A Bayesian analysis of plutonium exposures in Sellafield workers

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A Bayesian analysis of plutonium exposures in Sellafield workers

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Abstract

The joint Russian (Mayak Production Association) and British (Sellafield) plutonium worker epidemiological analysis, undertaken as part of the European Union Framework Programme 7 (FP7) SOLO project, aims to investigate potential associations between cancer incidence and occupational exposures to plutonium using estimates of organ/tissue doses. The dose reconstruction protocol derived for the study makes best use of the most recent biokinetic models derived by the International Commission on Radiological Protection (ICRP) including a recent update to the human respiratory tract model (HRTM). This protocol was used to derive the final point estimates of absorbed doses for the study. Although uncertainties on the dose estimates were not included in the final epidemiological analysis, a separate Bayesian analysis has been performed for each of the 11808 Sellafield plutonium workers included in the study in order to assess: A. The reliability of the point estimates provided to the epidemiologists and B. The magnitude of the uncertainty on dose estimates. This analysis, which accounts for uncertainties in biokinetic model parameters, intakes and measurement uncertainties, is described in the present paper. The results show that there is excellent agreement between the point estimates of dose and posterior mean values of dose. However, it is also evident that there are significant uncertainties associated with these dose estimates; the geometric range of the 97.5%:2.5% posterior values are a factor of 100 for lung dose, 30 for doses to liver and red bone marrow, and 40 for intakes: these uncertainties are not reflected in estimates of risk when point doses are used to assess them. It is also shown that better estimates of certain key HRTM absorption parameters could significantly reduce the uncertainties on lung dose in future studies.

Keywords: plutonium dosimetry, epidemiology, uncertainties on doses

(Some figures may appear in colour only in the online journal)
Radiation doses resulting from internal exposures are often delivered at a low rate and over a protracted time (i.e. low dose and low dose rate). In addition, these doses often arise from high linear energy transfer (LET) alpha particle radiation. In contrast, the risk estimates that underpin existing systems of radiological protection, including those for internal emitters, predominantly rely on studies of high acute exposures to low-LET external radiation. The principal source of these estimates is follow up studies of the survivors of the atomic bombings of Hiroshima and Nagasaki. Consequently, direct estimates of cancer risks from radionuclides that have entered the body are desirable to verify the extrapolation of risks from external to internal exposure. For this purpose, the joint analysis of the Russian Mayak worker cohort (MWC) and British Sellafield worker cohort (SWC), undertaken within the European Union framework programme 7 (FP7) SOLO project (SOLO 2015), aims to derive best estimates of cancer risk associated with occupational internal exposures to plutonium; in particular, cancers of the lung and liver and also leukaemia. This paper is concerned with the estimation of doses and associated uncertainties, resulting from internal exposure to plutonium for the MWC and SWC.

The SOLO dosimetry reconstruction protocol, which describes the methodology to be employed to estimate plutonium intakes and absorbed tissues doses from urine bioassay for the study, makes best use of the most recent models developed by ICRP and others for internal dose reconstruction (Birchall et al 2013); including the plutonium systemic model described by Leggett et al (2005) and recent revisions to the human respiratory tract model (HRTM). Both have been adopted by ICRP in its forthcoming publication on occupational intakes of radionuclides (ICRP 2015) to calculate revised dose coefficients for workers. The revised HRTM includes updates to the mechanism of particle transport clearance from the thoracic airways. Perhaps the most significant revision is to the alveolar-interstitial (AI) region. Data obtained since the derivation of the HRTM strongly suggest that particle transport from the AI region is significantly slower than described in the HRTM (Kuempel et al 2002, Gregoratto et al 2010). From these data, Gregoratto et al (2010) derived a model that can be incorporated into the structure of the existing HRTM (figure 1). The model replaces the compartments AI1–AI3 in the original ICRP Publication 66 HRTM (ICRP 1994a) with two compartments: one representing the alveolar region (ALV) and one the interstitial tissue (INT); all deposition in the AI region is assumed to occur in ALV. The proposed change assumes longer retention in the AI region and thus higher doses to this region, particularly from insoluble forms of plutonium. The effect of the revised structure on estimates of lung doses from plutonium has been investigated by Birchall et al (2010) and Puncher et al (2011).

The absorbed tissue doses for Mayak and Sellafield workers in SOLO were provided as point estimates (i.e. single estimates without uncertainties—Birchall et al 2013, Riddell et al 2015). However, a Bayesian approach was adopted where uncertainties on model parameter values and intakes were first derived as prior probability distributions (Riddell et al 2015). The point estimates of intake and doses for each worker were then obtained as follows:

1. The biokinetic model was populated with the mean values of the prior distributions derived for all model parameters.
2. A Bayesian posterior distribution of intake was calculated using an assumed prior distribution on intake and the model parameter values (still fixed at their prior means). The best estimate of intake was taken as the mean of the posterior distribution; this was then used to calculate absorbed tissue doses (Riddell et al 2015).
This approach is superior to the traditional maximum likelihood method (MLM) applied in internal dose reconstruction (Riddell and Britcher 1994) in that it takes some account of prior knowledge of the intake in the estimation of intake and dose: this superiority is evident when all the bioassay results for an individual are censored by the limit of detection (LOD) i.e. ‘less than LOD’ values or ‘non-detects’, as this approach provides unbiased estimates of intake and dose, which the MLM cannot (Riddell et al 2000). Note that ‘unbiased’ in this context is only with respect to the treatment of censored data and is conditioned on the assumption that the biokinetic, dosimetric and other modelling assumptions in the dose reconstruction protocol give unbiased estimates of intakes and dose from urine bioassay; this is unlikely to be the case in reality. As a significant percentage of both these worker cohorts are made up of individuals with all less than LOD bioassay data, this is a major aid to providing best estimates of doses needed for epidemiological analyses. However, as with the MLM, the uncertainty associated with dose estimates due to uncertainties on model parameters is not assessed using this approach and only single point estimates of dose are derived. Consequently, no account for the effect of the variance in dose estimates on risk estimates can be made in the subsequent epidemiological analyses, because uncertainties on doses are not completely assessed or propagated through. This raises two potential issues:

