Paper

FITTING BIOASSAY DATA AND PERFORMING UNCERTAINTY ANALYSIS WITH BIOKMOD

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Abstract—**We have developed a computer code called BIOKMOD that we have applied to analyze several sources of uncertainties in the evaluation of internal exposures using bioassay data: (1) Multiple constant and random intakes in occupational exposures taking into account periods without intake (weekends, holidays, etc.) are evaluated, and they are compared with chronic intakes showing that the chronic approximation is not always good; (2) An analytical method to evaluate the statistical uncertainties associated with the biokinetic model is described; and (3) Non linear techniques are applied to estimate intakes using bioassay data, where not only the quantities taken in are assumed unknown but also other non linear parameters (AMAD, f_1, etc). The methods described are accompanied with examples. Some of the most usual features of BIOKMOD can be run directly, using BIOKMOD-WEB, at the Web site: http://www3.enusa.es/webMathematica/Public/biokmod.html.**

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Key words: biokinetics; modeling, biological factors; intake, radionuclide; statistics

INTRODUCTION

BIOKINETIC MODELING is widely used in internal dosimetry to evaluate bioassay data. All current International Commission on Radiological Protection (ICRP) models, compiled in the ICRP Database of Dose Coefficients (ICRP 2001), can be represented by compartmental systems with constant coefficients. The conceptual model used by ICRP is represented in Fig. 1. It can be summarized as follows. The human body can be divided in three systems:

1. The human respiratory tract model (HRTM). This model is applied for modeling the intake of radioactive aerosols by inhalation. The detailed description is given in ICRP 66 (1994). If a person inhales instantaneously a quantity I, it is deposited directly in some compartments of the HRTM. The fraction deposited in each compartment is called the initial deposition fraction or *IDF*. It is a function of activity median aerodynamic diameter (AMAD), which includes size, shape, density, and anatomical and physiological parameters, as well as various conditions of exposure. The *IDF* values may be calculated either following the procedure described in ICRP 66 (1994) or obtained from Annex F of ICRP 66 (1994). The general model of the HRTM is common to any element, except that the absorption rates $\{s_{pt,}\ s_{p,}\ s_t\}$, which are related to the chemical form of the element, differ. ICRP gives default values of absorption rates according to types F, M, or S (fast, moderate, and slow, respectively).
2. The gastrointestinal tract (GI). Modeling the intake of particles in the GI tract follows the model provided in ICRP 30 (ICRP 1979). Particles can be introduced in the GI tract directly by ingestion or from the respiratory tract (RT). Deposition is in the stomach (ST). Part or all the flow is transferred, through the small intestine (SI), to the blood (B). The rate transfer from SI to B is given by $\lambda_B = f_1\ \lambda_{SI}/(1-f_1)$, where f_1 is the fraction of the stable element reaching the blood (or body fluids). If $f_1 = 1$ all flows from the stomach and is transferred to B. The value of f_1 is associated with the elements and their chemical form. The GI tract model will be replaced by the human alimentary tract model (HATM), which is not published yet.
3. Systemic compartments. These are specific to an element or groups of elements (ICRP 2001). ICRP 78 (1997) establishes three generic groups: (i) hydrogen, cobalt, ruthenium, cesium, and californium; (ii) strontium, radium, and uranium and; (iii) thorium, neptunium, plutonium, americium, and curium. For other elements not included in ICRP 78, the ICRP 30 model is applicable, and they have the same generalized compartmental model as group (i). For the elements of each group the same model is applied although some parameters are specific to the element. From a mathematical point of view we can establish two

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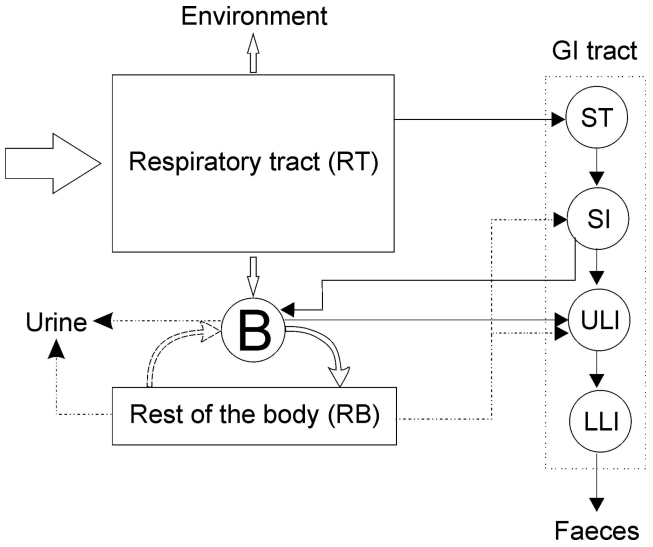

Fig. 1. Conceptual ICRP model applied for particle intakes by inhalation. The particles are deposited in some compartments of the respiratory tract (RT). From the RT the flow goes to the stomach (ST) or to the blood (B). "Rest of Body" represents the systemic compartments. The detailed flow diagram is specific to each kind of element. The dashed arrows mean that the flow can be followed this way or not, depending on the characteristic of the element.

groups: a) elements whose biokinetic model does not involve recycling, this includes the group (i) and the elements where ICRP 30 is still applicable; and b) elements whose biokinetic model involves recycling, which includes group (ii) and (iii).

