation, are known to be significantly higher than similar facilities elsewhere [13, 15]. In contrast to the findings from Russia, studies of plutonium workers in other countries have been inconclusive, which is likely the result of much lower tissue doses [16–22]. Remaining scientific uncertainty regarding the overall health effects of occupational exposure

to plutonium, particularly at lower levels, suggests that further epidemiological studies are important [23, 24]. It is clear that the reliability of these types of studies is directly related to the availability and accuracy of plutonium and other radionuclide exposure assessments for occupational intakes [23, 25]. Also of interest to epidemiological studies of plutonium workers are any doses due to occupational exposures to external sources of penetrating radiation (for plutonium workers, these are predominantly gamma radiation and neutrons), and other workplace exposures (e.g. asbestos), as such exposures can also affect health outcomes [4].

The absorbed dose of ionising radiation is defined as the energy deposited per unit mass, and has the SI unit of the *gray* (Gy), which is one joule per kilogram [26]. Some types of radiation, such as alpha-particles, are more densely ionising than others (e.g. gamma-rays) and more effective at causing biological damage at the cellular level [27]. This difference in effect is called the Relative Biological Effectiveness (RBE) and for the purposes of radiological protection the RBE is taken into account through the radiation weighting factor (w_R). Under the International Commission on Radiological Protection (ICRP) system, the absorbed dose (in *gray*) multiplied by w_R gives the equivalent dose for an organ/tissue which is expressed in *sieverts* (Sv) [26]. The w_R for gamma-rays is one, so one *gray* is equal to one *sievert*, while for densely ionising alpha-particles w_R is 20, so that one *gray* is equal to 20 Sv [26]. For doses from internally deposited radionuclides that are heterogeneously distributed among body tissues, the dose recorded for radiation protection purposes is often the effective dose, which is the sum of all the organ/tissue equivalent doses each weighted by the ICRP tissue weighting factor (w_T). The tissue weighting factor takes into account the radiosensitivity of the organ/tissue, mainly with respect to the risk of cancer induction but also including hereditary risks from gonadal doses [26]. The effective dose is also measured in *sieverts*. For epidemiological analyses the absorbed dose in *gray* is generally preferred because one of the purposes of epidemiological research is to determine the magnitude of any differences in health outcomes due to doses received from different types of radiation.

It is practically and technically straightforward to measure exposures to penetrating radiation and express it as a whole-body dose (at least for gamma-rays and x-rays, but not necessarily for neutrons) [28]. Exposure to external sources of penetrating radiation is usually measured directly using individual monitoring based on personal dosimeters such as film badges and thermo-luminescent dosimeters (TLDs), worn on the worker's outer clothing [26]. Because the radiation involved is penetrating, an easy simplifying assumption, for protection purposes, is that doses to all organs and tissues are the same (i.e. a whole-body dose), even though in practice some organs and tissues tend to be at least partially shielded by others, meaning doses to the shielded organs are actually lower. In epidemiological studies of nuclear workers with external exposures the doses used are, typically, annual whole-body doses, which can be summed to give the cumulative dose within any period of interest (used in, for example, [14, 21, 22]).

When the primary purpose of an epidemiological study is to investigate internal exposures, however, it is necessary to use organ/tissue-specific doses because internally deposited radionuclides often distribute heterogeneously within the body and doses tend to differ significantly by organ/tissue, hence it is the cumulative doses received by specific organs/tissues that are of interest.

Occupational doses from plutonium and other alpha/beta-particle-emitting radionuclides are mainly assessed indirectly using biological samples provided by workers considered to be potentially exposed to them. This is because the low penetration radiation they emit is difficult to detect directly when the source is located within the body, and the limit of detection for such *in vivo* monitoring can equate to a dose that substantially exceeds the annual limit. For plutonium, urine samples are generally used as the basis for most internal dose assessments,

as urine is relatively easy to collect in the required volumes, and plutonium continues to be excreted in urine long after intake has ceased [29]. Faecal sampling is principally used only for the assessment of acute exposures, because clearance through this route decreases rapidly following cessation of intake and also because there are more issues with sample collection [29]. Body tissues collected at autopsies have also been used to assess exposures within some populations (e.g. [21, 30, 31]).

As well as bioassay measurements (e.g. urinalysis), assessments of plutonium organ/tissue doses also rely on knowledge of the nature of the plutonium intake [29] and the way it is metabolised in the body. The absorption, distribution, retention, and excretion of plutonium depends on many factors including the initial chemical composition (material solubility affects absorption in the lung, gut and wound tissues), aerosol particle parameters (e.g. size, density) for inhalation exposures, organ/tissue residence times, and mode of exposure [10, 32–35]. Calculating intakes of, and organ/tissue-specific doses from, plutonium is therefore difficult and complex [29], and can be a labour-intensive and costly exercise [4]. Metabolic (biokinetic) models which relate urine concentrations to initial intake(s) and tissue burdens have changed over time as more information has become available [9, 10, 36, 37]. This improving knowledge of plutonium metabolism means that assessed intakes and doses, based on the same bioassay results, will change over time. This can lead to a situation in which epidemiological studies of plutonium workers are not directly comparable due to differences in dosimetry methodologies.