1. Confidence intervals on risk estimates do not include any contribution relating to uncertainty on dosimetry.
2. The point estimates of dose could deviate significantly from the posterior mean estimates of dose that would be obtained if prior uncertainties on model parameter values, other than intake, were included in the analysis: this could be a potential consequence of any non-linearity in the relationship between bioassay quantities and doses predicted by the biokinetic models for plutonium when different parameter values are assumed.
In order to properly account for the effect of uncertainties on doses requires calculating a joint posterior distribution of doses for all workers in the study that is conditioned on the combined bioassay data. This is a non-trivial problem and deriving a suitable approach to it was beyond the resources and scope of the SOLO project. Instead, in addition to the Bayesian point dose estimates, a separate Bayesian analysis was performed for each of the 11,808 Sellafield workers included in the study to obtain posterior distributions of intake, dose and model parameter values; these are conditioned only on the bioassay data for each worker in question (rather than across all data simultaneously). The weighted likelihood Monte Carlo sampling (WeLMoS) method (Puncher and Birchall 2008, Puncher et al. 2012) was used to calculate the Bayesian posterior probability distributions. Unlike the approach used to obtain the Bayesian point estimates, these distributions include uncertainties on biokinetic parameter values.

The present paper describes this analysis and compares the distributions of dose with the point estimates that were provided to the epidemiologists. These comparisons have been made primarily in order to assess the reliability of the point estimates; in particular to:

1. Determine the magnitude of the uncertainties in posterior estimates of dose (see point 1 above); this will also give some insight into the potential impact on estimates of risk.
2. Determine whether the posterior mean values derived using the WeLMoS method significantly differ from the point estimates (see point 2 above); in other words, assess the degree of correlation between Bayesian central posterior estimates and point estimates.

In addition, the posterior distributions of model parameter values are used to determine how informative the Sellafield urine data typically are for the model parameters and intake; in other words, assess whether the data provide any new information about the dosimetry model in addition to that already specified by the derived prior distributions. This information is potentially useful to future studies.

**Derivation of prior distributions on parameter values**

A full description of the biokinetic models used in the analysis is provided in the SOLO dosimetry protocol, including the derivation of prior distributions for model parameter values (Birchall et al. 2013). These distributions and supporting information are summarised in table 1. Most of the prior distributions for parameters had been derived for a previous epidemiology study (Puncher et al. 2011, 2014). The only notable exceptions were the HRTM slow dissolution rate for plutonium nitrates and oxides and the bound fraction (both revised in light of new results from more recent studies); also a new parameter distribution describing intersubject variation in the partitioning of circulating plutonium between skeleton and liver was introduced; these are discussed further below.

**The bound fraction, f_b**

A long-term bound fraction can significantly affect regional lung doses because bound plutonium is not subject to particle transport clearance and is also placed closer to target cells in the bronchial and bronchiolar regions compared with non-bound material (ICRP 1994a). In an earlier Bayesian analysis of plutonium intake and doses for a sample of United Kingdom Atomic Energy Authority (UKAEA) workers, Puncher et al. (2011) assumed a triangular distribution for the bound fraction, f_b, with a minimum and mode of 0 and maximum value of 8%. These values were derived from limited data; the upper bound value of 8% was based on...
a single study of lung, lymph node and systemic plutonium retention in United States Transuranium and Uranium Registries (USTUR) Case 269 by James et al (2007). More recent studies have been undertaken to better identify values of $f_b$. Puncher et al (2015a) undertook an analysis of new measurements of regional activity in the lungs of USTUR Case 269, which were not available to James et al (2007), and found that the plutonium activity observed in the tracheo-bronchial region of the lungs could not be reasonably explained without assuming a value of $f_b$ of between 0.4 and 0.7%. Puncher et al (2015b) performed an analysis of lung data from Beagle dogs exposed to plutonium nitrate and found that a value of $f_b$ of between 0.2 and 1.1% was required to explain the long term lung retention observed in these animals. Puncher et al (2015c) found that autopsy data of Mayak workers exposed to plutonium nitrate could be explained with or without a permanent bound fraction; if binding was assumed to occur then the data were compatible with a small value of $f_b$ of around 0.0–0.3%. Based on these studies, Birchall et al (2013) derived a uniform distribution for $f_b$ with a minimum value of 0% and maximum value of 0.4%, giving more weight to the Mayak data. Unlike the analysis of the UKAEA workers (Puncher et al 2011), however, the SOLO analysis assumed that the value of $f_b$ was the same in all regions of the lung.

The slow dissolution rate, $s_s$

The distributions assumed for the other dissolution rates, $f_i$ and $s_r$, are the same as those derived by Puncher et al (2011). However, the present work has been able to make use of more recent estimates of the slow dissolution rate, $s_s$, for plutonium compounds obtained from human data. Puncher et al (2015c, 2015d) performed Bayesian analyses of the autopsy data from 60 Mayak workers exposed to plutonium nitrate or plutonium oxide, and obtained narrow distributions with median values of 0.00025 d$^{-1}$ (geometric standard deviation, GSD, of 1.08) and 0.000047 d$^{-1}$ (GSD of 1.07), respectively. Based on this information, in the SOLO analysis a lognormal prior distribution was assumed for $s_s$ for plutonium oxides with a median value of 0.000047 d$^{-1}$ and GSD of 1.07.