A few computer codes have been developed to estimate intake and calculate internal dose using bioassay data. The main characteristics of most of them are summarized by Ansoborlo et al. (2003); perhaps the most complete is IMBA (Birchall et al. 2003). We have developed a code called BIOKMOD. It has the following features, which to our knowledge are not included in any other:

1. It gives analytical and numerical solutions (other codes only give the numerical). Even the solutions can be given as function of some parameters. The accumulated disintegrations in a compartment or region can be computed exactly by analytical integration, what is more precise than the method of the mean resident time (Loevinger et al. 1988) often applied for other codes;
2. Apart from acute, chronic and multi-inputs, it can practically be used for any kind of continuous inputs (exponentials, periodic, etc.), even for random inputs;
3. The intakes can be estimated fitting bioassay data where not only the intake quantities but also other parameters (AMAD, f_1, etc.) can be assumed unknown;
4. Analytical expressions instead of simulations can be used for sensitivity and uncertainty analysis; and
5. The user can easily build compartmental models which automatically generate the system of differential equations and their solutions (Sanchez 2005).

To run BIOKMOD with all capability it is necessary to use *Mathematica* (Wofram Research, Inc., Champaign, IL); however, some of the most usual features of BIOKMOD can be run directly at http://www3.enusa.es/webMathematica/Public/biokmod.html.

We have applied BIOKMOD to the evaluation of internal exposures using bioassay data. In particular, we refer to the random intakes in occupational exposures and their implication in the bioassays, the application of analytical methods to evaluate the uncertainties associated with the biokinetic model parameters, and the use of non-linear regression techniques to the bioassay data fitting. The methods described are accompanied with examples.

SOLVING THE ICRP MODELS

The mathematical criteria applied by BIOKMOD to obtain the content $q_i(t)$ at compartment i and to compute the intake retention functions $r_m(t)$ for different kinds of bioassays m, with m = {lung retention, daily urine excretion, thyroid content,. . . }, are described in Sanchez and Lopez-Fidalgo (2003). Below we summarize some details of these equations that we will need later.

The content $q_i(t)$ in each compartment i at time t, after an acute intake I at $t = 0$, is given by

$$q_i(t) = Iu_i(t), \tag{1}$$

where $u_i(t)$ is usually called the unit impulse-response function. It can be represented by the following pattern

$$u_i(t) = F_i(l_1, \ldots, l_m, s_p, s_{pt}, s_t, f_l, \lambda_l, \ldots, \lambda_n, h_l, \ldots, h_r, \lambda_R, t), \tag{2}$$

where l_i denote the rate transfers for HRTM compartments, λ_i the rate transfers for GI compartments, $h_1,\ldots,$ h_r the rate transfers for systemic compartments, and λ_R is the decay constant of the isotope; $u_i(t)$ is a sum of exponentials, that is

$$u_i(t) = \sum_{r=1}^{l} a_r e^{-h_r t}. \tag{3}$$

The predicted value for a kind of bioassay m after an acute input "1" at $t = 0$ is obtained by the sum of the

content of one or several compartments. It will also be a sum of exponentials:

$$r_m(t) = \sum_{v=1}^{l} c_v e^{-d_v t}, \quad (4)$$

where c_v and d_v are the coefficients obtained solving the model for the specific case.

In the case of inhalation eqn (4) can be written as

$$r_m(t) = \sum_{j,v} IDF_j(p) c_{j,v} e^{-d_{j,v} t}, \quad (5)$$

where p is the AMAD value in μm.

The retention function $R_m(t)$ for a single or acute intake I_0 at $t = 0$ is given by

$$R_m(t) = I_0 r_m(t). \quad (6)$$

The retention function $RC_m(t)$ for a continuous intake $I(t)$ can be obtained using the convolution theorem:

$$RC_m(t) = \int_0^t I(\tau) r_m(t - \tau) d\tau. \quad (7)$$

The chronic intake is a particular case of the continuous intake where $I(t) = I_d$ (daily rate intake constant) for $0 \leq t \leq T$.

The analytical expression of $r_m(t)$ given by the program cannot be checked directly with other programs because there are no others with this capability. So, we have compared the numerical solutions for acute intakes given by BIOKMOD for different times with the solutions given in ICRP 78 and in Potter (2002) obtaining a very good match.

MULTIPLE CONSTANT AND RANDOM INTAKES

In this section we will analyze two types of intakes: multiple constant and random. They are not included in other codes, at least with the extensions with which they are treated by BIOKMOD; however, they represent situations that happen frequently in the real world.

Multiple constant intakes

If we assumed multiple single intakes $\{I_1, \ldots, I_i, \ldots, I_n\}$ where I_j represents the intake that happens on day j, then the retention function $RM_m(t)$ on day t is given by

$$RM_m(t) = I_1 r_m(t) + I_2 r_m(t-1) + \cdots + I_t r_m(1) = \sum_{j=1}^{t} I_j r_m(t - j + 1). \quad (8)$$

In many situations the intake I_j happens for a few hours every day. However, from a practical point of view it can be assumed that I_j is an acute intake. But we are interested in considering $\{I_1, \ldots, I_i, \ldots, I_n\}$ as multiple constant intakes where each I_i occurs day t_i during time T_i (usually a shift). This case was studied by Bertelli and Lipsztein (1987) using the old models included in ICRP 30 (1979). We have expanded to include the current ICRP 2001 models using variable T_i periods.