Dosimetry information that would provide quantitative estimates of exposures from plutonium and other radionuclides may also be unreliable, missing or unusable for other reasons. Examples of this include adventitious contamination of biological samples, lack of person specific data as a consequence of administrative decisions on the monitoring of individuals, or changes in analytical methods, detection thresholds, and recording practices over time. These problems exist among the world's most important cohorts for assessing plutonium workers' exposure risks [18, 31, 38, 39]. For example, Wing *et al* [18] observed that the majority of workers in the US Hanford Site cohort had no bioassay monitoring in most years of employment, and Khokhryakov *et al* [31] reported that only 32% of the Russian Mayak workers had at least one urine bioassay sample. Riddell *et al* [39] noted that, due to the high reporting limit associated with some early urine samples, the historical monitoring data available for several hundred early UK Sellafield workers cannot provide the accurate and unbiased exposure assessments needed for risk analyses.

Another issue is that the internal monitoring of workers that has been undertaken was to meet regulatory requirements and for operational protection purposes, rather than for epidemiological research purposes [40, 41]. Because of the conservative approach encouraged in the systems used for such purposes, recorded doses have tended to be systematically overestimated.

All these problems pose a challenge to obtaining accurate, reliable and unbiased doses—from internally deposited plutonium and other radionuclides—for use in studies of the potential risks of occupational exposures. The primary purpose of this paper is to conduct a substantial review of the job-exposure matrix (JEM) approach as an alternative method of evaluating internal exposures (from plutonium and other radionuclides), particularly for epidemiological studies of nuclear workers where quantitative dosimetry data based on urine monitoring for the cohort (or parts thereof) are unreliable, cannot be obtained at all, or are missing, for the reasons discussed above. The motivation for this review was in the first instance to inform a JEM assessment of exposures to plutonium for early workers at the Sellafield nuclear complex in Cumbria, north-west England, but the paucity of summary

information on this approach will make the review of relevance to most, if not all, nuclear worker cohorts.

2. Rationale for using the JEM approach

In general, the problem of missing doses will reduce the statistical power of epidemiological studies due to subjects with missing doses. This is a particularly significant issue because the ability of an epidemiological study to detect any adverse health effects is usually directly related to the size of the study population and this has to be large when potential risks are small [42]. Occupational exposures to radiation are typically low dose and low dose-rate and are therefore associated with small increases in risk [43, 44]. Consequently, epidemiological studies of plutonium workers are hampered by the lack of exposure assessment data of the required quality (e.g. [16, 19, 22]). This is reflected in the limited number of studies of nuclear workers that have specifically examined exposures from internally deposited plutonium and other radionuclides, especially in terms of organ/tissue-specific doses [4, 45].

It should be noted that the missing data problem is not restricted to analyses of plutonium workers, but in reality affects nearly all epidemiological cohort studies. In the statistical literature, methods of multiple imputation [46], full information maximum likelihood [47] and mean imputation [48] are used to impute missing data, either for data missing completely at random and/or missing at random [49]. The review of the problems leading to missing doses in the preceding section indicates that missing historical dose data are not missing at random. Moreover, if historical exposure data from a whole time period are missing the imputed doses following these statistical imputation methods are likely to be flawed. Both of these issues have important implications for epidemiological analyses of plutonium workers indicating that a different framework for imputing missing data is needed. This framework should enable the building of exposure estimation methods, based upon available information on determinants that model exposure across time periods and jobs, so that missing combinations can be imputed from overall trends. Within the occupational epidemiology literature, the most common approach to retrospective exposure assessment is to use occupation (job title) and industry as an exposure proxy [50–52].

In lieu of direct information, principal among those retrospective exposure estimation techniques are the job-exposure matrices (JEMs), exposures self-reported by study subjects, and exposures assessed by experts [50–52]. In occupational epidemiology, cohort and case-control studies have long used the JEM approach where occupations and/or industries represent one axis, exposure agents the other (many studies have a third axis representing time periods/work durations for assessment of time trends), and the cells of the matrix indicate the likely presence, intensity, frequency, and/or probability of exposure to a specific agent in a specific job [52–54]. The approach is based on the observation that study subjects' job histories within a company can serve as a basis for assigning exposures [52–54], assuming that people with the same job, in the same time period, get approximately the same exposure.

3. Methods

The PubMed and MEDLINE databases for the period 1 January 1980–31 May 2015 were searched to identify relevant studies of workers who are potentially exposed to radioactive materials. Various combinations of the following search terms were used: epidemiology, nuclear workers, health risk, mortality, cancer, radiation exposure, internal exposure, internal contaminations, plutonium, plutonium isotopes, radioactive materials, radionuclides, internal

emitters, alpha emitters, intakes, bioassay measurements, occupational doses, internal doses, and organ/tissue doses. References in identified papers were reviewed for additional sources. Only studies published in peer-reviewed journals were considered. Papers published in the English language, which examined the health risk of occupational exposures to radiation from internally deposited plutonium and other radionuclides and used JEM techniques as alternative methods of evaluating internal exposures in the absence of quantitative dosimetry data based on urine monitoring, were selected for this present review. Specific review of the selected studies is provided in the next section, followed by an overall discussion on the quality of these JEMs in radiation epidemiology in section 5.

