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ESTIMATION OF INTERNAL EXPOSURE TO URANIUM WITH UNCERTAINTY FROM URINALYSIS DATA USING THE InDEP COMPUTER CODE

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Abstract

The National Institute for Occupational Safety and Health (NIOSH) is currently studying mortality in a cohort of 6409 workers at a former uranium processing facility. As part of this study, over 220 000 urine samples were used to reconstruct organ doses due to internal exposure to uranium. Most of the available computational programs designed for analysis of bioassay data handle a single case at a time, and thus require a significant outlay of time and resources for the exposure assessment of a large cohort. NIOSH is currently supporting the development of a computer program, InDEP (Internal Dose Evaluation Program), to facilitate internal radiation exposure assessment as part of epidemiological studies of both uranium- and plutonium-exposed cohorts. A novel feature of InDEP is its batch processing capability which allows for the evaluation of multiple study subjects simultaneously. InDEP analyses bioassay data and derives intakes and organ doses with uncertainty estimates using least-squares regression techniques or using the Bayes' Theorem as applied to internal dosimetry (Bayesian method). This paper describes the application of the current version of InDEP to formulate assumptions about the characteristics of exposure at the study facility that were used in a detailed retrospective intake and organ dose assessment of the cohort.

INTRODUCTION

Epidemiological studies of nuclear industry workers suggest evidence of long-term health effects from exposure to low-dose, protracted external ionising radiation[(1)]. Other studies of workers with internal exposure to various alpha-emitters such as ^{226}Ra and ^{239}Pu also indicate a potential increased risk of cancer[(2–5)]. However, few epidemiological studies have focused on cohorts whose primary exposure is to internally deposited uranium[(6)]. Commercial nuclear power production in the US is currently experiencing resurgence with concomitant expansion in commercial fuel cycle industries including mining, milling,

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CONFLICT OF INTEREST

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

uranium enrichment and fuel fabrication. Operations in these types of facilities present a potential for exposure of workers to various uranium compounds.

The National Institute for Occupational Safety and Health (NIOSH) is currently studying mortality in a cohort of workers at a former uranium processing facility. Bioassay data collected by this facility containing information on urine uranium concentration was used to reconstruct organ doses due to internal exposure to uranium for these workers[7]. Conventional methods of internal dose assessment utilise computational programs to analyse a single case at a time, which can take several hours to complete. However, the cohort in the current NIOSH mortality study consists of over 6000 workers with over 220 000 urine samples. NIOSH has been supporting the development of the computer program, InDEP (Internal Dose Evaluation Program), to be used as a computational tool for exposure assessment of workers exposed primarily to uranium and plutonium in support of epidemiological studies of nuclear industry cohorts. This paper describes the use of the current version of InDEP to formulate assumptions about the characteristics of exposure at the study facility that were used in the detailed retrospective assessment of intake and organ dose from uranium exposure for the study cohort.

DESCRIPTION OF INDEP

The InDEP program[8] analyses bioassay data and derives intakes using least-squares regression techniques or using Bayes' Theorem as applied to internal dosimetry (Bayesian method). The code is designed to operate on IBM-PC computers running Windows OS, including Windows XP, Windows Server, Vista and Windows 7. The code was programmed in the Analytica® programming language (Analytica Enterprise v. 4.1.2.4. Copyright 2008 Lumina Decision Systems, Inc., Los Gatos, CA 95033; http://www.lumina.com), and consists of a primary Analytica® file containing the bulk of the equations, and several secondary Analytica® files that contain intake retention/excretion functions, dose coefficients, and dose-rate functions. The user needs to install the Analytica® platform on his or her computer before using InDEP. The bioassay data to be analysed (e.g. urine uranium concentration data) are organised in a standard database, such as Microsoft Access, which is accessed by InDEP.

The current version of the code addresses exposures of adult workers to isotopes of uranium (^{234}U, ^{235}U, ^{236}U, ^{238}U) and plutonium (^{238}Pu, ^{239}Pu, ^{240}Pu, ^{241}Pu), as well as mixtures of plutonium or uranium isotopes. Derivation of intake and estimation of doses is based on the most recent biokinetic models and dose coefficients recommended by the International Commission on Radiological Protection (ICRP). The current respiratory tract model is provided by ICRP Publication No. 66[9]. The most recent systemic model for uranium is given by ICRP Publication No. 69[10]. The most recent systemic model for plutonium is described in Publication 67[11]. InDEP also incorporates a recently updated plutonium biokinetic model[12], which reflects recently published studies on plutonium exposure data from the Mayak plutonium production facility and the US Transuranium and Uranium Registries.

InDEP is capable of processing a large number of cases in a single run, meaning that intakes and organ-specific doses can be calculated simultaneously for many workers. Also, multiple cases can be analysed at the same time for the same worker (e.g. varying dates of exposure or absorption type of the uranium or plutonium compound). The number of cases that can be run in a single batch is limited by available computer memory or processor speed. The Bayesian method can only be used when analysing single cases.