The choice of a suitable prior for $s_s$ for plutonium nitrates was complicated by the fact that the value of 0.00025 d$^{-1}$ obtained for plutonium nitrates is around an order of magnitude lower than that derived from a re-analysis, by Puncher et al (2015e), of the lung, urine and systemic data from two human volunteers who inhaled an aerosol of plutonium-237 nitrate (the so called ‘Harwell’ volunteer study, described by Etherington et al 2003). This analysis gave an estimate of 0.0022 d$^{-1}$ with a standard deviation, SD, of ±0.0001 d$^{-1}$. This value is also more consistent with previous values derived from analyses of Sellafield plutonium bearing materials; these suggest a value of between 0.0012–0.007 d$^{-1}$, depending on the age of the plutonium bearing material (Moody et al 1993). Consequently, for the purposes of dose reconstruction for the SOLO project it was decided that two sets of dose estimates would be produced; one set assuming an $s_s$ value of 0.0022 d$^{-1}$ (derived from the Harwell volunteer study) and the other a value of 0.00025 d$^{-1}$ (the mean value that results from assuming a lognormal distribution with median value of 0.00025 and GSD of 1.08; derived from the Mayak worker data) (Birchall et al 2013). In order to provide a suitable comparison, the Bayesian analysis described in this study was also performed twice: once assuming a normal prior distribution for the slow dissolution rate for nitrates with a mean of 0.0022 d$^{-1}$ and SD of 0.0001, and secondly assuming a lognormal prior distribution with median value of 0.00025 d$^{-1}$ and GSD of 1.08. For brevity, these are referred to as the ‘Sellafield’ and ‘Mayak’ analyses, respectively; the former referred to as ‘Sellafield’ because it was considered, nominally at least, that the Harwell value was probably closer to the true value for Sellafield exposures than the ‘Mayak’ value.
### Table 1. Probability distributions for the ICRP human respiratory tract model and systemic model for plutonium.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distribution</th>
<th>Median</th>
<th>GSD/SD</th>
</tr>
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<td><strong>Lung deposition parameters</strong></td>
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<td></td>
</tr>
<tr>
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<td>Log-normal</td>
<td>4.4 μm</td>
<td>1.8</td>
</tr>
<tr>
<td>GSD</td>
<td>Log-normal</td>
<td>2.2</td>
<td>1.5</td>
</tr>
<tr>
<td>$B^a$</td>
<td>Log-normal</td>
<td>1.2 m$^3$ h$^{-1}$</td>
<td>1.7</td>
</tr>
<tr>
<td>$f_R^b$</td>
<td>$f_R = 7B + 8$ (min$^{-1}$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$F_n^c$</td>
<td>Triangular</td>
<td>0.4$^d$</td>
<td>$^e$</td>
</tr>
<tr>
<td>ET,$_1$, ET,$_2$ aerodynamic filter efficiency$^f$</td>
<td>Log-normal</td>
<td>1</td>
<td>1.82</td>
</tr>
<tr>
<td>ET,$_1$, ET,$_2$ thermodynamic filter efficiency$^f$</td>
<td>Log-normal</td>
<td>1</td>
<td>1.18</td>
</tr>
<tr>
<td><strong>Lung particle transport parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALV to $bb_1$</td>
<td>Log-normal</td>
<td>0.0013 d$^{-1}$</td>
<td>3.2</td>
</tr>
<tr>
<td>ALV to INT</td>
<td>Log-normal</td>
<td>0.001 d$^{-1}$</td>
<td>4.5</td>
</tr>
<tr>
<td>INT to LN$\text{TH}$</td>
<td>Log-normal</td>
<td>0.00003 d$^{-1}$</td>
<td>3</td>
</tr>
<tr>
<td>Other rates scaled by factor $K_{ptg}^g$</td>
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<td>1.73</td>
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<tr>
<td><strong>Lung dissolution parameters</strong></td>
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<tr>
<td>Plutonium nitrate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$f_t^i$</td>
<td>Log-normal</td>
<td>0.17</td>
<td>2</td>
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<tr>
<td>$s_t^i$</td>
<td>Log-normal</td>
<td>1 d$^{-1}$</td>
<td>4</td>
</tr>
<tr>
<td>$s_{t} \text{’Mayak’}^j$</td>
<td>Log-normal</td>
<td>0.00025 d$^{-1}$</td>
<td>1.08</td>
</tr>
<tr>
<td>$s_{t} \text{’Sellafield’}$</td>
<td>Normal</td>
<td>0.0022 d$^{-1}$</td>
<td>0.0001</td>
</tr>
<tr>
<td>Plutonium oxide</td>
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<td></td>
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<tr>
<td>$f_t^i$</td>
<td>Log-normal</td>
<td>0.0026</td>
<td>3.1</td>
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<tr>
<td>$s_t^i$</td>
<td>Log-normal</td>
<td>1 d$^{-1}$</td>
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<tr>
<td>$s_{t}$</td>
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<td>0.000047 d$^{-1}$</td>
<td>1.07</td>
</tr>
<tr>
<td><strong>Bound state parameters</strong></td>
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</tr>
<tr>
<td>$f_b^h$</td>
<td>Uniform</td>
<td>0$^i$</td>
<td>0.004$^i$</td>
</tr>
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<td><strong>Pu systemic model parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeleton/liver partitioning ($B$ factor)</td>
<td>Log-normal</td>
<td>1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

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* $^a$ Distribution for breathing rate, $B$, (m$^3$ h$^{-1}$) based on a review of breathing rates in male subjects at rest and vigorous exercise, and assuming 68.7% of time is spent in light exercise and 31.3% sitting (Puncher et al 2011).

$^b$ It was assumed that respiratory frequency (min$^{-1}$), $f_R$, was correlated with $B$; the given equation was determined by regressing $f_R$ on $B$ using collated values for $B$ and $f_R$ (Puncher et al 2011).

$^c$ Distribution for fraction breathed through the nose, $F_n$, based on measurements of inter-subject variation in nose breathing, adjusted for time spent sitting (31.3%) and light exercise (68.7%) (Puncher et al 2011).

$^d$ Minimum value of triangular pdf.

$^e$ maximum value and mode of triangular pdf.

$^f$ Achieved by multiplying the scaling coefficient, $a$, which occurs in the expressions used to calculate the deposition efficiency for the aerodynamic and thermodynamic filters in the HRTM (ICRP 1994a), by a lognormally distributed random variable with a median of unity and GSD of 1.82 or 1.18; the distributions are taken from Table 14 of ICRP publication 66 (ICRP 1994a) and assumed to represent variability in these processes. $ET_1 = \text{anterior nasal passage}$, $ET_2 = \text{posterior oral and nasal passages, the pharynx and larynx}$. The reference value of $a$ is unity.

