A HUMAN METABOLIC MODEL FOR ^{14}C-LABELLED METABOLITES USEFUL IN DOSE ESTIMATION*

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Abstract

An average individual (70-kg man) takes in some 350 g of carbon per day, and his total body content of carbon is about 14 kg. Assuming uptake to blood is essentially complete, this corresponds to a biological half-time (T_b) of 28 days. Metabolic models used in ICRP Publication 10 allow only for $T_b \cong 12$ days for glycine and of less than 1 day for CO_2. To be in agreement with the stable carbon data, one or more terms of longer half-life are needed. Such a model is defined in this paper and is more conservative than that for glycine in ICRP Publication 10 by about a factor of 3. Data of D. L. Buchanan on uptake of $^{14}CO_2$ in mice indicate that the equilibrium level approached 10^{-4} times the specific activity of $^{14}CO_2$ in air, suggesting uptake of about 1% to blood with further dilution by dietary stable carbon of ~ 0.01. G. V. LeRoy *et al.* have determined the retention of $^{14}CO_2$ in man during the first day, but need for a compartment of long biological half-life is indicated here also. When these compartments are included in the models given in ICRP Publication 2 and ICRP Publication 10, it is found that the former model overestimates dose to the total body by a factor of ~ 30, while the latter underestimates it by a factor indicated to be at least 16 and which might be as high as ~ 100.

Introduction

The purpose of this report is to present a mathematical model for ^{14}C metabolism which can be used in health physics for estimating radiation dose to man from intake of ^{14}C. This model is needed for an adequate estimation of radiation dose received by research workers or others who work with ^{14}C-labelled compounds and incidentally or accidentally take ^{14}C into their bodies. In this paper, experimental data provided by others will be used and interpreted with a mathematical model.

Experimental Data

D. L. Buchanan[1] obtained data from a study of $^{14}CO_2$ inhalation by mice in stable CO_2 levels ranging from 0.03% to $\sim 5\%$ CO_2 in air. He let the mice inhale $^{14}CO_2$ for as long as 40 days, and then he studied the retention out to 50 days after the end of exposure. By serial sacrifice, both during exposure and following the cessation of inhalation exposure, he took many tissues (but not bone) and plotted the results expressed as the ratio of specific activities

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in tissues to the specific activity of air. He called this the air carbon fraction, and from his graphs, the value increased from zero at time zero up to $\sim 10^{-4}$ at 40 days or so. Thus, the equilibrium level of the specific activity was only 0.01% of the corresponding level in the air breathed by the mice.

Other data are available also, e.g., the paper by Skipper[2] which deals with the trapping of ^{14}C in bone following injection into blood of ^{14}C-labelled Na_2CO_3. Here the bone was seen to retain a small fraction for a long time, but there seemed to be no chronic accumulation of C in bone.

Data are available from another experiment of Buchanan[3] involving continuous feeding of a ^{14}C-labelled diet of sucrose and yeast for a period of 40 to 50 days and serial sacrifice of mice and rats from which tissues were obtained. These data show the ratios of labelled to unlabelled C in tissues and foods applied and equilibrium set in at ~ 40 days after intake began.

ICRP Publication 2[4] refers to data of Nardi for its T_b value of 10 days for total body. A T_b value for bone based on studies on mice and a value for fat are given in Publication 2 also. Note that all of these were obtained on small animals (mice and rats).

Metabolic Model for ^{14}C

Denote by R(t) the fractional retention of dietary ^{14}C in the body at time t after uptake of a unit amount into the bloodstream. Let E(t) denote the cumulative excretion (via all paths), and we write

$$E(t) = 1 - R(t). \tag{1}$$

It is assumed that

$$R(0) = 1 \qquad \text{and} \qquad R(\infty) = 0,$$

that is, the life span of man is considered to be long enough so that retention at 50 to 70 years $\to 0$. The mean residence time (MRT) in the body is

$$\begin{aligned} MRT &= \int_0^\infty t \frac{dE(t)}{dt}\, dt \\ &= -\int_0^\infty t \frac{dR(t)}{dt}\, dt \\ &= -tR(t)\Big|_0^\infty + \int_0^\infty R(t)\, dt \\ &= 0 + \int_0^\infty R(t)\, dt. \end{aligned} \tag{2}$$