The InDEP computer code estimates intakes by analysing data on radionuclide activity in 24-h urine samples, 24-h fecal samples, lung, liver, whole body or wounds. Analysis of bioassay data is done assuming that exposure occurred either as a single acute or chronic intake. For an acute exposure, intake estimation consists of using pre-calculated retention and excretion functions developed from the most current biokinetic models to calculate the inhaled or ingested activity (in Bq) that would result in the observed activity in urine, feces, lung, liver or whole body. For a chronic exposure, bioassay data are analysed to estimate an average intake rate (in Bq d^{-1}) over the duration of the exposure. The bioassay data are analysed analytically using least-squares equations similar to those used by other internal dosimetry codes, or are analysed numerically using the Bayesian method. Uncertainties are propagated using Monte Carlo techniques for the least-squares methods. The posterior distribution from the Bayesian method is assumed to represent the uncertainty in an estimated intake when this method is used. InDEP reports the intake (*I*) in bequerel (Bq) (International System of Units) as well as pCi, nCi or μCi (conventional units).

Least-squares method

When using the least-squares method, the intake is obtained with one of several user-selected formulations defined according to assumptions regarding the variance of the bioassay measurements. Under the assumption of normally distributed measurement errors, the intake is given by

$$I=\frac{\sum_{i=1}^{n} w_i R_i X_i}{\sum_{i=1}^{n} w_i R_i^2} \quad (1)$$

where X_i is the bioassay measurement for the *i*th data point (Bq d^{-1} for excretion and Bq for retention); $i=1,...,n$; R_i is the expected 24-h activity excreted in urine or feces or expected activity retained in a tissue, per unit intake, at the time point of measurement X_i; n is the number of bioassay measurement points; $w_i=1/\sigma_i^2$ is the weight assigned to each measurement, according to the variance σ_i^2 of the measurement.

Six formulations of the least-squares method are available for selection in this case: Weighted Least-Squares ($\text{weight}=1/\sigma_i^2$ for each measurement *i*), Uniform Absolute Error (or Un-weighted Least-Squares; $\sigma_i^2=\text{constant}$), Ratio of the Means ($\sigma_i^2$ proportional to the expected bioassay value), Average of Slopes (σ_i^2 proportional to the square of the expected

value), Square-Root Error (σ_i^2 proportional to the measured bioassay value), and Uniform Relative Error (σ_i^2 proportional to the square of the measured bioassay value).

A seventh available least-squares method assumes that measurement errors are lognormally distributed, with 'uniform' or equal variances of the logarithms for all measurements (Uniform Logarithmic Error method). In this case, an estimate of intake is given by

$$log\,(I) = \frac{\sum_{i=1}^{n} log\,(X_i/R_i)}{n} \quad (2)$$

When one of the least-squares methods is used, the organ dose D (in Gy) is estimated as the product of the intake obtained from the bioassay data by the least-squares method and a dose conversion factor (DCF) which is a dose per unit intake appropriate for acute (Gy per Bq) or chronic (Gy per Bq d^{-1}) intakes:

$$D = I \cdot DCF \quad (3)$$

The DCFs used for acute inhalation or ingestion exposures represent annual doses per unit intake, and are stored as calculated values for each year up to 75 y post exposure. On the other hand, the DCFs for chronic exposure are calculated by integration of time-independent dose-rate functions based on the time length of exposure provided by the user for the study subject. InDEP can report annual doses, committed doses (over 50 y post exposure) or cumulated doses (defined as the total dose from exposure up to a user-provided limiting date). Doses can be reported as absorbed (Gy or rad) or equivalent (Sv or rem) doses for 33 different organs or tissues. To obtain equivalent doses, a radiation weighting factor is applied to the high LET portion of the absorbed dose. The default weighting factor is 20 for alpha radiation[13], however, the user can modify the weighting factor to any value desired.

When using the least-squares method, the uncertainty in the intake, I, is estimated by using Monte Carlo methods to propagate the uncertainties in X provided by the InDEP user and the uncertainties in R provided in InDEP. The uncertainty in I estimated by InDEP is again propagated with the uncertainties in the DCF, provided in InDEP, to estimate the uncertainty in the organ dose, D.

Bayesian method

The formulation of Bayes' theorem as it applies to internal dosimetry is

$$P\,(I|X)\,\mathrm{d}I = \frac{P\,(X|I)\,P\,(I)\,\mathrm{d}I}{\int_0^\infty P\,(X|I)\,P\,(I)\,\mathrm{d}I} \quad (4)$$

where $P(I|X)\,\mathrm{d}I$ is known as the *posterior* distribution and describes the probability of possibly true values of intake I given the set measurements X; $P(X|I)$ is the *likelihood* function of intake I; $P(I)\,\mathrm{d}I$ is the *prior* distribution of possibly true values of intake I and; X is the set of bioassay measurements.

The Bayesian method as formulated above assumes perfectly known excretion or retention functions $R(t)$ or doses per unit intake (DCF). In reality, $R(t)$ or DCF are predicted using biokinetic and dosimetric models with parameters L_m ($m = 1, M$) and model structures affected by substantial uncertainties. Thus, $R(t)$ and DCF themselves are affected by uncertainties.