$^g$ The median particle transport rates adopted in the HRTM, excluding the rates from ALV and INT.

$^h$ Minimum of uniform distribution.

$^i$ maximum of uniform distribution.
Plutonium absorbed to blood from the lungs is primarily taken up by the skeleton and liver (Leggett et al. 2005). However, there is significant inter-subject variation in the relative proportion of activity taken up and retained in the skeleton compared with the liver in humans, which is also influenced by other factors; particularly alcohol related liver disease (Leggett et al. 2005). Puncher and Harrison (2012) found that inter-subject variability in uptake to skeleton and liver could be modelled by multiplying all rates from blood to skeleton compartments, in the systemic model proposed by Leggett et al. (2005), by a scaling factor, B, which was sampled from a log-normal distribution with median value of 1 and GSD of 1.3. The rate from blood to liver, \( R_{BL} \), was then calculated using the following equation:

\[
R_{BL} = 0.693 - B \times 0.231
\]  

Where 0.693 \( \text{d}^{-1} \) is the sum of the baseline model rates from the primary blood compartment, designated ‘Blood 1’ in the Leggett et al. model (2005), to both the liver and skeleton compartments and 0.231 \( \text{d}^{-1} \) is that to the skeleton compartments only.

In order to reduce computation times, the effect of this approach on liver and red bone marrow doses was approximated by varying doses to the liver and skeleton directly using the factor B, after solving the HRTM and (baseline) plutonium systemic model, rather than by varying the systemic rates as described above using equation (1), and then solving the HRTM and (perturbed) plutonium systemic model to calculate the doses. The adjusted absorbed dose for red bone marrow \( <RBMY> \) and liver \( <LIVY> \) received in each year, \( Y \), was therefore calculated as follows:

\[
<RBMY> = RBMY \times B
\]

\[
<LIVY> = LIVY \times (0.693 - B \times 0.231)/0.462
\]

Where \( RBMY \) and \( LIVY \) are the unperturbed doses; 0.462 \( \text{d}^{-1} \) is the baseline mode rate from compartment ‘Blood 1’ to liver. It was found that this approximation gave reasonable agreement with the full solution: the 2.5% and 97.5% percentile values of the distributions of doses calculated using equations (2) and (3) were typically within 2–15% of the same values calculated using the method described by Puncher and Harrison (2012), based on prospective dose calculations assuming a chronic inhalation of plutonium. Note, however, that the approach described by Puncher and Harrison (2012) also has a small effect on predicted urinary excretion rates and hence assessment of intakes from urinalysis results which is not accounted for using this approach.

Analysis of Sellafield plutonium workers

Methods

Bioassay data and measurement uncertainties. The dose assessment procedures derived for Sellafield workers assume that urine measurement uncertainties are lognormally distributed. More precisely, this assumes that if the measurement procedure could be hypothetically repeated at a given time point then it would be described by a lognormal distribution with a median value equal to the product of the true intake and a function that describes excretion per unit intake at the required time; the likelihood function for this model is described elsewhere (Doerfel et al. 2006). The assumption of log-normality is based on an analysis of historical Sellafield urine data (Britcher et al. 1994); this and a description of the derivation of geometric
standard deviations for these data are described by Birchall et al (2013); geometric standard deviations for the data were 2.8 (data collected before 1970) or 1.6 (data collected after 1970).

**Reconstruction of exposure histories and intake regimes for Bayesian analysis.** Bayesian analyses were performed for all 11,808 workers from the Sellafield cohort considered in the SOLO epidemiology study. An overview of the reconstruction of exposure histories and hence potential intake regimes for Sellafield workers is described in detail by Birchall et al (2013). Briefly, a constant chronic daily intake (Bq d$^{-1}$) is assumed to represent background occupational intakes that occurred over the duration of the working history where the worker was believed to be exposed to plutonium bearing aerosols. Depending on the available information about a worker’s exposure history, different background chronic rates might be assumed for separate periods of exposure or rates might be constrained to be the same in certain periods. The times of additional acute intakes are assigned at times where occupational records indicate that these may have occurred and the pattern of urinary excretion is consistent with a significant acute intake.

To perform the Bayesian analysis and also to obtain point estimates of dose for each worker, the overall intake pattern for each worker was initially constructed using the method described by Puncher et al (2012). In this approach, a maximum a-posteriori (MAP) simultaneous fit of all assigned intake regimes (times of acute intakes and times and duration of constant chronic daily background intakes) is performed with the values of HRTM parameters set at the modes of their respective prior distributions given in table 1. Relatively uninformative prior assumptions were used for the plutonium intake levels, these were described by lognormal distributions with median values of 20 Bq for acute intakes or 20 Bq year$^{-1}$ for chronic intakes, with a geometric standard deviation of 6$^{1}$. The MAP method then determines the value of intake for each regime that is associated with the estimate of overall intake with the maximum posterior probability. The relative values of the fitted intakes are then used to construct what is termed a ‘complex intake regime’ (CIR) for each case history in order to perform the Bayesian analysis using the WeLMoS method (Puncher and Birchall 2008, Puncher et al 2012). This CIR is simply a single compound intake profile with a pattern that corresponds to the superposition of all the regimes (acute and chronic) for an individual scaled by their relative contribution to the total intake. Thus if $I$ is the total MAP intake and $J$ is the number of individual regimes contributing to that total intake, then for each of these regimes $h$ (where $h = 1$ to $J$) the intake in that regime $I_h$, can be related to the total intake as follows:

$$I = \sum_{h=1}^{J} I_h = I \sum_{h=1}^{J} a_h$$

Where $a_h$ is a probability vector of $J$ constant fractions which defines the CIR for the worker’s exposure history (each intake, $I_h$, is one of the intakes fitted using the MAP procedure described above). The important point to note is that when the CIR is used with the WeLMoS method (or any other suitable Monte Carlo method), the value of each intake in the CIR constitutes a constant fraction of the total intake. In other words, the WeLMoS method calculates a posterior distribution of total intake for the exposure history with each sub-intake in the CIR 100% correlated with the total intake (Puncher et al 2012). It has been shown that this expediency provides a reasonable approximation of the full posterior distribution of total intake (all putative intakes are assigned individual priors and varied independently in the Bayesian

$^{1}$ This value of 20 Bq per intake event or per year was derived from an analysis of historical personal air sampler data. A description of the derivation of this prior is provided by Puncher et al (2014); its application in the SOLO project is described by Birchall et al (2013).
integration) and cumulative lung dose for UKAEA plutonium exposure histories—which are qualitatively similar to the Sellafield exposures considered here—calculated using Markov Chain Monte Carlo (MCMC) with the same data (posterior means are typically within 10% when calculated using either method) (Puncher et al 2012).