Thus it has been proved (and this was also noted by Bergner[5] and probably others) that the integral of the retention function over all time is the mean of the probability distribution of residence times for an atom to be released from the body after the initial introduction of one atom at time zero. Now, one additional expression is needed to prove the MRT is given by the ratio of the body burden, q(t), to the daily uptake into blood. Snyder[6] noted that for chronic intake with $f_1 I d\tau$ units of the isotope entering the body in $d\tau$ units of time, the retention at a time t is given by, $\tau \leq t$,

$$q(t) = \int_0^t f_1 I \, d\tau \, R(t - \tau). \tag{3}$$

By changing the variables, i.e., by letting $t - \tau = T$ and $dT = -d\tau$, then (3) becomes

$$q(t) = \int_0^t f_1 I \, d\tau R(t - \tau) = f_1 I \int_0^t R(T) \, dT. \tag{4}$$

Rearranging the equation, one obtains

$$\frac{q(\infty)}{f_1 I} = \int_0^\infty R(T) \, dT = MRT. \tag{5}$$

Application of the Model

In applying the model to man, it is assumed that body carbon is 14 kg and the diet contains 350 g/day of carbon[3] such that

$$MRT = \frac{14{,}000 \text{ g}}{350 \text{ g/day}} = 40 \text{ days},$$

which corresponds to a biological half-life of $0.693 \times 40 \cong 28$ days. For mouse and rat, it is assumed that 1/5 of the body weight (and food weight per day) is carbon. Thus, for a 25-g mouse ingesting 4 g of food per day,

$$MRT)_{mouse} = \frac{1/5 \times 25 \text{ g}}{1/5 \times 4 \text{ g/day}} \simeq 6 \text{ days};$$

and for a 200-g rat eating 20 g of food per day,

$$MRT)_{rat} = \frac{200}{20} \text{ day} = 10 \text{ days}.$$

In the above estimates, it is assumed that complete (100%) uptake of dietary C occurs.

The above values for mouse and rat agree with Buchanan's tissue data (from the experiment using a diet labelled with ^{14}C) in that the ratio of specific activity of organs and tissues to specific activity in diet is approximately given by

$$\frac{q^*/q}{I^*/I} = 1 - e^{-\lambda_b t}$$

which approaches 1 at large times (40 to 50 days in the case of rats and mice) where the asterisk denotes ^{14}C. Then we can show

$$1 - \frac{q^*/q}{I^*/I} = e^{-\lambda_b t}$$

which indicates that the exponential decreases with the reciprocal mean residence time as the decay constant. Buchanan's feeding data are in approximate accord with this equation. However, in some cases (brain and muscle, for example) more than one exponential is indicated, but the MRT for most tissues is 4 to 10 days which is approximately correct. Now Buchanan's inhalation experiment can be interpreted.

New Model for $^{14}CO_2$ Inhalation

The daily intake of C in inhaled air is needed. For a mouse inhaling 0.15 cc per breath (the tidal volume) and 163 breaths per minute,[8] 23 cc of air are taken in per minute which corresponds to an intake of 33 liters per day. Air normally has 0.03% CO_2, and since CO_2 has 44 g/mole and 1 mole of any gas occupies 22.4 liters, then

$$3\times10^{-4} \times \frac{33 \text{ liters}}{\text{day}} \times (22.4)^{-1} \frac{\text{mole}}{\text{liter}} \times \frac{12 \text{ g C}}{\text{mole}} = 0.005 \text{ g C/day}$$

is inhaled by the mouse. Since he eats 4 g of food per day with 1/5 being C, he ingests

$$4\ (1/5) \text{ g C/day} = 0.8 \text{ g C/day.}$$

So he inhales $\sim 10^{-2}$ as much carbon as he ingests. Thus the inhaled radioactive $^{14}CO_2$ is diluted 100 times by ingestion of uncontaminated C present in food. This accounts for 10^{-2} of the 10^{-4} fraction observed by Buchanan. Evidently only 1% of the inhaled C is taken up by the blood in a form metabolically similar to C in food. This could be related to the fact that alveolar air has 3 to 5% CO_2 concentration or 100 times the air inhaled. Thus the specific activity of the inhaled air is diluted by another factor of 100 to produce the equilibrium level in tissue.