The Bayesian formulation above may be modified[14–16] as follows to include the fact that the excretion or retention functions are uncertain and can be described by a probability $P(R)$:

$$P(I|X)\,\mathrm{d}I = \frac{\int_0^\infty P(X|I,R)\,P(I)\,P(R)\,\mathrm{d}I\mathrm{d}R}{\int_0^\infty \int_0^\infty P(X|I,R)\,P(I)\,P(R)\,\mathrm{d}I\mathrm{d}R} \quad (5)$$

A similar formulation can be written for estimating the probability of dose values (D) given the set of measurements X. InDEP assumes that no prior knowledge about intake (or dose) is available before the measurements are analysed; thus, the prior distribution of intake (or dose) is assumed to be uniform (i.e. constant) between a minimum and a maximum value either estimated automatically or provided by the user. This prior is equal to zero outside these limits, and the value of the constant cancels out from the equation above. For estimation of intake, the automatic procedure sets the minimum to be equal to zero and the maximum to the mean of the Ratio of the Means method plus two standard deviations. For estimation of dose, the minimum and the maximum doses are obtained by multiplying the 5th (95th) percentile of intake by the 5th (95th) percentile of the appropriate dose per unit intake (i.e. dose coefficient), respectively. These limits for the prior distributions can be overridden by the user.

The prior knowledge introduced by the biokinetic models (i.e. $P(R)$) is represented by lognormal distributions. The likelihood function can be specified as being normal (i.e. Gaussian) or lognormal. Numerical integration is used to estimate the posterior distribution for intake or dose. As opposed to the least-squares methods which are implemented in the batch mode, the Bayesian method in InDEP can be used only for one case (i.e. one set of bioassay data) at a time.

Biokinetic and dosimetric database

To greatly increase the speed of the calculations, the biokinetic models are used to pre-calculate the expected activities of uranium or plutonium in urine, feces, lung, liver or whole-body from a unit intake of radionuclide, known as intake excretion functions (IEFs) and intake retention functions (IRFs). Organ doses from a unit intake of radionuclide are also pre-calculated to create dose conversion factors (DCFs).

For inhalation exposure, the IEFs, IRFs and DCFs are available for inhalation of particles with 13 discrete activity median aerodynamic diameters (AMAD) ranging from 0.001 to 10 μm and absorption (solubility) Types S, M, or F compounds.

For ingestion of uranium, IEF/IRFs and DCFs are available for two gastrointestinal tract absorption fractions (f_1):

- UO_2, U_3O_8 and most tetravalent compounds—low absorption—f_1=0.002
- All other uranium compounds—high absorption—f_1=0.02.

The IEF/IRFs and DCFs were calculated using the ICRP biokinetic models with ICRP recommended parameter values. IEF/IRFs and DCFs can be developed for other biokinetic models, and selection of other particle sizes, absorption types and model parameter values, and added to the code. An uncertainty factor is assigned to each pre-calculated IEF/IRF and DCF. Each uncertainty factor is described by a lognormal probability distribution with a geometric mean (GM) equal to 1.0 and a geometric standard deviation (GSD) specific to a given radionuclide, organ and exposure type[8].

The magnitude of the uncertainties are derived from Monte Carlo calculations using continuous probability distributions assigned to parameters of the biokinetic model as described in uncertainty analysis studies performed at the University of Florida[17, 18] and complemented by Aden and Scott[19], from subjective evaluations of uncertainties performed by groups of experts such as Bouville *et al*.[20], Goosens *et al*.[21] and the National Council on Radiation Protection and Measurements (NCRP)[22, 23], and based on personal communications with Dr Richard W. Leggett of Oak Ridge National Laboratory. Other relevant data that were reviewed and used include variability of the absorption fraction from the gastro-intestinal tract (f_1)[24] and an uncertainty analysis study for another bone seeker (i.e. ^{90}Sr)[25]. The magnitudes of uncertainties (i.e. GSDs) in IEF/IRFs and DCFs were taken directly from the above-mentioned publications, when possible, or were assigned using subjective professional judgements based on analyses of uncertainties performed by our group. The estimated uncertainty in IEF/IRFs and DCFs intend to incorporate all uncertainties in biokinetic and dosimetric parameters due to inter-individual variability and lack of knowledge for a given radionuclide, organ and type of exposure. However, the uncertainties in DCFs do not include the uncertainty associated with the biological effectiveness of different types of radiation.

In the current version of the code, the Bayesian method operates only for a given AMAD and absorption type (e.g. AMAD=5 μm, Type M), provided by the user based on knowledge about the exposure situation for the individual whose bioassay data are being analysed. However, combined distributions for particle size or absorption type (e.g. 70 % chance that the radionuclide was Type M and 30 % chance that the radionuclide was Type S) can be defined and used with the least-squares method, but not with the Bayesian method.