**Dosimetric modelling assumptions.** Doses to tissues were calculated with the dosimetry methodology used to calculate doses for workers in ICRP Publication 68 (ICRP 1994b), but using gender specific ICRP reference organ masses for red bone marrow and liver (ICRP 1975), and regional lung tissues: bronchial basal cells ($BB_{bas}$), bronchial secretory cells ($BB_{sec}$), bronchiolar cells (bb) and the alveolar region (AI) (ICRP 1994a). Lung doses were calculated as a weighted average of the absorbed dose to the four lung tissue regions as follows:

$$\text{Lung Dose}(Gy) = 0.333 \times \text{Dose}(BB_{bas}) + 0.333 \times \text{Dose}(BB_{sec}) + 0.333 \times \text{Dose}(bb) + 0.333 \times \text{Dose}(AI)$$

(5)

Note that this formalism is identical to that used by ICRP to calculate weighted equivalent lung dose, but uses absorbed, instead of equivalent, tissue dose and excludes the 0.1% contribution from dose to the thoracic lymph nodes (Birchall et al 2013).

**Bayesian analysis of intakes and doses.** The Bayesian posterior distributions of intakes, doses and model parameters were calculated for each of the 11 808 workers in the study population using the Weighted Likelihood Monte Carlo Sampling (WeLMoS) method. Each analysis used the MAP derived CIR for that worker as summarised above and described by Puncher et al (2012). Lung parameters were sampled from the prior distributions given in table 1 using the Latin-Hypercube method (McKay et al 1979) to generate 1000 vectors of parameters (each vector contains one sampled value of each parameter). The WeLMoS analysis of each worker was performed using a software tool that uses the dosimetry code IMBA Professional Plus (Birchall et al 2007) to calculate doses and bioassay quantities.

The following steps were performed for each vector of sampled parameters:

1. The sampled HRTM parameter values were input to the dosimetry code IMBA Professional Plus (Birchall et al 2007).
2. Bioassay quantities, and absorbed tissue doses received in each calendar year, commencing from the start of exposure until the study cut-off date of 31st December 2005 were calculated. Tissue doses were calculated for the liver, red bone marrow and lung. Lung dose was calculated employing the regional tissue dose weighting scheme described above.

Posterior distributions of total intake and absorbed doses received in each year were calculated from the quantities output in Step 2 using the WeLMoS method in the usual way (Puncher and Birchall 2008). These calculations assumed a relatively uninformative lognormal prior distribution of intake with a GSD of 6, as used to derive the CIR above, and median value calculated for each worker using the following equation:

$$\text{Median intake}(Bq) = 20(X + Y)$$

(6)

Where $X$ is the number of reported (putative) acute exposures and $Y$ is the overall number of years of chronic exposure for an individual. Note that this gives a constant chronic pattern of exposure over time, including at early times; this was considered appropriate for Sellafield workers. For Mayak workers on the other hand, a stepwise rate function was used that allocated higher intake rates at earlier times of exposure in the Mayak facility (Birchall et al 2013).
To monitor convergence the WeLMoS Monte Carlo analysis using the ‘Sellafield’ solubility prior was run twice; each run used a different random seed to construct the Latin Hypercube matrix of model parameter values.

**Point estimates of intakes and doses.** For the purposes of comparison, the point estimates of intake and dose produced for the SOLO epidemiology study were used. The methodology used to produce these point estimates of dose is described in detail by Birchall *et al* (2013); briefly, however, they were calculated for each worker as follows:

1. The Complex Intake Regime (CIR) for the worker was constructed as described above.
2. The values of biokinetic parameters were set at the mean values corresponding to the prior distributions given in table 1.
3. A Bayesian posterior distribution of total intake was calculated assuming a lognormal prior for intake with a geometric standard deviation of 6 and a case specific median value calculated using equation (5). The mean of this distribution was then used to calculate the absorbed tissue dose received in each calendar year from the start of exposure up to the reference date (31st December 2005) assuming the biokinetic parameter values in (2).

This approach was adopted on the basis that it was considered to be the one most likely to obtain the best point estimates of dose: those that are as close as possible to the posterior mean values obtained using the WeLMoS method, and hence the posterior mean value that would be obtained if a full MCMC analysis was performed for each worker in the cohort: as stated above, one of the primary objectives of this analysis was to test this assumption.

**Results**

**Convergence of the posterior distributions of intake, doses and model parameters.** It was found that good convergence was achieved using a sample vector of $N = 1000$ parameter values for each WeLMoS run: posterior mean lung doses from two separate runs were typically within 5%, with a geometric mean (posterior mean from run1: posterior mean from run 2) of 0.98 and GSD of 1.09 (for doses cumulated from the start of exposure to the reference date). For intakes, the geometric mean was 1.01 with a GSD of 1.08. A similar level of convergence was observed for the HRTM parameters.