4. Results

Nine studies of nuclear worker cohorts in France, Russia, the USA and the UK that had incorporated JEMs in their exposure assessments were selected and reviewed in depth. Table 1 summarises these studies: four assessed internal exposure to plutonium and other radionuclides [18, 55–57]; three assessed internal exposure to uranium [58–60]; one assessed internal exposure to thorium and its decay products [61]; one assessed internal exposure to tritium [62].

Specific reviews of these studies follow.

4.1. Studies of workers at the Oak Ridge site [55, 59, 60]

The study by Polednak and Frome 1981 [59] examined the mortality of a cohort of 18 869 white males who were employed between 1943 and 1947 at the Y-12 plant (a uranium conversion and enrichment plant) in Oak Ridge, operated by the Tennessee Eastman Corporation (TEC). The authors reported that uranium levels in the urine of over 1000 male and female chemical workers were determined at TEC in 1945. They however considered these data of limited value since a small percentage of workers were monitored, the criteria for selection of persons to be monitored were unknown, and measurable urinary uranium levels were mainly only suitable for the assessment of exposures to more soluble uranium compounds (workers at Y-12 were also exposed to less soluble compounds).

Therefore, the authors used original company records documenting codes and descriptions of departments and job titles, uranium air-sampling data, and other historical material and documents from TEC to reconstruct individual uranium exposure. Subgroups of workers were defined on the basis of departments and average levels of uranium dust where they worked: if a worker was ever employed in an alpha or beta department, he was assigned to that group; if not, he was then assigned to either the ‘electrical worker’ group or to the ‘other’ group, as appropriate.

In the statistical analyses, standardised mortality ratios were calculated by subgroup based on departments of employment. The authors considered air-sampling data useful in approximating the average exposure of a group of workers performing the same repetitive task or operation (referring to a publication by Eisenbud and Quigley [63]). In the statistical analyses, the authors further divided groups of workers who shared similar work activities into subgroups (e.g. the alpha chemistry only group, the beta chemical only group). This should have helped to address a common major concern when developing a JEM: that job titles do not provide substantive distinctions between tasks at a facility since job titles and area codes may represent information used for administrative tasks, rather than for research purposes [64].

The study by Checkoway et al 1985 [55] of workers at the US Department of Energy (DoE) sites in Oak Ridge employed JEM techniques to reconstruct individual dose from internally

Table 1. Summary of studies reviewed.

Reference	Country, site	Risk assessment type, study population	Exposure of interest	Data used in the JEM	Exposure unit used in statistical analyses	Whether or not JEM methods were validated
[59] Polednak and Frome (1981)	USA, Oak Ridge Y-12 plant, operated by the Tennessee Eastman Corporation (TEC).	Mortality among 18 869 white males who were employed by TEC between 1943 and 1947.	Uranium compounds.	Descriptions of job titles and departments. Uranium air-sampling data. Review of other historical material and documents.	Four general exposure categories based on department of employment. Subgroups of similar work activities.	Validity of the JEM method discussed. Evaluation of the JEM method not reported.
[55] Checkoway <i>et al</i> (1985)	USA, Oak Ridge National Laboratory (ORNL).	Mortality among 8375 white males who had worked at the ORNL between 1943 and 1972.	Plutonium and other radionuclides. External sources of radiation (primarily gamma rays).	Descriptions of job titles. Descriptions of departments and associated dates of employment. Review of materials used. Review of health physics and industrial hygiene monitoring data.	12 exposure categories based on job categories by duration of employment.	Validity of the JEM method briefly discussed. Evaluation of the JEM method not reported.
[60] Dupree <i>et al</i> (1995)	USA, four uranium processing or fabrication operations: two operations at the Y-12 plant in Oak Ridge, operated by TEC (also see Polednak and Frome 1981 [59]); one operation at two different sites in Missouri; one operation in Ohio.	Lung cancer. Eligible cases were employed at any of the four facilities and died before 1 January 1983. Altogether 787 lung cancer cases, matched with one control.	Uranium compounds.	Time-weighted job summaries of uranium dust exposure had been made for jobs in specific areas at specific points in time during facility operation.	Individual annual lung doses (expressed in Gy) calculated for each year of employment.	Possible dose misclassification mentioned, but no discussion on its cause(s) and extent.