METHODS

An individual study subject was selected from the cohort of uranium workers currently being evaluated by NIOSH to investigate the assumptions and procedures that were used in the intake/dose assessment of the larger cohort (n = 6409). This individual study subject had the potential for exposure to uranium during his employment at the facility in the 1950s. The bioassay data for this study subject were in the form of urine uranium concentration (in μg l^{-1}) from single void urine samples. Urine samples were adjusted for background levels of naturally occurring uranium in urine by subtracting the median annual concentration of uranium from pre-employment urine samples on record for the cohort.

Because the uranium concentration data were for single void urine samples, it was necessary to normalise these urine samples to 24-h samples, and this was done by multiplying by the Reference Man urinary output volume of 1.6 l d^{-1}[26]. Also, gravimetric concentration was converted to activity concentration by multiplying by the specific activity of natural uranium (0.025 Bq μg^{-1}).

Uncertainty in bioassay samples was characterised by using Monte Carlo propagation methods to combine uncertainties from various sources. Uncertainty in the factor used for normalisation of a spot urine sample to a 24-h sample was assumed to be lognormally distributed. A GSD of 1.6 was estimated using data from studies of 24-h urine voiding in asymptomatic men and women[27, 28].

Uncertainty due to conversion of gravimetric uranium concentration to activity concentration was assumed to be represented by a lognormal distribution of the specific activity, with a median value equivalent to the specific activity of natural uranium and with lower 5th and upper 95th percentiles equivalent to the specific activity of depleted (0.2 wt. %) uranium and low-enriched (2.0 wt.%) uranium, respectively. This assumption was based on information found in a facility memorandum (West H. Memorandum to N. Ingle. Technical Basis for Decision Made on Uranium Internal Dosimetry of FMPC Employees. Oak Ridge, TN: Oak Ridge Institute for Science and Education; 12 April 1994). However, for this facility, uncertainty in the specific activity of the bioassay samples (estimated GSD=1.11) was found to be negligible compared with that from normalisation. Therefore, the log-normal distribution (GM=1.0; GSD=1.6) that represents the uncertainty in the 24-h normalisation process was applied as a representation of the uncertainty in all urine data. Bioassay data collected for this individual, including the assumed associated uncertainty, was organised into a standard Microsoft Access® database file.

Intakes and doses calculated using InDEP were compared with intakes and doses calculated with another commonly used internal dose program, IMBA (v. 4.0.9, ACJ and Associates and Health Protection Agency, Radiation Protection Division (HPA). Incorporating HPA's IMBA Suite©1997–2005. IMBA Expert ORAU Edition ©2000–2005). For this comparison exercise, the 24-h normalised gravimetric uranium concentration was converted to an activity concentration of ^{234}U by multiplying by the specific activity of ^{234}U. Calculated intakes and doses were also compared in both programs assuming exposure to a natural uranium aerosol. Type M absorption was assumed and the particle size of inhaled uranium was assumed to be 5-μm AMAD. In both programs, bioassay data were assumed to have uniform logarithmic errors with a GSD of 1.6; that is, the uncertainty in each bioassay data point was assumed to be described by a lognormal distribution with a GM=1.0 and GSD=1.6 and the Uniform Logarithmic Error method was selected as the preferred method for estimation of intake and doses.

In a second exercise, intended to show the effect of the choice of a fitting method for bioassay data on central estimates and confidence intervals, InDEP was used to calculate intakes and doses with all seven least-squares fitting methods and the Bayesian method. Where it was necessary to assume the data were normally distributed, a coefficient of variation (CV) of 0.5 was assumed for each bioassay data point to estimate the standard

deviation (SD) as the product of the mean and the CV. When the data were assumed lognormally distributed, a GSD of 1.6 was assumed. The intake via inhalation was assumed to be a chronic exposure to a ^{234}U, Type M, 5-μm AMAD aerosol.

When analyses are carried out assuming an exposure to mixture of uranium isotopes, the uncertainty in the isotopic abundance of the uranium exposure aerosol also contributes to the uncertainty in the estimated intakes and organ doses. This contribution was examined by varying the assumed specific activity of uranium from depleted (0.2 wt.% ^{235}U) to low enriched (2.0 wt.% ^{235}U). Again, for this exercise, a 5-μm AMAD, Type M aerosol was assumed and the analysis was carried out under the assumption of uniform logarithmic errors with a GSD of 1.6 for the bioassay samples.

Often particle size or absorption type are not adequately characterised, and it is useful to investigate the additional uncertainty in estimated intakes and doses introduced due to the choice of particle size distribution and chemical form of a natural uranium exposure aerosol. In this analysis, particle size was varied discretely assuming aerosols of 1, 5 and 10 μm AMAD. The rate of absorption of uranium from lungs to blood (Absorption Type) was varied from Type F (fast absorption or relatively soluble) to Type S (slow absorption or relatively insoluble). The InDEP program also allows for the user to define a distribution of particle sizes or absorption types, e.g. an assumed mixture of 50 % Type M, 50 % Type S uranium compounds or a mixture of 33 % 1-μm, 33 % 3-μm, 34 % 5-μm AMAD aerosols. Intakes and doses were also estimated assuming these mixtures.