The retention function $rc_m(t)$ for a constant intake $I = 1$ for $0 \leq t \leq T$, which ceases at $t = T$, is given by

$$rc_m(t, T) = \frac{1}{T}\int_0^t r_m(\tau) d\tau \text{ for } 0 \leq t \leq T$$

$$rc_m(t, T) = \frac{1}{T}\int_{T-t}^{t} r_m(\tau) d\tau \text{ for } t > T. \quad (9)$$

Then, assuming multiple constant intake, the retention function $RMC_m(t)$ can be computed as follows:

$$RMC_m(t) = I_1 rc_m(t, T_1) + I_2 rc_m(t-1, T_2) + \cdots + I_t rc_m(1, T_t) = \sum_{j=1}^{t} I_j rc_m(t - j + 1, T_j). \quad (10)$$

We can compare the retention using these equations with those obtained assuming a chronic intake. This comparison will be shown later in example 1.

Random intakes

In real situations, for workers being exposed to radioactive aerosols during the working days, the individual daily intake I is usually a random variable. In a previous article (Lopez-Fidalgo and Sanchez 2005), we found that when the daily intake $\{I_1, \ldots, I_j, \ldots, I_n\}$ can be fitted by a log-normal distribution then the retention function for random intake, called $RA_m(t)$, can be approximated by

$$RA_m(t) = \mu_I \sum_{j=1}^{t} r_m(j) \pm z\sigma_I \sqrt{\sum_{j=1}^{t} r_m^2(j)}, \quad (11)$$

where

$$\hat{\mu}_I = \frac{1}{N}\sum_i I_i;$$

$$\hat{\sigma}_I^2 = \frac{1}{N-1}\sum_i (I_i - \hat{\mu}_I)^2;$$

and z is the 100 $(\gamma + 1)/2$ – the quantile of the standard normal distribution.

We realize that eqn (11) can be applied even if $\{I_1,\ldots, I_j\ldots, I_n\}$ is not a lognormal distribution. In fact, if in eqn (8) I is a random variable, then $I_j\, r(t-j+1)$ will usually take small values, and considering a large number (<100) of single inputs I_i, then eqn (8) will be a sum of random and independent variables. In this case eqn (11) can be used without requiring that $\{I_1,\ldots, I_j\ldots, I_n\}$ be fitted to any distribution. It is a consequence of the Central Limit Theorem. We have also checked it by simulation using different distributions to generate $\{I_1,\ldots, I_j\ldots, I_n\}$ and testing that eqn (11) is verified.

The following example (based on data from the Juzbado Uranium Fuel Fabrication Plant) shows how these developments can be applied.

Example 1. A worker has been exposed to UO_2 (AMAD 5 μm and type S) radioactive aerosols during the last 2,000 d. He works 5 d per week 8 h a day; he also has 4 holiday weeks per year (with these criteria 2,000 days are 1,330 working days). It is estimated that in this time he has taken in 13,300 Bq uranium. It is also known from historical data that the relative standard deviation of the daily intakes for workers in this area is about 20%, which is $\sigma_I/\mu_I = 0.2$. We want to calculate the lung retention evolution. Regular weekends and holidays will be assumed.

The lung retention contents, $RMC_{Lung}(t)$, can be obtained applying eqn (10) with $I_j = \hat{I} = 13{,}300$ Bq U/1,330 working days = 10 Bq U/working day and $T = T_i = (8\text{ h})/(24\text{ h})\text{ d} = 1/3$ d. It can be also computed assuming a chronic daily intake of $I_d = 13{,}300$ Bq U/2,000 d = 6.65 Bq U/d, then $R_{Lung}(t) = I_d \int_0^t r_{Lung}(t)dt$. Both solutions are represented in Fig. 2. It can be observed that the differences between both methods are negligible in the middle of periods between two holiday seasons, and largest just after the holiday periods, but even in these cases they are not too important (lower than 5%). However, if we consider they are random inputs, then applying eqn (11), with $\mu_I = 10$ Bq/working day and $\sigma_I = 0.2 \times 10$ Bq U/d = 2 Bq U/working day, we obtain the solution shown in Fig. 3. We find that the differences between the random and the chronic input can be very important. For instance, on day 2,000 after the first intake, the estimated lung content for chronic intake is given only for one value $R_{Lung}(2000) = 240$ Bq U. However, the predicted retention will be better given as an interval than a value. So as

$$\sum_{j=1}^{2000} r_{Lung}(j) = 23.97$$

and

$$\sum_{j=1}^{2000} r^2_{Lung}(j) = 574.70,$$

then the estimated lung content is $RA_{Lung}(2000) = 10 \times 23.97 \pm 2 \times 2\sqrt{574.70}$ Bq U (computed with a confidence interval of 95%, $z \approx 2$), and, hence, 143.8 Bq U $\leq RA_{Lung}(2000) \leq$ 335.6 Bq U.

Remark: The holiday periods and the random intake effects should be taken into account when evaluating the bioassay analysis.