**Comparison of the Bayesian distributions with point estimates of intakes and doses.** To compare a distribution parameter (mean, median, etc.) from the posterior distribution of intake or dose, with the corresponding point estimate (PE), geometric means of the ratio of the posterior sample statistic (PSS) to the point estimate (PE) were calculated; to further investigate if there was any temporal variation in the distribution of dose estimates, two methods were used:

1. Geometric means for both intakes and doses were calculated using the following equation:

   $$\text{PSS:PE} = \sqrt[N]{\prod_{i=1}^{N} \frac{\bar{X}_i}{PE_i}}$$  \hspace{1cm} (7)

   Where $\bar{X}_i$ is the distribution parameter (sample mean, median etc.) derived from the posterior distribution for a worker $i$ in a cohort of $N$ workers (i.e. 11,808 workers in this instance) and $PE_i$ is the corresponding point estimate for that worker. So for intake, $\bar{X}_i$ and $PE_i$ were simply the required sample statistic (e.g. the mean) from the posterior distribution of intake and the point estimate of the total intake, respectively; for doses, the values of $\bar{X}_i$ and $PE_i$ were drawn
from the posterior distributions and point estimates of the cumulative absorbed tissue dose from the start of exposure to the study cut-off date (31st December 2005).

(2) In addition, for doses only, geometric means were also calculated using the following equation:

\[
\text{PSS} : \text{PE} = \sqrt[\text{Y}]{ \prod_{i=1}^{\text{N}} R_i } \tag{8}
\]

Where the \( R_i \) for each worker was calculated as follows:

\[
R_i = \sqrt[\text{Y}]{ \prod_{y=1}^{\text{Y}} \frac{\bar{X}_y}{\text{PE}_y} } \tag{9}
\]

In this case, \( \bar{X}_y \) is the distribution parameter (sample mean, median etc.) of the dose received in year \( y \) for worker \( i \); \( Y \) is the number of years from the start year of exposure to the study end year (2005). It was found that there was little difference between the geometric means of the ratios of PSS:PE of dose calculated using either equation (7) or equation (8). This suggests that the estimated temporal pattern of dose delivery is relatively similar whether calculated as a point estimate or derived from the posterior distribution. In this particular case, the similarity arises because the Bayesian analysis and point estimates for each worker were obtained using the same complex intake regime (CIR), derived for that particular worker; i.e. the CIR largely determines the pattern of dose delivery. The results of the comparison are summarised in table 2. The GMs provided for doses were calculated using method (2) (equation (8)).

The main points to note are:

1. There is excellent agreement (within 10%) between the posterior mean estimates and the point estimates of intakes and dose; median values are around 30–50% lower than the point estimates, suggesting that the distributions are positively skewed (trending to log-normal). The geometric standard deviations of the ratios (posterior mean: point estimate) were 1.3 (‘Sellafield’ prior) and 1.4 (‘Mayak’ prior).
2. The ratios of the 2.5th and 97.5th percentiles over the point estimates indicate that the posterior distributions of intakes and doses vary over a wide range; most notably for lung dose which has a geometric range of around 100 in both analyses.
3. The geometric differences between posterior means or quantiles and the point estimates are the same whether the analysis assumed the ‘Sellafield’ or ‘Mayak’ prior distribution for the slow dissolution rate for plutonium nitrate.

The posterior means and point estimates are closely correlated. This is supported by a plot of the logarithm of the posterior estimates of mean lung dose versus the logarithm of the point estimates of lung dose, calculated assuming the ‘Sellafield’ slow dissolution rate prior, presented in figure 2. Linear regression of the logarithm of the posterior mean as the dependent variable versus the logarithm of the point estimate as the independent variable gives a gradient of unity and intercept near zero (0.09), consistent with a close 1:1 relationship between posterior mean and point estimate. However, greater scatter is observed for around 5% of the cases with lung doses above 0.01 Gy. The Pearson correlation coefficient of the logged values for all 11 808 cases is 0.996; however, at doses greater than 0.01 Gy the coefficient is reduced to 0.85.

**Comparison of the Bayesian distributions with point estimates of intakes and doses.** As noted in point (3) above, the geometric ranges of the distributions with respect to the point estimates were similar whether the ‘Sellafield’ or ‘Mayak’ prior distribution of \( s_s \) was assumed.
However, it is clear that assuming either distribution has a significant effect on the absolute values of lung dose. This is illustrated in table 3 which shows the geometric mean difference between the posterior mean of the distribution of intake or dose calculated for each worker using the two prior distribution assumptions for $s$. Posterior mean lung doses calculated using the ‘Mayak’ prior are around 3 times higher than for the ‘Sellafield’ prior, although there is

<table>
<thead>
<tr>
<th></th>
<th>Intake</th>
<th>Lung</th>
<th>Liver</th>
<th>Red bone marrow</th>
</tr>
</thead>
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<tr>
<td><strong>Sellafield Nitrate Prior</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean$^a$</td>
<td>1.07</td>
<td>1.03</td>
<td>0.95</td>
<td>0.94</td>
</tr>
<tr>
<td>Median</td>
<td>0.61</td>
<td>0.56</td>
<td>0.67</td>
<td>0.64</td>
</tr>
<tr>
<td>2.5%</td>
<td>0.11</td>
<td>0.04</td>
<td>0.09</td>
<td>0.08</td>
</tr>
<tr>
<td>97.5%</td>
<td>4.46</td>
<td>4.34</td>
<td>2.48</td>
<td>2.72</td>
</tr>
</tbody>
</table>

| **Mayak Nitrate Prior** |        |      |       |                 |
| Mean$^a$              | 1.03   | 0.97 | 0.95  | 0.93            |
| Median                | 0.57   | 0.54 | 0.63  | 0.60            |
| 2.5%                  | 0.09   | 0.03 | 0.07  | 0.07            |
| 97.5%                 | 4.43   | 3.97 | 2.67  | 2.90            |

$^a$ The geometric mean of the ratio of each sample statistic from the posterior distribution of dose (or intake) over the point estimate of dose for 11,808 Sellafield workers.

Figure 2. Plot of the logarithms (base 10) of posterior mean cumulative lung doses (Gy) versus the logarithm of point estimates of lung dose that were used to derive risk estimates in the SOLO epidemiology study ($n = 11,808$).

Table 2. Comparison of uncertainties on intakes and doses calculated for the Sellafield cohort with the point estimates of doses obtained for the SOLO epidemiology study.
a reasonable amount of variation about this value for individual workers as evidenced by a geometric standard deviation of 1.4. As expected, there is little or no effect on systemic doses (liver and red bone marrow), and a small effect for intake. The implications of assuming the ‘Sellafield’ or ‘Mayak’ values for estimates of lung cancer risk will be investigated.