The effect of the assumed number of exposures on the magnitude of intakes and doses was also investigated for the same individual using the InDEP program's utility for projecting bioassay data. Estimates of total intake and organ dose for two chronic intakes occurring during the same period of time of a 10-μm AMAD Type M natural uranium aerosol were compared with estimates of total intake and organ equivalent dose based on an assumed single chronic intake. Also, intake dates for a single chronic intake were varied to examine the effect on intake and organ dose.

RESULTS AND DISCUSSION

Figure 1 shows the variation of gross uranium concentration in urine samples (n = 37) during the exposure period. Bioassay data for this individual consisted of 37 urine spot samples with a mean gross uranium concentration of 45±38 μg l^{-1} (median 31 μg l^{-1}; range 9.0–180 μg l^{-1}). The annual median pre-employment uranium concentrations in urine samples for the cohort varied from 3 to 23 μg l^{-1}. The mean and median net uranium concentrations in urine samples for the example study subject were 35 and 20 μg l^{-1}, respectively, with a range 1–170 μg l^{-1}. Table 1 shows descriptive statistics for activity concentration in urine samples normalised to 24 h depending on assumptions regarding specific activity of uranium.

Table 2 shows intakes and organ equivalent doses for an assumed inhalation of both ^{234}U and natural uranium calculated using both the IMBA and InDEP computer programs. The two programs produced comparable results with the IMBA program making use of the maximum likelihood method. Minor variations are due to rounding when converting

uranium mass to activity (0.025 Bq μg^{-1} used for InDEP versus 0.02527 Bq μg^{-1} used by IMBA). With IMBA, it is also possible to use the least-squares method to estimate the uncertainty in the intake, but IMBA currently does not include errors due to uncertainty in biokinetic model parameters.

Uncertainties in intake calculations using InDEP include both uncertainty in the measurement provided by the user as well as predetermined uncertainties in the intake retention/excretion functions due to uncertainty in the biokinetic model from variation in deposition, absorption and transfer between organs. Uncertainties in dose calculations in InDEP account for uncertainty in intake and uncertainty in the dosimetry specific to the radionuclide in a given organ.

The effect of using various least-squares fitting methods or using the Bayesian method on intake calculations is shown in Table 3. Intakes varied by as much as two orders of magnitude depending on the model assumed for the variance in the bioassay data. Uniform Absolute Error, Ratio of the Means and Average of Slopes methods provided the highest estimate of intake, while the uniform relative error method provided the lowest estimate. The uniform logarithmic rrror method resulted in an intake estimate similar to that resulting from using the Bayesian method, because both methods assume that the uncertainty in the bioassay data is described by lognormal distributions with the same GSD for all bioassay data points. Both the least-squares methods using Monte Carlo for error propagation and the Bayesian method produced probability distributions that could be approximated as lognormal, although the Bayesian method produced a probability distribution with the best lognormal fit. The Bayesian method produced the narrowest confidence interval. Lognormality of the uncertainty in the bioassay data points is probably the most appropriate assumption, because lognormal distributions were obtained when the bioassay measurements were converted into normalised 24-h excreted activities. Thus, it follows that the uniform logarithmic error method or the Bayesian approach would produce more reliable results than all other methods for cases similar to the one presented in this paper.

Table 4 illustrates the variation in calculated intakes and organ equivalent doses due to the assumption of different enrichment levels of the uranium in the exposure aerosol. There was less than a factor of 3 between intakes and organ doses calculated assuming exposure to depleted uranium and exposure to 2.0 % enriched uranium and uncertainty intervals for all three exposure scenarios overlapped.

Varying particle size and absorption type also affected intake and organ equivalent dose estimates as shown in Table 5. The 90 % confidence intervals for the intakes were tighter than for the organ dose estimates, with a factor of ~50 between the lower 5th percentile and upper 95th percentile. The size of the confidence intervals for intakes did not vary significantly with particle size or absorption type. The confidence intervals for organ dose estimates were wider than for intakes and varied between a factor (ratio of upper 95th to lower 5th percentile) of 200 for 1-μm AMAD aerosols and 2000 with 5- and 10-μm AMAD aerosols. Using a probability distribution to account for uncertainty in both particle size and absorption type increased the ratio of upper 95th to lower 5th percentile to 300 for intakes and 8600 for lung dose, while the ratio for bone surface dose remained at ~2000. This

emphasises the importance of obtaining as much information as possible about the particle size and chemical form for a given exposure case. Using a distribution to represent the absorption type significantly impacts the size of the confidence interval for lung dose estimates.