(Continued)

Table 1. (Continued)

Reference	Country, site	Risk assessment type, study population	Exposure of interest	Data used in the JEM	Exposure unit used in statistical analyses	Whether or not JEM methods were validated
[61] Liu <i>et al</i> (1992)	USA, a thorium-processing plant.	Mortality among 3119 male and 677 female workers employed at the plant between 1915 and 1973.	Thorium and its decay products.	Job classification based on duration of employment and the daily estimated exposures of 84 male employees to thorium and thoron in 1952.	Three exposure categories based on job categories and duration of employment.	Evaluation of the JEM method not reported.
[56] Rooney <i>et al</i> (1993)	UK, employees of the United Kingdom Atomic Energy Authority (UKAEA).	Prostatic cancer. 136 cases diagnosed between 1946 and 1986, and 404 matched controls.	Plutonium and other radionuclides. Exposure to other hazards (metals, chemicals, physical agents, and other types of radiations).	Review of work areas and associated time period (work duration) and work activity. 125 buildings or work areas identified; each was assigned a level of potential exposure, for each of the 15 radionuclides identified.	Four levels of potential exposure to each of the 15 radionuclides identified.	Validity of the JEM method briefly discussed. Evaluation of the JEM method not reported.
[18] Wing <i>et al</i> (2004)	USA, Hanford site.	Mortality among 26389 workers with periods of employment in jobs with potential for plutonium exposure between 1944 and 1978.	Plutonium. External radiation exposure.	Classifying plutonium exposure potential on the basis of job titles, work areas and department codes (where particular activities and processes were carried out), dates of hire, termination, and job changes.	Three exposure categories of potential for exposure to plutonium.	Ability of the JEM to identify a group of workers with definite contamination was evaluated using recorded dosimetry data, but results were not presented or discussed.

(Continued)

Table 1. (Continued)

Reference	Country, site	Risk assessment type, study population	Exposure of interest	Data used in the JEM	Exposure unit used in statistical analyses	Whether or not JEM methods were validated
[57] Shilnikova <i>et al</i> (2003) [31] Khokhryakov <i>et al</i> (2013)	Russian Federation, Mayak Production Association (Mayak PA).	A cohort of over 22 000 workers between 1948 and 1982.	Plutonium. External radiation exposure (primarily gamma radiation).	Review of occupational history data, including work locations, starting dates, the distribution of measured plutonium body burdens, and expert knowledge of working conditions over time within the different facilities of the Mayak PA.	Six categorical surrogate Pu indices not available.	Published validation data dedicated to the development and implementation of the surrogate Pu indices not available. Published literature of the Mayak PA workers lacks reporting of sensitivity analyses comparing results of workers with bioassay results to results of workers with surrogate Pu indices.
[62] Hamra <i>et al</i> (2008)	USA, Savannah River Site (SRS).	The JEM included 18 883 SRS workers who met the entry criteria for inclusion in the study cohort for the period 1951–99.	Tritium.	Information on dates of employment and job title changes. Data on the 'health physics area', a system for classifying workers based on location and similarity of procedure. Quantitative dosimetry data.	Imputed tritium dose values for 53 378 (19%) employment-years for which tritium-dose information was unknown (missing).	Imputed dose values validated using recorded dosimetry data. Results presented and discussed.

(Continued)

Table 1. (Continued)

Reference	Country, site	Risk assessment type, study population	Exposure of interest	Data used in the JEM	Exposure unit used in statistical analyses	Whether or not JEM methods were validated
[58] Guseva Canu <i>et al</i> (2009)	France, the AREVA NC facility at Pierrelatte.	Covering the period between 1960 and 2006.	Occupational exposure to uranium-bearing and other chemical compounds.	Descriptions of job titles, job activities, and period of employment.	Two four-level scales were used to describe the potential exposure frequency (never, rarely, occasionally and frequently) and magnitude (material quantity—none, negligible, moderate and significant). The final 'frequency and quantity' scores used were the arithmetic means of the values obtained for a specific job-period pair as determined according to the stated statistical criteria.	Sensitivities analyses conducted. Results presented and discussed.

deposited plutonium and other radionuclides. This retrospective cohort study examined the deaths from all causes among 8375 white male workers who had worked at the Oak Ridge National Laboratory for at least 30 d at any time from 1 January 1943 to 31 December 1972. The bioassay programme only commenced in 1951 and much of the information (i.e. data from 1951 to 1972), needed to calculate internal doses, had not been computerised. Consequently a simple approach to investigating potential internal exposure effects was taken.

The authors obtained data on subjects' employment (jobs, departments and associated dates of employment) from employment records. The several hundred distinct job and department classifications found were then grouped into 11 broad job categories considered to be relatively similar with respect to job duties and potential for exposure to radiological and non-radiological substances. These job categories were based on reviews of job descriptions, materials used and, where data permitted, on health physics and occupational health monitoring data.

Standardised rate ratios for all cancer sites combined were computed according to duration of employment for each of the 11 job categories, plus an 'Unknown' category containing workers whose job history information was insufficient or unavailable. The epidemiological analysis then looked for any trends between length of employment in a particular job category and health outcomes. The authors reported that assignments of the 11 job categories were assisted by knowledgeable plant personnel; they did not provide any other discussion related to the validation of the JEM method.