It is believed that this is an important parameter to use in the case of inhalation intake of $^{14}CO_2$ by a man who had inhaled, accidentally or otherwise, $^{14}CO_2$.

To get μCi-days residence, we use

$$0.01 \text{ μCi} \int_0^\infty e^{-0.693t/28} \text{ dt days} = 0.4 \text{ μCi-days}$$

where 0.01 μCi represents uptake of 1% of 1 μCi inhaled by man. Compare this to the ICRP Publication 2 value of

$$0.75 \int_0^\infty e^{-0.693t/10} \text{ dt μCi-days} = 10.8.$$

Thus from their model, one overestimates the dose (given by

$$D = 51 \times \left(\frac{q}{m} \frac{\text{μCi}}{\text{g tissue}}\right) \times \left(\mathcal{E} \frac{\text{MeV}}{\text{dis}}\right) \times \left(\text{MRT days}\right)$$

so dose is proportional to μCi days) by a factor of

$$\frac{10.8}{0.4} = 27.$$

When the above is compared to the model in Publication 10 of ICRP,[7] care must be taken because Publication 10 only gives μCi-days residence for intake to the blood. There, for $NaH^{14}CO_3$, they give a value of 0.58 μCi-day for bone, but this is for uptake to bone of 1 μCi and not for inhaled ^{14}C. For the case of injection into blood, that fraction f, which has the metabolism of C taken in food, would give

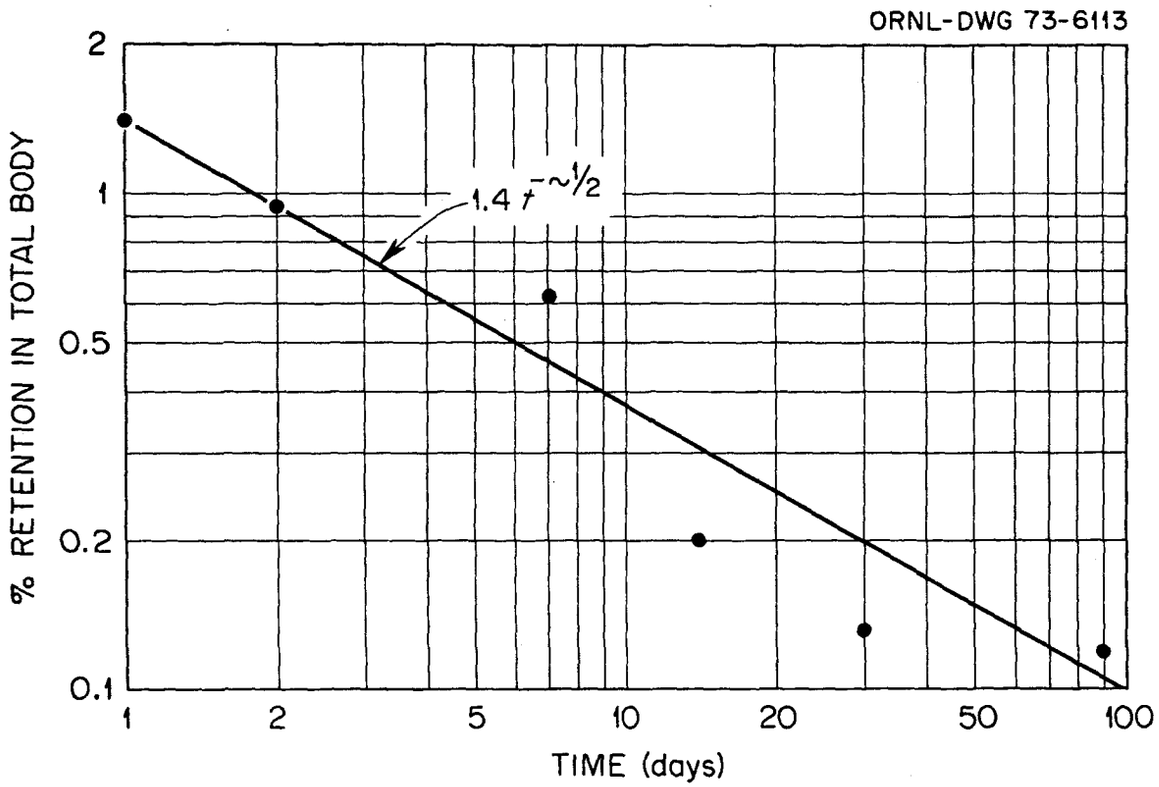
$$f \times \int_0^\infty R(t) \text{ dt} = 40 \text{ f μCi-days.}$$