Intakes and doses calculated assuming either one chronic exposure or two overlapping chronic exposures of a natural uranium aerosol were similar. For the analysis assuming two exposures, the first intake was assumed to extend from the beginning to the end of employment (Days 1–2695), while an additional intake was assumed to have occurred between days 1168 and 1285 from the beginning of employment. Total amount inhaled assuming one intake was 5.1×10^{4} Bq (7.3×10^{3}–3.9×10^{5} Bq) (median and 90 % CI), whereas the total amount inhaled assuming two separate chronic intakes was 5.6×10^{4} (9.2×10^{3}–3.3×10^{5} Bq). Lung equivalent doses resulting from either intake scenario were also similar: 3.5×10^{-1} Sv (9.3×10^{-3}–1.3×10^{1} Sv) (median and 90 % CI) assuming one intake versus 3.7×10^{-1} Sv (8.5×10^{-3}–1.8×10^{1} Sv). Intakes calculated assuming a chronic exposure to a uranium aerosol and varying intake begin and end dates by 30 days did not vary significantly for this case.

The results presented here are based on a GSD of 1.6 representing uncertainty introduced by normalisation of spot samples to 24-h samples. This GSD is smaller than the ‘lognormal scattering factor (SF)’ recommended in the guidelines produced from the IDEAS Project[29]. The default GSD value for a spot sample in the IDEAS General Guidelines is 2.0, however that was determined by Moss *et al.*[30] based on urine plutonium, not uranium, measurements. For the Fernald mortality study internal dose assessment[7], a GSD of 1.8 was used to describe the uncertainty in the urine bioassay data for the cohort. That GSD accounts for additional uncertainty contributions from sampling and measurement errors, and other potential sources. The effect of increasing the GSD from 1.6 to 1.8 on the intake estimated for the individual case presented in this paper was found to be negligible.

The least-square methods and the Bayesian method described in this paper use pre-calculated bioassay predictions and doses per unit intake in order to reduce the amount of data handled and increase the speed of calculation. This approach allows for batch-mode, independent analyses of many workers, each with multiple bioassay data points, when least-square methods are used. The current version of InDEP does not have the capability to use the Bayesian method when running in batch mode and it cannot derive a true posterior distribution for the entire cohort, nor do the authors have the computational power yet to use a posterior distribution for the entire cohort as given by a Bayesian method. Thus, the organ doses and uncertainties that were used in the recently completed epidemiological study were calculated using the least-squares method with Monte Carlo methods to estimate uncertainty[7].

CONCLUSION

As a step in the process of conducting epidemiological studies for more than 6000 workers at former uranium processing facilities, NIOSH has been supporting the development of InDEP (Internal Dose Evaluation Program), a bioassay analysis computer program. This

program is intended as a computational tool for exposure assessment of workers exposed primarily to either uranium or plutonium. The current version of InDEP calculates intakes and organ doses, with uncertainty, for individuals exposed to uranium or plutonium, by applying the least-squares method or Bayes' Theorem to analyse the bioassay data. InDEP propagates uncertainty from various sources, including user-provided bioassay uncertainty, uncertainty in retention/excretion fractions and uncertainty in dose coefficients. InDEP uniquely allows for intake and dose calculation from exposure to user-defined uranium or plutonium isotopic mixtures. The program has a batch feature which allows for the evaluation of large numbers of individuals simultaneously using a variety of bioassay data. Additionally, the program permits the evaluation of single cases, allowing the user to investigate the effect of various exposure scenarios and parameter assumptions on intake and dose.

A specific subject was selected from the current NIOSH uranium mortality study cohort to test the assumptions made for the exposure scenario and parameters that were based on information obtained from the study facility reports, memoranda, and other documents on operation, plant industrial hygiene, and health physics. A single chronic exposure to uranium over the course of the subject's work history was determined to be a reasonable intake scenario given the type of facility and the nature of the work. Based on facility documents, although particle size and absorption type varied with the type of operation, a reasonable assumption for the type of exposure is a natural uranium aerosol with a 10-μm AMAD particle size and Absorption Type M (moderately soluble). The specific activity of uranium at the facility varied between depleted and less than 2-wt.% enriched, thus uncertainty in the level of enrichment did not contribute significantly to uncertainty in the intake and dose estimates. Sensitivity analyses indicate that the largest source of uncertainty in the bioassay data is due to normalisation of the uranium concentration in the spot urine samples to a 24-h excretion.

Overall, the features of the current version of InDEP are invaluable for more effective and individualised exposure assessment of large numbers (thousands) of workers in epidemiological studies of uranium exposed cohorts. At this time, epidemiology relies on point estimate of organ doses (e.g. mean or median doses assigned to each subject). However, epidemiological methods that explicitly account for the uncertainty in doses for each member of a cohort are being developed. These methods rely not only on the uncertainty in doses for each individual, as produced by the current version of InDEP, but also on the correlation of doses among individuals in the cohort. At this time, InDEP does not account for shared and unshared errors among members of a cohort neither for least-square methods nor for Bayesian method. In particular, derivation of a Bayesian posterior distribution for the entire cohort is computationally non-trivial even at the current computing power. The authors plan to investigate the possibility of modifying the current setup of the program to account for shared and unshared errors using the least-squares method for future analyses of uranium worker cohorts.