The study by Dupree et al 1995 [60] also linked area uranium in air monitoring to work locations for a case-control study of lung cancer mortality among uranium workers employed in four uranium processing or fabrication operations in Missouri, Ohio and Tennessee in the USA. Two of these operations were located at the Y-12 plant in Oak Ridge (also see [59]). Different methodologies were used to estimate annual radiation lung doses from deposited uranium for each study member from the four operations (altogether 787 lung cancer cases were identified from death certificates; each case was matched with one control). Of relevance here is the JEM methodology used for uranium exposure assessment: time-weighted job summaries of uranium dust exposure had been made for jobs in specific areas at specific points in time during facility operation. An employee's total work experience was divided into periods, which were linked to appropriate average uranium dust concentrations. These exposure concentrations were multiplied by days worked and the annual integrated activity in the lung was calculated. This activity was then converted to a dose using the appropriate S-factor developed by Dunning *et al* [65]. Thus, the statistical analyses were based on individual annual lung doses (expressed in Gy) calculated for each year of employment.

The authors explicitly listed possible dose misclassification as a shortcoming of the study. However, they did not discuss the cause(s) of dose misclassification and the extent of such misclassification.

4.2. *The Liu et al 1992 study of thorium-processing workers [61]*

Liu et al [61] studied the mortality of workers employed in a US thorium-processing plant between 1915 and 1973. The study was limited to 3119 male and 677 female workers whose social security numbers and year of birth were known or matched. Information on work conditions and exposure to radioactivity at the plant was provided by an unpublished report of an industrial hygiene survey conducted by Klevin and Fresco in 1952 [66]. However, no individual doses were available for the study population. Therefore, job classification and duration of employment were used to provide information relevant to thorium exposure. The jobs were classified into three exposure groups, 'Group 1' having the highest thorium exposure and

'Group 3' having the lowest thorium exposure. The exposure group classification was based on daily estimated exposures of 84 male employees to thorium and thoron in 1952 calculated from the Klevin and Fresco data [66] by Stehney *et al* [67].

In the statistical analyses, the authors used the Poisson regression to describe the joint effects of exposure factors on lung cancer mortality; job classification and duration of employment were two of such factors in the Poisson regression analysis. The authors provided no information which would indicate whether and/or how they evaluated the validity of their exposure group classifications, although the classifications being based on recorded dosimetry data (albeit only for 84 workers who were all male and for 1952 only) would indicate a certain level of validity.

4.3. The Rooney *et al* 1993 study of UKAEA employees [56]

The JEM developed by Rooney *et al* [56] was constructed for a case-control study investigating prostatic cancer risk among employees of the United Kingdom Atomic Energy Authority (UKAEA). The study subjects were 136 cases diagnosed between 1946 and 1986 and 404 matched controls. It should be noted that, dose records for internal exposures from plutonium and other radionuclides has only been legally required since 1 January 1986 in the UK [68] and as a result monitoring data sometimes is not—or is only sporadically—available before that time for some sites. The authors observed that, although some employees of UKAEA had been investigated for possible internal contamination since the late 1940s, not all of the subjects identified for the study had useful monitoring information.

Based on a list of 125 buildings or work areas where exposure to any of the 15 specific radionuclides might have occurred, and with the aid of health physicists and other experienced UKAEA staff, a JEM was constructed. Each of these buildings or work areas was assigned an exposure category, using one of four levels of potential exposure (none, possible, probable but relatively low level, probable and relatively high level), for each radionuclide. Each subject's work and exposure history was reviewed by health physicists with detailed knowledge of the UKAEA's activities and radiation protection practices over time. Health physicists recorded whether the subject had ever worked in each of the 125 workplaces and, if so, the calendar years and type of work done. Individual exposure to, and dose from, internally deposited radionuclides was reconstructed on the basis of workplace, associated work duration (time period) and work activity.

Relative risks for prostatic cancer in relation to levels of exposure to radionuclides and other possible hazards were estimated. The authors reported that (1) assignment of exposure categories was aided by health physicists and other experienced UKAEA staff, and (2) classifications of the subjects were made without knowing who was a case or a control; they provided no additional information on their procedure of validating the JEM.

4.4. The Wing *et al* 2004 study of Hanford Site workers [18]

This was a cohort study to evaluate the risks of cancer and non-cancer mortality among plutonium workers at the US DoE Hanford Site. Wing *et al* [18] concluded that it was practically impossible to derive internal doses for the majority of workers in the Hanford cohort due to the paucity of urinalysis monitoring data, high urinalysis detection limits, and lack of information on chemical and physical properties of contaminant materials. Consequently, the authors constructed a JEM to classify plutonium exposure potential on the basis of job title, work area and time period.

Hanford employment history files for 1944–1989 were reviewed to establish logical and consistent dates of hire, termination, and job changes. An occupational hygienist constructed job title categories to use when assessing potential for plutonium exposure. Work area/process categories were also designed for particular activities and processes. Using these data, a JEM was created with three dimensions: job title, area/process (reactor, separations, research and development, other) and time period (1944–1967 and 1968–1989). Based on historical information about Hanford processes and health physics monitoring practices, the authors populated each cell of the matrix using three exposure categories of potential for exposure to plutonium (minimal, non-routine or limited, routine).

The authors reported that they had used several hundred workers with a confirmed systemic deposition of plutonium to evaluate the ability of the JEM to identify a group of workers with definite contamination. They however, did not present or discuss the results of their evaluation of the JEM.