Posterior estimates of HRTM parameters and intakes. Posterior estimates of the human respiratory tract model parameters and intake are provided in table 4. This summarises the posterior mean and median values for each parameter, averaged over the cohort. For the posterior means and the posterior median values for parameters other than those assigned log-normal priors, the value given represents the arithmetic mean of the posterior mean or median values for all 11 808 workers (standard deviations in parentheses). For parameters with lognormal prior distributions, the median value is the geometric mean of the posterior median values from all 11 808 workers (geometric standard deviations in parentheses). The corresponding prior values are provided for comparison. The posterior distributions of parameters for each worker were typically as broad as their priors, consistent with the fact that the urine bioassay data are generally uninformative for many of the parameters, particularly the deposition parameters and to a lesser extent those governing particle transport clearance. This is also supported by the fact that the posterior mean and median values are also close to the prior values; for the deposition parameters in particular, the dispersion around the mean or median is relatively small. Interestingly though, the posterior values of the rapid fraction and rapid dissolution rate are higher than their prior values. This is particularly noticeable for the rapid fraction for oxide; the posterior median value of 0.01 is around a factor of three higher than the prior median value of 0.0026. The only other parameter that appears to differ significantly from its prior value is the rate from the alveolar region to the bronchiolar region. It can be seen that the posterior values for the rapid fraction and rapid rate remain largely unaffected whether the ‘Mayak’ or ‘Sellafield’ $s_s$ values for nitrate are assumed; although both sets of posterior values have increased slightly, possibly indicating that the data supports more rapid lung clearance to blood overall, with the slightly higher values for the ‘Mayak’ prior likely to be a consequence of the much lower value of $s_s$ (0.000 25 d$^{-1}$) assumed for that analysis as compared to the ‘Sellafield’ value (0.0022 d$^{-1}$).

Goodness-of-fit. In order to assess the consistency between the modelling assumptions and data (‘goodness-of-fit’), the code that performed the WeLMoS calculations also performed a maximum likelihood estimate of intake for the 386 workers who had urine bioassay measurements that were all above the limit of detection; this calculation was performed assuming the prior mean values of the HRTM model parameters. This code recorded the chi-squared goodness-of-fit statistic and corresponding alpha-probability. If it is assumed that an alpha probability value of greater than 0.05 is consistent with a ‘good fit’ then 91% of the estimates were in good agreement with the data assuming the ‘Sellafield’ prior mean value for $s_s$; 92% for the ‘Mayak’ (compared with an expectation of 95% if the assumed intake regimes, model
and parameter values accurately represent the data). This analysis perhaps also gives some insight into the fraction of workers who have exposures and urinalysis data that are potentially informative with respect to lung solubility parameters.

**Discussion**

This paper describes the application of Bayesian inference to calculate uncertainties on intakes and lung doses for the cohort of Sellafield plutonium workers included in the recent SOLO epidemiological study. These are compared with the point estimates of dose that are to be used in the study to investigate possible associations between dose and cancer incidence among Mayak and Sellafield workers. This comparison demonstrates excellent agreement between...
the posterior mean values and the point estimates, indicating that the adopted method of point estimation is not ‘ill posed’ and is robust.

It is noteworthy however, that for around 5% of the cases with lung doses >0.01 Gy, the differences between posterior mean values and point estimates of lung dose are more variable (figure 2). A comparison of these case histories with those that fall near the trend suggests that the deviation results from the fact that the former cases possess more informative measurement data; these likely more strongly influence posterior estimates of lung model parameter values, and hence lung dose, compared with the cases that fall nearer the trend. The reliability of the point estimates will be assessed in the epidemiology study by comparing risk estimates computed using posterior means and point estimates; in this regard, the influence of the cases with informative data on risk estimates could be assessed by performing an additional comparison where posterior means are used for these cases but point estimates are used for the rest of the cohort (and vice versa).

The purpose of the Bayesian analysis was to estimate the general uncertainty on dose estimates and to support the use of point estimates in the epidemiology study, rather than obtain dose estimates in order to directly inform the estimate of risk. In this regard there are two issues that should be highlighted:

1. The CIR-WeLMoS method has been shown to give good agreement with regard to posterior estimates of total intake and cumulative dose when compared with analyses of the same exposure histories using Markov Chain Monte Carlo (MCMC) (Puncher et al 2012), thus supporting its use in the present context. However, greater discrepancies between CIR-WeLMoS and MCMC are observed regarding the temporal delivery of dose—a result of the fact that the fraction of the total intake assigned to each intake in the exposure history remains constant after derivation of the CIR; whereas, in reality, the magnitude of putative intakes assigned at different times within the exposure history is also uncertain and this was accounted for in the MCMC analyses described by Puncher et al (2012). The temporal pattern of dose delivery, in addition to the magnitude of doses, may affect the estimate of risk.

2. The analysis described here calculates distributions of doses independently for each worker; consequently, if the distributions were to be used to obtain estimates of risk, these estimates would ignore the effect of parameter values in the dose reconstruction protocol that are shared between workers. Ignoring the effect of shared uncertainties can potentially lead to biased estimates of risk (Gilbert 2009); to properly account for this requires calculating a joint posterior distribution of doses across all 11808 workers in the cohort. The calculation of such a distribution poses a significant computational challenge and is certainly beyond the capabilities of an importance sampling method such as WeLMoS.

A more definitive approach to assess the reliability of point estimates—which by definition ignore the effects of temporal and shared uncertainties, in addition to those inherent in the biokinetic model—could be to compare risk estimates calculated for a representative sub-population of (say) a 1000 workers using point estimates of dose with those obtained from doses sampled from a joint distribution calculated using MCMC. This could be achieved using a tool such as MCSim (Bois and Maszle 1997); this freely available simulation code has been used to perform joint analyses of large datasets (Allen et al 2007).