SENSITIVITY AND UNCERTAINTY ANALYSIS

The estimation of isotope content in a compartment or region involves many uncertainties even assuming that the ICRP metabolic models are a good representation of the real behavior of the particle intake in the human body. This is so because most of the true values of the

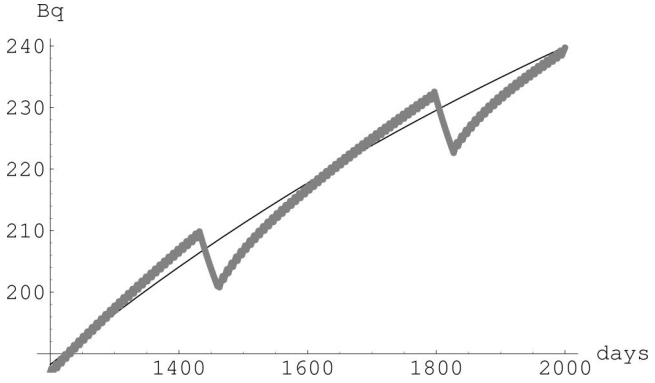

Fig. 2. Predicted lung retention for a worker being exposed to uranium aerosols (type S, AMAD 5 μm, and $\lambda_R \approx 0$). The smoothed line corresponds to a daily chronic intake. The bold line represents the same total quantity taken in, but the effect of the weekends and holiday seasons without exposure has been taken into account.

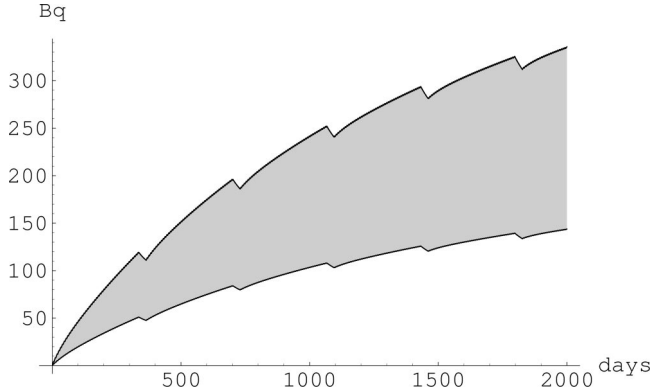

Fig. 3. Predicted lung retention probability bands (confidence interval 95%) for a worker being exposed to a random intake of uranium aerosols (type S, AMAD 5 μm, and $\lambda_R \approx 0$). Periods without exposure have been taken into account.

parameters in a real situation are unknown. In these cases the parameters usually applied are the reference worker values given by ICRP for a reference worker.

Assume $r(t)$ expressed as function of certain parameters $\{k_1, \ldots, k_r\}$ with their associated uncertainties: $\{u(k_1), \ldots u(k_r)\}$, then

$$r(t) = F(k_1, \ldots, k_n, t) \pm u_C(t), \quad (12)$$

where $u_C(t)$ is he combined standard uncertainty.

Assuming that $\{k_1, \ldots, k_r\}$ are uncorrelated and taking the first-order Taylor series terms of $F(k_1, \ldots, k_n, \lambda, t)$, then $u_C(t)$ can be evaluated using

$$u_C^2[r(t)] = \sum_{i=1}^{r} \left(\frac{\partial F}{\partial k_i}\right)^2 u^2(k_i). \quad (13)$$

This is the expression used by BIOKMOD for computing $u_C(t)$.

Of course, eqn (13) can be only applied when we can obtain the analytical solution of the model as function of the parameters $\{k_1, \ldots, k_r\}$, but it is only possible when the model does not involve recycling and in some particular cases of models with recycling. No recycling models can be discomposed in catenary branches (Skrable et al. 1974); then, when $\{k_i \neq k_j\}$, the solution can be expressed as function of the parameters $\{k_1, \ldots, k_r\}$.

The HRTM is a non recycling model. So, eqn (13) can be use to study the HRTM uncertainties as shown in the example below.

Example 2. We want to evaluate for a reference worker the lung retention after an acute intake ($I = 1$ at $t = 0$) of radioactive aerosols type S and $\lambda_R \approx 0$ assuming a relative standard deviation of 10% of the IDF_i (that is $\sigma_i/IDF_i = 0.1$).

The lung retention $r_{Lung}(t)$ according with eqn (5) has the following pattern:

$$F_{Lung}(t, p) = A_1(t)IDF_{A1}(p) + A_2(t)IDF_{bb(fast+sec)}(p) + A_3(t)IDF_{bb(slow)}(p) + A_4(t)IDF_{BB(fast+sec)} + A_5(t)IDF_{BB(slow)}(p), \quad (14)$$

where $IDF_i(p)$ are the initial deposition fractions, which depend of the AMAD p, in the regions $i = \{AI, bb_{fast+sec}, bb_{slow}, BB_{fast+sec}, \text{and } BB_{slow}\}$. These regions are defined in ICRP 66.