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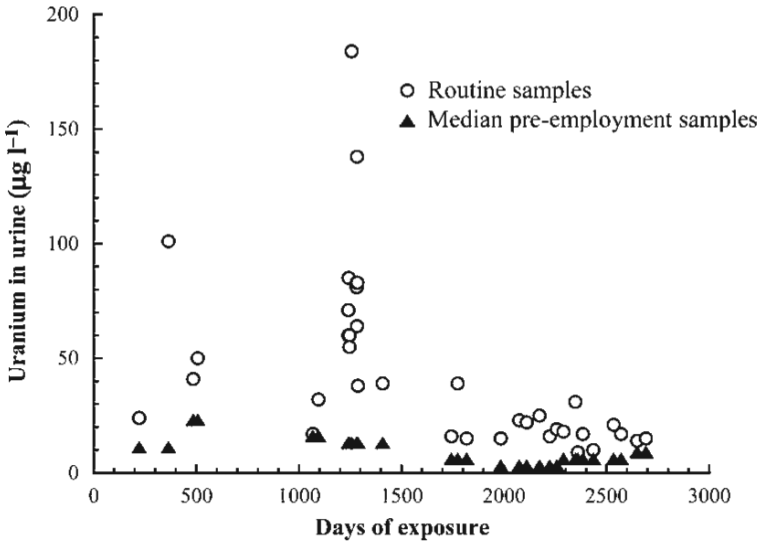

Figure 1.

Uranium concentration in routine urine spot samples and median uranium concentration in pre-employment urine samples for the cohort. The study subject was assumed to have been exposed continuously for about 8 y during the 1950s. The data points for the pre-employment samples represent the annual median pre-employment samples among all study subjects.

Table 1

Descriptive statistics of net uranium activity concentrations in normalised urine samples (n=37) for the example study subject, for different assumed isotopic mixtures.

	^{234}U (Bq d^{-1})	Natural Uranium (Bq d^{-1})	Depleted Uranium (Bq d^{-1})	Enriched Uranium (Bq d^{-1})
Mean	13 000	1.4	0.82	2.4
SD	13 000	1.5	0.85	2.5
Median	7400	0.80	0.47	1.4
Range	370–63 000	0.040–6.8	0.024–4.0	0.069–12

Table 2

Comparison of intakes and organ equivalent doses calculated using IMBA and InDEP.

	234U		Natural Uranium	
	IMBA[a]	**InDEP**	**IMBA[a]**	**InDEP**
Intake (Bq d^{-1})	1.2×10^{5}	1.2×10^{5}	1.3×10^{1}	1.3×10^{1}
Lung (Sv)	5.1×10^{3}	5.1×10^{3}	5.0×10^{-1}	4.9×10^{-1}
Bone surface (Sv)	8.5×10^{2}	8.4×10^{2}	8.8×10^{-2}	8.6×10^{-2}
Kidneys (Sv)	3.1×10^{2}	3.1×10^{2}	9.2×10^{-3}	9.0×10^{-3}
Liver (Sv)	1.2×10^{2}	1.2×10^{2}	3.2×10^{-2}	3.2×10^{-2}
Red marrow (Sv)	8.8×10^{1}	8.7×10^{1}	1.2×10^{-2}	1.2×10^{-2}

Intake was assumed to be a chronic inhalation exposure to a Type M, 5-μm particle size aerosol of either ^{234}U or natural uranium for 2695 days. Analysis was performed under the assumption of uniform logarithmic errors for the bioassay data.

[a]Values are best estimates obtained using the IMBA default maximum likelihood method, and medians are reported for InDEP.

Table 3

Comparison of intakes calculated with the InDEP program by different least squares fitting methods and a Bayesian method.

Fitting method	Median (Bq d^{-1})	Mean (Bq d^{-1})	90 % Confidence interval (Bq d^{-1})
Weighted Least Squares	1.4×10^{4}	3.0×10^{4}	1.8×10^{3}–1.0×10^{5}
Uniform Absolute Error	1.9×10^{5}	4.0×10^{5}	2.6×10^{4}–1.4×10^{6}
Ratio of the Means	1.9×10^{5}	4.0×10^{5}	2.7×10^{4}–1.4×10^{6}
Average of Slopes	1.9×10^{5}	4.0×10^{5}	2.8×10^{4}–1.4×10^{6}
Square-Root Error	3.9×10^{4}	1.3×10^{5}	<0–4.4×10^{5}
Uniform Relative Error	5.1×10^{3}	1.7×10^{4}	<0–7.4×10^{4}
Uniform Logarithmic Error	1.2×10^{5}	2.4×10^{5}	1.6×10^{4}–8.6×10^{5}
Bayesian	1.3×10^{5}	1.3×10^{5}	9.3×10^{4}–1.9×10^{5}

Intake was assumed to be a chronic inhalation exposure to a ^{234}U, Type M, 5-μm particle size aerosol for 2695 days.

Table 4

Intakes and organ equivalent doses calculated assuming a chronic exposure to a 5-μm AMAD, Type M uranium aerosol varying specific activity from depleted (0.2 wt.% ^{235}U) to enriched (2.0 wt.% ^{235}U).