This study shows that the uncertainties on dose estimates are large: the ratios of the 97.5%:2.5% values are around two orders of magnitude for lung dose and a factor of 30 for liver and RBM dose, and 40 for intakes; these ranges are the same for both the ‘Mayak’ and ‘Sellafield’ plutonium nitrate lung solubility prior analyses (table 2). Large uncertainties on
lung dose were also observed in a previous Bayesian analysis of UKAEA workers that used mostly the same prior distributions (Puncher et al 2011). The significant uncertainties result from large prior uncertainties in biokinetic parameter values and the fact that the bioassay data are largely uninformative for these parameters (discussed below); this means that the uncertainties on parameter values are propagated more or less directly into the uncertainty on dose. Interestingly though, the geometric range of 97.5%/2.5% values for intake and lung dose appear to be larger in this analysis than those observed by Puncher et al (2011): 30 versus 100 in this study (lung), 18 versus 40 in this study (intake), for what the author’s termed ‘moderately soluble’ plutonium (comparable to the ‘Sellafield’ analysis in this study). Given that the prior distributions on most parameters, except the slow dissolution rate and bound fraction (which were in fact narrower in this study) were the same in both analyses, it seems likely that the broader range of intakes and doses results from the larger measurement uncertainties assigned to early (pre-1970) urine data for the Sellafield workers compared with those for the sample of UKAEA workers considered by Puncher et al (2011): a GSD of 2.8 compared with a GSD of 1.5–2.0 for the latter; that the large measurement uncertainties are responsible is further supported by the fact that the distribution of doses for liver and red bone marrow are also very broad (the geometric differences between 97.5% and 2.5% values is a factor of 30). A significant source of the uncertainty on lung dose appears to result from the combination of parameters whose uncertainties can be considered ‘reducible’: the aerosol deposition parameters (AMAD, and the aerosol dispersion GSD), and the absorption parameters; when the ‘Sellafield’ analysis was repeated with these parameters fixed at their prior mean values (all other parameters—those assumed to represent inter-subject variability—were varied) the geometric range on lung dose was reduced from a factor of 100 to 30 (with the posterior means being around 20% higher than the point estimates). It is very likely that much of the observed reduction results from not varying the dissolution parameters, \( f_r \) and \( s_r \) in particular. This is demonstrated by the previous analysis by Puncher et al (2011), who inferred that much of the uncertainty on dose could be accounted for by uncertainties on the values of the absorption parameters.

Although the prior distributions for \( f_r \) and \( s_r \) are the same as those derived by Puncher et al (2011), the present work has been able to make use of the results from more recent studies that obtained estimates of the slow dissolution rate, \( s_s \), for plutonium compounds, from human data (discussed in the section ‘derivation of uncertainties’ above). However, these have revealed a significant discrepancy in estimates of \( s_s \) for nitrates that has a substantial effect on the estimates of lung dose: using the lower (i.e. slower) ‘Mayak’ value results in lung dose estimates that are on average a factor of three higher than those derived using the higher (i.e. faster) ‘Sellafield’ value (table 3). The reason for the difference in the two values is presently unclear, but under investigation.

The posterior mean and median estimates of model parameter values were on average very close to their prior values, indicating that the urine bioassay data for the typical Sellafield worker does not provide much additional information concerning the values of biokinetic model parameters than is already provided by the prior distributions. This is perhaps not surprising because: A. Many parameters that influence the calculated value of dose per unit intake do not influence predicted urinary excretion (e.g. particle transport clearance), B. Occupational urine bioassay data are often compromised (e.g. unreliable, poor resolution, censored and with large uncertainties) and C. The default assumption of a chronic exposure pattern means that while estimates of intake are much less sensitive to errors in temporal information (e.g. exposure dates) than when using an acute assumption, the bioassay information is then also much less informative about temporal information such as the rate at which plutonium is entering the blood. Interestingly though, there does appear to be a small
upward shift in the values of the rapid fraction, $f_r$ and rapid dissolution rate, $s_r$, particularly the former for oxides, which may indicate that the lung solubility of Sellafield plutonium compounds is slightly higher than assumed. To confirm this requires a further analysis of workers with good quality urine and other bioassay data, which were not available to the authors during the development of the SOLO dosimetry protocol. Such analyses would also help identify the reasons for the difference between the ‘Sellafield’ and ‘Mayak’ estimates of the slow dissolution rate, $s_s$, for plutonium nitrate. On that note, it should be pointed out that performing a joint Bayesian analysis of all workers simultaneously, as highlighted in point 2 (above), would help to identify the values of important parameters that are shared or correlated between workers (such as the absorption parameters) because their values would be identified by workers in the cohort with good data and simultaneously ‘shared’ with workers with poor data.

It is also noteworthy that there is very good agreement between the prior and posterior mean and median values of intakes, and this serves to validate the adopted dosimetry protocol: intakes predicted from the bioassay data using the assumed intake regimes, biokinetic models and parameter values agree very well with those inferred a priori from air sampler and other data; the latter were used by Puncher et al (2014) to infer the constant of 20 Bq year$^{-1}$ that is used to set the median value of the intake prior for each worker. In contrast, in their analysis of UKAEA plutonium workers, Puncher et al (2014) obtained a posterior median value that was on average around 10 fold higher than the prior value; this was the result of very high intake predictions arising from extreme prior values of the slow dissolution rate, $s_s$, which again reinforces the desirability of work to improve the prior estimates for key parameters.

It should be noted that the application of Bayesian methods for plutonium intake and dose reconstruction from bioassay data is not new. Miller et al (1999) describe numerical methods for identifying occupational intakes of plutonium, and the magnitude of these intakes, from routine monitoring data. On that note, it should be pointed out that the Bayesian methodology, applied in the present study, does not consider uncertainties on the times or number of intakes: background intakes are assumed to be adequately represented by a constant chronic daily rate of intake, and accidental acute intakes that are suspected to have occurred at reported times, are assumed to have occurred—only the magnitude of the intakes are uncertain. However, as indicated above, uncertainty on the time of intake is not thought to be generally significant as such acute exposure assumptions have only been used when they are supported by a detailed review of the available information. Although it is acknowledged that uncertainty in the intake regime will have an additional effect on the posterior distribution of intakes and dose, the exposure assumptions used should help to limit this effect.

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