$A_i(t)$ is a sum of exponential terms whose expressions can be obtained by BIOKMOD solving the model for the specific case. In our example (reference worker and type S) they are:

- $A_1(t) = 1.6522 \times 10^{-7} \exp(-110.1\ t) - 4.16099 \times 10^{-6} \exp(-102.1\ t) + 0.0003030 \exp(-100.12\ t) + 0.0005992 \exp(-100.101\ t) + 0.00008317 \exp(-100.10\ t) + 0.00001663 \exp(-100.1\ t) + 0.0001654 \exp(-10.00\ t) - 0.004165 \exp(-2.0001\ t) + 0.3033 \exp(-0.0201\ t) + 0.5998 \exp(-0.0011\ t) + 0.08326 \exp(-0.00022\ t) + 0.01665 \exp(-0.0001\ t)$;
- $A_2(t) = -0.0002477 \exp(-110.1\ t) + 0.001239 \exp(-102.1\ t) + 6.9860 \times 10^{-6} \exp(-100.1\ t) - 0.2480 \exp(-10.00\ t) + 1.2400 \exp(-2.00\ t) + 0.00699 \exp(-0.0001\ t)$;
- $A_3(t) = -1.2565 \times 10^{-6} \exp(-0.1\ t) - 8.7325 \times 10^{-6} \exp(-102.1\ t) + 0.0010 \exp(-100.13\ t) + 6.9860 \times 10^{-6} \exp(-0.1\ t) - 0.001258 \exp(-0.0001\ t) - 0.008741 \exp(-2.0001\ t) + 1.0020 \exp(-0.0301\ t) + 0.0069930 \exp(-0.0001\ t)$;
- $A_4(t) = 0.0009910 \exp(-110.1\ t) + 6.9860 \times 10^{-6} \exp(-100.1\ t) + 0.9920 \exp(-10.0001\ t) + 0.006993 \exp(-0.0001\ t)$; and
- $A_5(t) = -6.9860 \times 10^{-6} \exp(-110.1\ t) + 0.0009980 \exp(-100.13\ t) + 6.9860 \times 10^{-6} \exp(-100.1\ t) - 0.006993 \exp(-10.0001\ t) + 0.9990 \exp(-0.0301\ t) + 0.006993 \exp(-0.0001\ t)$.

The IDF_i parameters have associated uncertainties that we denote respectively by u_1, u_2, u_3, u_4, and u_5. Then, replacing eqn (14) in eqn (13), the combined uncertainty is obtained:

$$u_{Lung}(t, p) = \sqrt{\sum_i^5 A_i^2(t)u_i^2}$$

If we assume a confidence interval of 95%, $u_i \approx 2\ \sigma_i$, and as $\sigma_i = 0.1\ IDF_i$, then

$$u_{Lung}(t, p) = 0.1 \times 2\sqrt{\sum_i^5 A_i^2(t)IDF_i^2(p)},$$

and, hence,

$$r_{Lung}(t, p) = F_{Lung}(t, p) \pm 0.2\sqrt{\sum_i^5 A_i^2(t)IDF_i^2(p)}. \quad (15)$$

The solution for AMAD 5 μm is plotted in Fig. 4.

Remark: It can be observed that small differences in the IDF_i values with respect to the reference values can have an important influence on the lung retention predicted.

FITTING BIOASSAY DATA

The bioassay measurements can be used to estimate intake, and then to infer the internal dose.

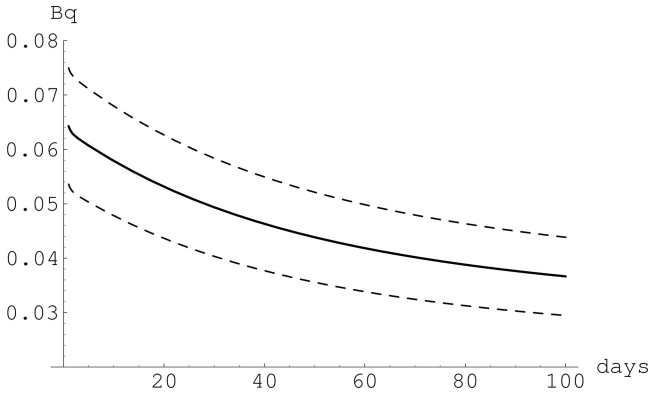

Fig. 4. Average predicted lung retention (central line) for a single intake of 1 Bq U at $t = 0$ (type S, AMAD 5 μm, and $\lambda_R \approx 0$). The dashed lines represent the confidence interval (95%) associated with the IDF_i uncertainties (assuming $\sigma_i/IDF_i = 0.1$).

Let's suppose a single intake I_0 (unknown) at $t = 0$ of radioactive particles, whose characteristics (AMAD, solubility, etc.) are known, by a worker with a metabolism that responds to the ideal model for the standard worker. At time t after the intake, a bioassay is made obtaining a measurement m, with negligible uncertainties. Then, in eqn (6) it will be verified that $m = R_A(t)$ and hence $I_0 = m/r(t)$; in this case the intake I_0 will be known with only one measurement. This is an unrealistic situation, however; in the real world the evaluation of internal exposures using bioassay data involves a lot of uncertainties. In fact, in an intercomparison exercise where the same cases, using the same data, have been evaluated by different experts, large discrepancies have been obtained (Doerfel 1999).