4.5. Studies of plutonium workers at the Mayak Production Association in the Russian Federation

The Mayak Production Association (Mayak PA) worker cohort is one of the world's most important cohorts for assessing plutonium workers' exposure risk. Nearly all of the epidemiological studies of plutonium workers at the Mayak PA have included both external dose and internal dose from plutonium, where they could be reconstructed, for the cohort of over 22 000 workers [31]. As noted earlier, in the Mayak Worker Dosimetry System 2008 (MWDS-2008) used in recent epidemiological analyses (e.g. [13, 14, 69]), only 32% of the cohort had at least one urine bioassay sample [31].

Of interest here is the 'categorical surrogate index of plutonium exposure' [57] that has been developed and implemented to rank exposures for those Mayak workers who did not have any plutonium monitoring information (i.e. bioassay results) that would provide quantitative exposure (dose) estimates. The surrogate Pu index was developed on the basis of occupational history data, including work locations, starting dates, the distribution of measured plutonium body burdens and expert knowledge of working conditions over time within the different facilities of the Mayak PA [57]. This suggests that the method of defining a surrogate Pu index for an individual worker is essentially analogous to that of the JEM approach [18, 55, 56, 59–61]. Six surrogate Pu indices were defined indicating the relative (increasing) assessed level of plutonium contamination within worker groups over time [57].

It should be noted that this surrogate Pu index was only developed to permit analyses of external dose risks within the full Mayak worker cohort, which includes both plutonium and non-plutonium workers, and has not been used to investigate plutonium exposure risks *per se*. Hence, some recent epidemiological studies of the Mayak workers included this surrogate Pu index and discussed how it was used in their analyses (e.g. [70, 71]); others did not include it (e.g. [13, 14, 72], or did not explicitly say whether or not they included it (e.g. [69]). Analysis of the literature reveals that there are no published validation data dedicated to the development and implementation of the surrogate Pu index. Furthermore, the published literature lacks reporting of sensitivity analyses comparing results of workers with bioassay results to results of workers with surrogate Pu indices. Therefore, it is hard to assess the validity of the surrogate Pu index. Shilnikova *et al* 2003 [57] discussed that (1) mean body burden and lung dose estimates for monitored workers increased with increasing levels of the surrogate measure; and (2) workers thought to have been at risk of exposure to the highest levels of plutonium were more likely to be selected for monitoring at Mayak PA. On such a basis, the categorical

surrogate Pu index may be considered more appropriate than the mean plutonium body burden (dose) for monitored workers as an unbiased representative value for all workers [57].

4.6. *The tritium JEM for employees at the Savannah River Site [62]*

Hamra *et al* 2008 [62] combined the principles of JEM development with quantitative measures of recorded annual whole-body dose to estimate personal tritium doses, for Savannah River Site (SRS), a US nuclear fuel facility, employees without a recorded tritium dose, using regression modelling. The JEM included 18 883 SRS workers who met the entry criteria for inclusion in the study cohort for the period 1951–1999. Information about these workers' dates of employment and job-title changes was gathered. Thirty-four major occupational groups were defined based on job titles. 'Employment-years' were created on the basis of such information: the term 'employment-year' was used to describe the unit of observation contributed by a person each year he/she was employed at SRS.

The 18 883 workers in the study cohort contributed a total of 277 735 employment-year records. Each of these employment-years was matched with an appropriate 'health physics area' (a health physics area represented a single work location or a number of work locations which took part in similar processes). Each of these employment-years was also matched with dosimetry information derived from historical dosimetry logbooks. Recorded tritium doses were available for 224 357 (81%) of the total employment-years of the study cohort. Thus, the JEM was to impute a value for each of the remaining 53 378 (19%) employment-years for which tritium-dose information was unknown (missing).

This was done as follows: the proportion of a worker's annual whole-body dose (AWBD) due to intake of tritium was estimated by fitting a linear regression model in which the dependent variable was the annual tritium dose and the independent variable was the annual whole-body external dose. The model was stratified by occupational group, health physics area and calendar year, thereby allowing for different estimates of the fraction of AWBD due to tritium within each stratum defined by these factors. In addition, stratification by categories of AWBD was employed to account for potential differences in the relationship between tritium and AWBD within subgroups defined by occupation, area and calendar year.

The authors described their procedures for evaluating the JEM method and reported the evaluation results. Most of the estimated tritium values were well matched with the observed tritium dose. However, the model over-predicted lower values and under-predicted higher values. The tritium dose estimated by this JEM [62] was used in a subsequent epidemiological study [75] to examine the association between tritium exposure and leukaemia mortality in the SRS worker cohort.

4.7. *The JEM for the main uranium conversion plant in France [58]*

The JEM approach was employed to assess occupational exposure to uranium-bearing and other chemical compounds used at the AREVA NC facility at Pierrelatte (the main uranium conversion plant in France) [58]. First, 73 job titles were identified from company records. Each job title grouped together employees involved in the same activities within a department or facility. For each job title, any significant change in the potential for exposure over time was assessed. Changes in strategy, processes, techniques, raw materials and/or products used, as well as any administrative or ergonomic reorganisation of jobs, were considered and specific exposure periods were determined. Altogether 232 'job-period pairs', covering the period between 1960 and 2006, were created.