	Depleted Uranium[a]	Natural Uranium[a]	Enriched Uranium[a]
Intake (Bq d^{-1})	7.6×10^{0} (1.0×10^{0}–5.5×10^{1})	1.3×10^{1} (1.7×10^{0}–9.3×10^{1})	2.2×10^{1} (3.0×10^{0}–1.6×10^{2})
Lungs (Sv)	2.9×10^{-1} (8.9×10^{-3}–1.2×10^{1})	4.9×10^{-1} (1.5×10^{-2}–2.0×10^{1})	8.5×10^{-1} (2.6×10^{-2}–3.5×101)
Bone Surface (Sv)	5.1×10^{-2} (1.2×10^{-3}–2.4×10^{0})	8.6×10^{-2} (2.1×10^{-3}–4.0×10^{0})	1.5×10^{-1} (3.6×10^{-3}–7.0×10^{0})
Kidneys (Sv)	1.9×10^{-2} (5.3×10^{-4}–8.0×10^{-1})	3.2×10^{-2} (9.0×10^{-4}–1.4×10^{0})	5.6×10^{-2} (1.6×10^{-3}–2.4×10^{0})
Liver (Sv)	7.0×10^{-3} (2.0×10^{-4}–3.0×10^{-1})	1.2×10^{-2} (3.4×10^{-4}–5.1×10^{-1})	2.1×10^{-2} (5.8×10^{-4}–8.8×10^{-1})
Red Marrow (Sv)	5.3×10^{-3} (1.4×10^{-4}–2.4×10^{-1})	9.0×10^{-3} (2.3×10^{-4}–4.0×10^{-1})	1.6×10^{-2} (4.0×10^{-4}–7.0×10^{-1})

The least-squares method assuming uniform logarithmic errors in the bioassay data (GSD=1.6) was used to calculate intakes.

[a]Values are medians and 90 % confidence intervals.

Table 5

Intakes and organ equivalent doses calculated assuming a chronic exposure to a natural uranium aerosol varying particle size and absorption type.

Particle size (μm)	Absorption type	Intake[a] (Bq d^{-1})	Lung[a] (Sv)	Bone surface[a] (Sv)
1	F	3.6×10^{0} (5.9×10^{-1}–2.2×10^{1})	3.1×10^{-3} (1.7×10^{-4}–5.4×10^{-2})	8.5×10^{-2} (4.0×10^{-3}–1.7×10^{0})
1	M	9.0×10^{0} (1.3×10^{0}–7.2×10^{1})	5.7×10^{-1} (3.4×10^{-2}–8.3×10^{0})	8.7×10^{-2} (3.7×10^{-3}–1.8×10^{0})
1	S	1.2×10^{2} (2.0×10^{1}–8.4×10^{2})	2.4×10^{1} (1.6×10^{0}–3.0×10^{2})	1.4×10^{-1} (6.5×10^{-3}–3.0×10^{0})
5	F	3.0×10^{0} (4.7×10^{-1}–2.0×10^{1})	2.8×10^{-3} (8.9×10^{-5}–9.1×10^{-2})	8.0×10^{-2} (2.2×10^{-3}–3.1×10^{0})
5	M	1.3×10^{1} (1.8×10^{0}–8.8×10^{1})	4.9×10^{-1} (1.6×10^{-2}–1.4×10^{1})	8.1×10^{-2} (2.2×10^{-3}–3.2×10^{0})
5	S	2.0×10^{2} (2.9×10^{1}–1.3×10^{3})	2.2×10^{1} (6.6×10^{-1}–5.8×10^{2})	1.4×10^{-1} (3.3×10^{-3}–5.2×10^{0})
10	F	3.8×10^{0} (5.6×10^{-1}–2.4×10^{1})	2.9×10^{-3} (8.5×10^{-5}–1.0×10^{-1})	8.4×10^{-2} (2.0×10^{-3}–3.3×10^{0})
10	M	1.9×10^{1} (2.7×10^{0}–1.4×10^{2})	3.5×10^{-1} (9.3×10^{-3}–1.3×10^{1})	8.1×10^{-2} (1.9×10^{-3}–3.6×10^{0})
10	S	3.4×10^{2} (5.1×10^{1}–2.5×10^{3})	1.6×10^{1} (5.0×10^{-1}–5.1×10^{2})	1.2×10^{-1} (2.7×10^{-3}–6.2×10^{0})
Distribution[b]		4.1×10^{1} (2.5×10^{0}–8.2×10^{2})	3.1×10^{0} (3.2×10^{-2}–2.8×10^{2})	1.2×10^{-1} (2.4×10^{-3}–4.8×10^{0})

The least-squares method assuming uniform logarithmic errors (GSD=1.6) for the bioassay data was used to calculate intakes.

[a] Values are median and 90 % confidence interval.

[b] Particle size distribution: 33 %/33 %/34 % 1-/3-/5-μm AMAD; Absorption type distribution: 50 %/50 % M/S.