If all parameters (AMAD, absorption parameters, etc.) of the model, except the quantity intakes, are assumed to be known, the only uncertainties will be those of the measurements. The linear statistical model can be applied to estimate $\hat{I}$ and its associated uncertainty u_I (e.g., Skrable et al. 2002; Potter 2002) obtaining

$$\hat{I} = \frac{\sum_{i=1}^{N} r_{C,j}(t_i)\frac{m_i}{u_i^2}}{\sum_{i=1}^{N} \frac{r_{C,j}^2(t_i)}{u_i^2}}, \; u_I = \frac{1}{\sqrt{\sum_{i=1}^{N} \frac{r_{C,j}^2(t_i)}{u_i^2}}}, \qquad (16)$$

where t_i is the time from the start of the intake to the measurement I; m_i and u_i are the measurement and their associated uncertainties (calculated with the same confidence level as u_I); $r_{C,j}(t)$, where $C = \{A$ (acute) or Cr (Chronic)$\}$ is the retention function, with $I_0 = 1$ or $I_d = 1$, associated with measurement m_i; and j is the type of bioassay (note: different kinds of bioassays can be applied simultaneously).

Other authors recommend (ICRP 2006) the maximum likelihood method, which uses eqn (17) instead of eqn (16)

$$\ln(\hat{I}) = \frac{\sum_{i=1}^{N}\left(\frac{\ln[m_i/r_{C,j}(t_i)]}{(\ln SF_i)^2}\right)}{\sum_{i=1}^{N} \frac{1}{(\ln SF_i)^2}}, \qquad (17)$$

where SF_i is the scattering factor for m_i. If the bioassay data are log-normally distributed, then SF is the geometric standard deviation (SG) of the log-normal distribution.

Most of the codes, including BIOKMOD, use eqn (16) or (17). The chi-squared test (χ^2) should be used to estimate the goodness of the fitted data (ICRP 2006).

BIOKMOD also has other possibilities. It can be assumed that not only the intake I but also other parameters $\{k_1, \ldots, k_r\}$ are unknown (AMAD, f_1, etc.); then it applies eqn (18) for fitting the bioassay data (minimizing χ^2):

$$(\hat{I}, \hat{k}_1, \ldots, \hat{k}_r){:}Arg \underset{[I,k_1,\ldots,k_r]}{\text{Min}} \times \left[\sum_{i=1}^{N} \frac{[Ir_C(t_i, k_1, \ldots k_r) - m_i]^2}{u_i^2}\right], \qquad (18)$$

Restrictions:

$I > 0$, k_1 (min) $\le k_1 \le k_1$ (max), $\ldots k_r$ (min) $\le k_r \le k_r$ (max).

If the bioassay data are log-normally distributed, then eqn (19) is used:

$$(\hat{I}, \hat{k}_1, \ldots, \hat{k}_r){:}Arg \underset{[I,k_1,\ldots,k_r]}{\text{Min}} \times \left[\sum_{i=1}^{N} \frac{\{\ln[Ir_{C,j}(t_i, k_1, \ldots k_r)] - \ln[m_i]\}^2}{SG_i^2}\right], \qquad (19)$$

Restrictions:

$I > 0$, k_1 (min) $\le k_1 \le k_1$ (max), $\ldots k_r$ (min) $\le k_r \le k_r$ (max).

The minimization of eqn (18) or (19) is a problem of nonlinear optimization. BIOKMOD applies the algorithms available from *Mathematica* (http://documents.wolfram.com/mathematica/functions/AdvancedDocumentationNMinimize; accessed 15 June 2006); these are probably the state of the art in optimization.

Identification problems

On some occasions when using the same bioassay data, several solutions, which are mathematical equivalents,

can be obtained. For instance, for substances of type F (rapid absorption) and $f_1 = 1$, almost all particles deposited in the respiratory tract (excluding those returned directly to the environment) are transferred quickly into the blood (B). This means that in this case an intake I_0 at $t = 0$ of radioactive aerosols of AMAD p can be approximated by an instantaneous input b_B in B at $t = 0$ given by

$$b_B = I_0 \sum_i IDF_i(p), \quad (20)$$

where $\Sigma_i IDF_i(p)$ includes all IDF factors except IDF_{ET1}.

If I_0 and p are unknown, and therefore IDF_i values will also be unknown, then eqn (20) will be verified for an infinite number of values. So if we replace $b_B(t)$ in eqn (6) using eqn (20), it will be found that bioassay data m_i can be fitted to different values of I_0 and p. However, as $I_0 \Sigma_i IDF_i(p)$ = constant, then the content $q_i(t)$ in each compartment i will be the same, and hence the committed effective dose E will be also the same. For instance, if E has been obtained by fitting an intake I_1 assuming an AMAD p_1 and the true (unknown) value is I_2 with AMAD p_2, then it will be verified that $I_1 \Sigma_i IDF_i(p_1) \approx I_2 \Sigma_i IDF_i(p_2)$ and $E_1 \approx E_2$ where $E_1 = I_1\ DCF(p_1)$ and $E_2 = I_2\ DCF(p_2)$, where $DCF(p_i)$ are the dose conversion factors corresponding to an AMAD p_i. Case 1 below shows an example of this kind.

In the same way, an intake I_0 by ingestion with $f_1 = 1$ is practically equivalent to an instantaneous input $b_B = I_0$ at $t = 0$. These conclusions are extended to inputs that are not acute as a consequence of the convolution theorem.

APPLICATIONS

In the following cases we will use BIOKMOD to estimate the intake fitting bioassay data. Case 1 is an example where different solutions, which are mathematically equivalent, are obtained. In case 2 an accidental exposure happens in a worker who has been previously exposed to a chronic intake. Case 3 is an example of multi-response fitting.

Case 1

A researcher has been exposed to a single acute intake of ^{125}I. After the exposure the ^{125}I in the thyroid was measured (Table 1) (bioassay data taken from French et al. 2003).