The potential exposure within each of the job-period pairs was then assessed, with the help of active and retired employees, on the basis of a semi-quantitative estimation of two exposure indicators for each job-period pair, frequency of exposure to a material and the quantity of material that the workers handled. Two four-level scales were used to describe the potential exposure frequency (never, rarely, occasionally and frequently) and magnitude (material quantity - none, negligible, moderate and significant). The final 'frequency and quantity' scores used were the arithmetic means of the values obtained for a specific job-period pair as determined according to the stated statistical criteria.

Finally, exposure results obtained by the JEM were validated, by experts within the facility, in light of the changes in each job over time and in relation to all the different jobs: this procedure indicated that the JEM was satisfactory in terms of internal and external consistency. For further validation purposes, exposure results were also compared with results found in the medical records of a random representative sample of workers (1% of the worker population). This validation procedure showed very good agreement (kappa (κ) coefficient = 0.85 [73]). Standard indicator statistics, such as sensitivity and specificity, were calculated to allow overall appraisal of JEM validity [74]. This validation procedure indicated good matrix performance, with the observed values close to 1.

4.8. Other studies

The German SAG/SDAG Wismut uranium miners cohort. The JEM approach has also been used to estimate radiation exposure (i.e. to radon and its decay products, external gamma radiation, and long-lived radionuclides) [76] and dust, silica and arsenic exposures [77] for the German SAG/SDAG Wismut uranium miners cohort. Technical papers on these two JEMs have been published in German [78–80].

The JEM for the Rocky Flats Plant worker cohort [28]. For the purpose of investigating lung cancer mortality in the worker cohort (~18000 individuals) employed at the US DoE Rocky Flats Plant from 1951 to 1989, Rutenber *et al* 2001 [28] constructed a JEM based on expert judgement and quantitative data and used it to (1) correct the systematic underestimation in neutron doses for workers for the years 1952 to 1966; and (2) impute doses from external penetrating radiation and chemical exposures, for workers for whom such data were missing. The authors provided no information to confirm that this JEM had also been used to evaluate occupational internal exposures to plutonium and other radionuclides. Of relevance here are the techniques for using the JEM to impute individual exposure (dose) which are unique in the literature (though the techniques used to build the JEM were similar to others reviewed in this paper).

The JEM, combined with the neutron dose data, was used to identify all buildings with potential neutron exposures and to compute neutron doses for workers in these buildings who did not have separate neutron doses recorded, for the years 1952 to 1966. The JEM was also used, along with all available plutonium urinalysis results and external dosimetry, to create a flat-file database for the entire cohort that included a record for each year a worker was employed and for that year radiation dose and chemical exposure data, or a flag indicating missing data. For external radiation doses that were missing for a period of less than 5 years, the authors implemented the 'nearby' imputation algorithm [40] and for longer periods (i.e. 5 or more years), imputation was based on the geometric mean exposure of all workers who had the same combination of work year, building, job and organisation. The approach to imputing missing chemical exposures was similar to the one used for external radiation doses. The authors did not report how the imputed values were validated; this JEM was used to estimate chemical exposures in the analysis by Brown *et al* [81].

5. Discussion

The JEMs reviewed in this paper have typically been constructed in the absence of sufficient quantitative data. The JEM techniques reviewed are used to deal with missing historical exposure data that are not missing at random [49]. They are based upon available information on determinants that model exposure across time periods, jobs and work locations (activities) so that missing combinations can be imputed from overall trends. This approach is generally considered better than the generalised standard methods of imputation for dealing with data missing completely at random and missing at random [49].

These JEMs have typically constructed the job dimension of the matrix on the basis of detailed information on employment and job history, including: job title, job duty and work area, plus one extra axis with consistent dates of hire and termination, and dates of job title, job duty and work area changes. Such detailed information was then typically used to assign values for the exposure dimension of the job-exposure matrix based on expert knowledge of where and when an exposure was likely to occur and/or on existing exposure monitoring data.

This present review reveals that the overall trend in the development and use of JEMs in nuclear industry studies has been toward increased complexity and sophistication in the detail of the qualitative information on subjects' employment, occupation (job title and job duty) and work area/process (activities and materials used at the workplace), and also the techniques of deciding the levels of potential exposure over time. For example, earlier studies (i.e. [55, 56, 59, 61]) tended to use the JEM to derive levels of potential exposure, which were then directly used to stratify the risk assessment analyses. The later studies either combined task- and time-dependent weighting factors with duration of employment to derive exposure indices to be used in the risk assessment [18, 57, 58] or combined known dosimetry data to impute exposure dose values to be used in the risk assessment [60, 62].