Included here is a logxlog graph of Skipper's data on $^{14}CO_2$ total body retention in mouse after a single injection of $NaH^{14}CO_3$ (Fig. 1). From here it can be noted that the power function will fit the data, and the MRT out to 900 days is only 1 day, somewhat lower than the earlier estimate of 6 days. This might indicate rapid exhalation of 5/6 of the total activity injected. Also, although the power function implies some trapping, it should be noted that there is no excessive concentration of C in bone or other organs in the body. More data on larger animals are needed here. Meanwhile, the value f = 1/6 is suggested from the above data on mice.

Thus, from the above considerations, it can be seen that a model for $^{14}CO_2$ inhalation of a single intake has been derived. Note, however, the value of 1% uptake of ^{14}C into blood from inhalation is based on a very small animal--a mouse. The author knows of no data on a larger animal, such as a dog, from which the 1% could be verified. Note also in the above that the mean residence time factor indicates how fast the specific activities rise for the case of continuous intake. Also, when more than one exponential is involved in the retention, then the integral of the retention function gives the MRT; hence, it can be said, conversely, where the MRT is known, one can infer the approximate correctness of the retention function. For example, Publication 10 gives the retention function for injection of $NaH^{14}CO_3$ into the blood of man as

$$R(t) = 0.7\, e^{-0.693t/0.05} + 0.3\, e^{-0.693t/0.4}, \quad t \text{ in days},$$

and from this



Skipper's $^{14}Co_2$ Data Injection of $NaH^{14}Co_3$ into Mice.

Fig. 1.

$$\int_0^\infty R(t)\,dt = MRT = \frac{0.7 \times 0.05 + 0.3 \times 0.4}{0.693} \text{ days} = 0.22 \text{ days}$$

which is much below the value of 40 days. This suggests the existence of longer-term exponentials. If one exponential is added in the amount of 2% with a 1400-day half-life, then

$$R(t) = 0.7\, e^{-0.693t/0.05} + 0.28\, e^{-0.693t/0.4} + 0.02\, e^{-0.693t/1400}$$

and then

$$MRT \cong 43 \text{ days.}$$

Although this MRT concept implies longer-term exponentials, it does not tell how many to add, and only experiments will indicate that.

A Model for ^{14}C-Labelled Glycine

While the above is for $^{14}CO_2$ (or $NaH^{14}CO_3$), a model is given in Publication 10 for ^{14}C-labelled glycine (an amino acid) injected into blood of man. There it is recommended that

$$R(t) = 0.2\, e^{-0.693t/0.12} + 0.2\, e^{-0.693t/0.9} + 0.3\, e^{-0.693t/6} + 0.3\, e^{-0.693t/35}.$$

From this function, the MRT can be seen to be $\sim$ 15 days, lower by a factor of 3 than the value above of 40 days. Thus it would be recommended that a component with a coefficient of 0.02 and a T_b of $\sim$ 1200 days be included to increase the MRT up to $\sim$40 days.

Conclusions and Recommendations

From the above it is concluded that in mice, 1% of the inhaled $^{14}CO_2$ enters into long-term retention in the body. The mean residence time of C in the diet of mouse is 6 days, while for man, it is 40 days. It is recommended that the 1% uptake to blood be used rather than 75% (ICRP Publication 2 value) and the residence time of 40 days be used for metabolites (compounds which are involved in the buildup and breakdown of cells and tissues) ingested into the body of man. For a single injection of $NaH^{14}CO_3$ into blood, some studies indicate a lower residence time in mice ($\sim$1 day) than for food labelled with ^{14}C (6 days). When the above models are used in dose estimation for CO_2, it is found that ICRP Publication 2[9] overestimates the dose to the total body by a factor of $\sim$30, while the ICRP Publication 10 model underestimates it by a factor indicated to be at least 16 and which might be as high as $\sim$ 100. Probably the single exponential is an oversimplification and should be replaced by several exponentials of fairly long half-times, but to determine these, further data on man, or on several species of animals, would be desirable.

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