The bioassay data have been fitted (Fig. 5) to the iodine thyroid retention function assuming AMADs of $p_1 = 1\ \mu$m, $p_2 = 5\ \mu$m, and $p_3 = 10\ \mu$m. The solutions obtained have been, respectively, $I_1 = 57{,}518$ Bq, $I_2 = 41{,}463$ Bq, and $I_3 = 46{,}782$ Bq. As

$$d_1 = \sum_l IDF_i(1\ \mu\text{m}) = 0.34665;$$

$$d_2 = \sum_l IDF_i(5\ \mu\text{m}) = 0.480875; \text{ and}$$

$$d_3 = \sum_l IDF_i(10\ \mu\text{m}) = 0.426196;$$

Table 1. Bioassay data for Case 1 and Case 2.

Case 1		Case 2	
Time after intake (d)	Thyroid activity of ^{125}I (Bq)	Time after intake (d)	Lung activity of U (Bq)
7	5,143	1	186
14	4,773	5	181
15	4,403	30	161
21	4,070	70	149
28	3,471	120	143
42	2,546	250	113

hence $I_1\ d_1 = I_2\ d_2 = I_3\ d_3 = 19{,}938$ Bq.

In the same way, the DCFs for ^{125}I are DCF_1(1 μm) = 5.3×10^{-6} mSv Bq^{-1}, DCF_2 (5 μm) = 7.3×10^{-6} mSv Bq^{-1}, and DCF_3 (10 μm) = 6.5×10^{-6} mSv Bq^{-1}. Therefore, $E_1 = I_1\ DCF_1 = 0.30$ mSv; $E_2 = I_2\ DCF_2 = 0.30$ mSv; and $E_3 = I_3\ DCF_3 = 0.30$ mSv; that is $E_1 \approx E_2 \approx E_3$.

Case 2

A worker has been exposed from $t = 0$ to $t = 2{,}000$ d to a chronic intake by inhalation of 3 Bq U d^{-1} of UO_2 aerosols type S and AMAD 5 μm. On day $t = 2{,}000$, he accidentally has an intake by inhalation of an unknown I quantity of UO_2. The uranium lung content has been measured (Table 1) using a lung body counter with a standard deviation of 15 Bq U. We want to know the accidental quantity of intake.

Note: The lung measurements have been simulated using a single intake of 1,700 Bq U with AMAD 7 μm with a random noise. The lung counters usually measure the ^{235}U but here it has been converted to give the data in Bq U. The chronic and the accidental intakes are assumed to be from approximately the same enrichment (4.4% of ^{235}U).

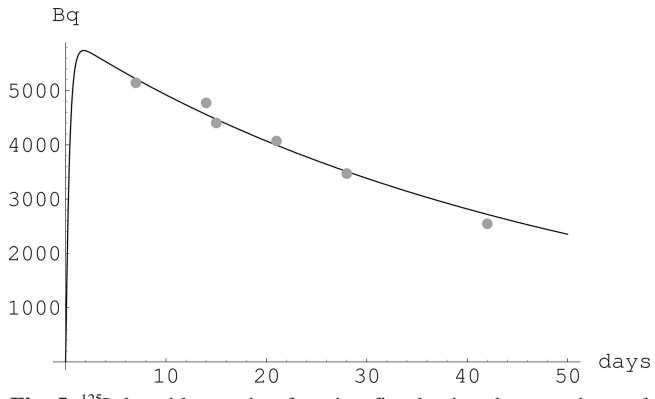

Fig. 5. ^{125}I thyroid retention function fitted using the experimental data (case 1 of the main text). The continuous line is actually three lines superposed corresponding to three combinations of intakes and AMADs. It can be observed that they are indistinguishable.

If an AMAD of 5 μm is assumed (the recommended value by ICRP 66 when AMAD is unknown), then eqn (16) can be applied. The solution obtained is that the accidental intake was 1,255 ± 254 Bq U (computed with a confidence interval of 95%, $z \approx 2$). If it is supposed that the AMAD is unknown, then eqn (19) is applied obtaining 1,875 Bq U and AMAD 7.8 μm. These are nearer to the "true" values (1,700 Bq U and AMAD 7 μm). The solution is represented in Fig. 6.

Remark: If the AMAD value is not really known, the bioassay data should be fitted taking the AMAD as an unknown parameter to be fitted. This does not apply for substances of type F and $f_1 = 1$.

Table 2. Bioassay data for Case 3.

Time after intake (d)	Daily urinary excretion rate of ^{60}Co (Bq d^{-1})	Whole body activity of ^{60}Co (Bq)
10		2.39×10^4
14	709	2.92×10^4
17		2.01×10^4
20		1.82×10^4
27	64	2.16×10^4
40	71	1.98×10^4
60	37	2.16×10^4
80	29	1.75×10^4
190	11	1.16×10^4
370	1.7	8.1×10^3
747		4.8×10^3
1,010		2.7×10^3

Case 3

An operator has been exposed to a single accidental intake by inhalation of ^{60}Co. The cobalt form was metal and oxide. A program (Table 2) of in-vivo monitoring was carried out 10 d after the event and continued up to 3 y. Urine samples were also taken. Additional information: It is recommended to assume that the whole body and urine measurements be approximated by a log-normal distribution with a geometric standard deviation of 1.07 Bq and 1.8 Bq, respectively. (Data from IM 2005 European workshop on individual monitoring of ionizing radiation, Vienna, April 2005; available at http://www.ideas-workshop.de; Accessed 15 June 2006.)