The JEMs reviewed are, by their nature, study-specific or cohort-specific JEMs. In comparison, 'generic' JEMs have been developed to describe exposures across the range of jobs and industries that might be relevant to the general population [82–84]. Validation studies have indicated that generic JEMs have relatively poor sensitivity [85–87] and fail to account for heterogeneity in exposure levels within jobs [88]. A significant advantage of these specific JEMs is that exposures are assigned to a very detailed list of jobs identified within the study or cohort in question, therefore leading to improved sensitivity [52, 85, 89]. A remaining limitation is that even specific JEMs are unable to fully account for variability in exposures within a job—whether across different plants or departments or in the same area between different individuals with varying degrees of interaction with the agent in question [52]. Task-exposure matrices (TEMs) have been developed to address this (e.g. [90]), but the detailed information required to build them is hardly ever available, especially not retrospectively. A further limitation of their study-specific development is that they cannot be used for any other cohort, thus making direct comparisons of results across studies difficult.

In general, the JEM approach is based on the observation that study subjects' job histories within a company can usually serve as the basis for assigning exposures [52–54]). The majority of the studies [18, 55–57, 59–61] provided insufficient information or discussion as to how the JEMs used were validated. It is understandably difficult to validate JEMs because, by definition, they are developed for parts of the study where exposure data are missing (so there are often no data available to validate against). These JEMs were constructed and used on the basis of the assumption that workers undertaking similar job tasks at similar work areas/processes over the same period of time would have received the same or similar level of exposures from sources of ionising radiation. Accordingly, assessment of exposure levels was based upon the similarity of exposures in the industrial process combined with expert

knowledge and judgement (e.g. from occupational health and safety personnel, as well as the workers under study). Given that comparisons of groups of workers involved in the same work often show similar urinary excretion of radionuclides over an extended period [43], the validity of a JEM approach based upon this assumption has some support. In other industries, some validation has been attempted by, for example, setting aside part of the data prior to JEM development and then using the JEM to estimate the withheld data [91].

Two of the studies [58, 62] provided sufficient information on their procedures for validating the JEM and the evaluation results were reported and discussed. The evaluation results indicate that the JEM method generates acceptable estimates of exposure. The validation procedures reported in these two papers provide valuable insights for the development of future JEMs.

Some of the JEMs were built upon purely qualitative information [18, 55, 56, 58]; others were a mix of qualitative and quantitative data [57, 59–62]. When quantitative dosimetry data are not available at all, qualitative JEMs become essential as they are built using only experts' knowledge and experience. Such an approach is, however, difficult to validate as it does depend on the subjective judgement of experts [92] and therefore it cannot provide the objective estimates that can be achieved by a quantitative approach. JEMs built upon a mix of qualitative and quantitative data (the 'hybrid method' [62]) seem desirable since they combine the best aspects and mitigate the problems, of each approach.

Two examples of the hybrid method were the studies by Dupree *et al* 1995 [60] and Hamra *et al* 2008 [62] (also see [28]). These two studies contained detailed information on work history, but this was not used to assign the exposure level in terms of exposure categories or exposure indices, as was typically used in the other JEMs reviewed in this paper. Instead, detailed qualitative information was combined, with area uranium in air monitoring results in Dupree *et al* [60] and with recorded dosimetry data in Hamra *et al* [62], to impute quantitative dose values. Dupree *et al* [60] identified possible dose misclassification as an issue; and organ/tissue-specific doses from tritium exposure [62], which distributes relatively homogeneously throughout body tissues, are comparatively simple to calculate given adequate urinalysis results [4]. However, the techniques [60, 62] used are promising for future research in this area. The hybrid method employed by Hamra *et al* [62], using a JEM in conjunction with known quantitative dose data and regression modelling, has been successfully applied in epidemiological studies in various industries; including, for example, the rubber industry [93]. One remaining methodological concern with the hybrid method is that it is difficult to weight the input from each type of information (qualitative, quantitative and expert judgement) if they do not agree. Nonetheless, a transparent hybrid JEM should be adaptable to, or facilitate benchmarking of, exposure data for other cohorts, thereby enabling direct comparison or even pooling of different nuclear workers' cohorts and allow whole cohorts, rather than just those with complete monitoring data, to be included.

6. Conclusions

With respect to epidemiological analyses, there are limitations in occupational radiation monitoring data, particularly for internally deposited radionuclides, such as plutonium, in the early years of operation of the nuclear industry. A methodology to better estimate levels of exposure for the purposes of epidemiological studies is required. One such approach is the job-exposure matrix and studies that have used this JEM approach have been reviewed here. The JEM approach becomes essential when measurement data are missing, limited or unreliable. Previous validation results suggest that the JEM method can generate acceptable

estimates of exposure. It is important that future JEMs in radiation epidemiology use a systematic approach to validating the JEM techniques employed, and they should also report on this validation approach and the results of it in any description of the JEM analysis or its results.

Acknowledgments

This paper is independent research commissioned and funded by the Department of Health Policy Research Programme (091/0204). The views expressed in this publication are those of the authors and not necessarily those of the Department of Health (England).

A competing financial interests declaration

The authors declare they have no actual or potential competing financial interests. RW conducts some paid consultancy for industry, including the nuclear industry, but has received no payment from industry in respect of this paper.

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