The default parameters recommended by ICRP 78 for cobalt oxide values are AMAD 5 μm, absorption type S, $f_1 = 0.05$. If we applied the chi-squared test (χ^2), the goodness of the data fitted is very bad. For this reason we used eqn (19) assuming that p (AMAD value in μm), the absorption rates $\{s_{pt}, s_p, s_t\}$, and f_1 are unknown. This is a case where multiple data sets must be fitted to a nonlinear model. To avoid a too long time of computation, some restrictions about the fitted parameters were established. Also the number of steps to find the minimum of eqn (19) was limited. The best fit obtained corresponds to 398.5 kBq with AMAD 5.5 μm, $\{s_{pt}, s_p, s_t\} = \{10, 90, 0.0007\}$ and $f_1 = 0.1$. The committed effective dose, $E(50)$, calculated using these values is 4.5 mSv.

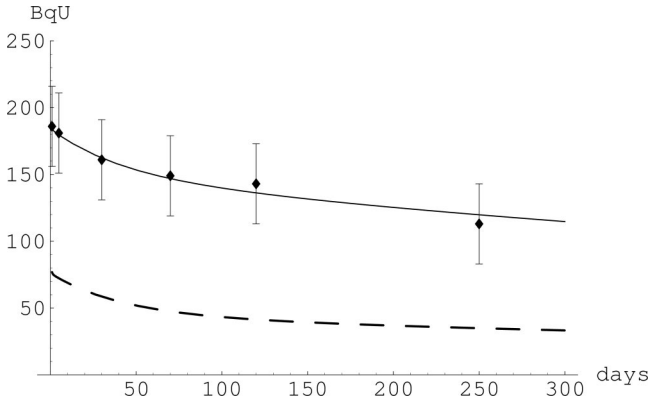

Fig. 6. Predicted lung retention after an acute intake assuming a previous chronic intake (case 2 of the main text). The dashed line represents the underlying contribution from the chronic intake.

The above solution can be compared to that given in Annex B of ICRP (2006), where the method applied is different. The AMAD is assumed to be 5 μm, then eqn (17) is applied several times: one set with $f_1 = 0.1$ testing with different combinations of radioactive aerosol types S and M. The procedure is repeated with $f_1 = 0.05$. The chosen solution is the one where the chi-squared test (χ^2) is the smallest. The computation was made using IMBA. The solution reported is an intake of 404 kBq and a committed effective dose, $E(50)$, of 5.0 mSv.

DISCUSSION

The uncertainties in the estimation of the intakes from bioassay data are caused by a variety of circumstances such as a limited number of measurements, large natural variations in individual biological characteristics, uncertainties in the biokinetic models, and interferences from natural background radiation. We must also take into account that most of the biokinetic data are from experiments with animals, and their application to humans is limited.

In accidental exposures the situation is even more complex because the characteristics of the source term (AMAD, breathing rate, f_1, absorption rates, etc.) are often not well-known. On these occasions nonlinear regression techniques can be applied to estimate the intakes for fitting the bioassay data. We have shown that in some cases a set of mathematically equivalent solutions can be obtained.

The values of internal dose estimation when the uncertainties are included are usually not too big. This is because usually only one source of uncertainty is taken into account. But if all uncertainties associated with the

bioassay evaluation are taken together, the combined uncertainty will usually be bigger. For this reason, it is not rare that large discrepancies are found in the intercomparison exercises.

In our experience bioassay data analyses for workers occupationally exposed to radioactive aerosols are usually lower than the level of detection limits (LLD) or are very close to them. If we also take into account that the intakes are random, then the uncertainties of the dose estimation using bioassay data will be huge. For this reason, we think that bioassay monitoring programs should be used as additional controls, but they should not be used to estimate internal dose.

When dealing with accidental exposures, bioassay analysis can very useful. Fortunately, there are very few cases of this kind and as a consequence there are fewer experimental data.

Great advances have been made to reduce the uncertainties in accidental exposure analyses. The application of the optimal experimental design (Lopez-Fidalgo et al. 2005) can be one way to reduce the uncertainties. Another way could be simplifying the biokinetic models (many compartments involve many parameters and, therefore, many sources of uncertainties). In fact, it can be tested that the committed effective dose is often determined by a very small number of compartments.

CONCLUSION

There are some good computer codes that can be applied in the interpretation of bioassay data. We have developed a new one, BIOKMOD, with some innovations that can be useful mainly for advanced studies. The standard version of BIOKMOD is available for free download at the author's Web site: http://web.usal.es/guillermo.

Furthermore, there is a Web version (available at http://www3.enusa.es/webMathematica/Public/biokmod.html, sponsored by ENUSA Industrias Avanzadas. S.A.), which can be used wherever an Internet connection exists.

BIOKMOD has been used in the evaluation of internal exposures using bioassay data: multiple constant and random intakes in occupational exposures taking into account periods without intake (weekends, holidays, etc.) have been described; an analytical method to evaluate the statistical uncertainties associated with the biokinetic model has been developed; and non-linear techniques have been applied to estimate the intakes using bioassay data.

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