# ESTIMATION OF RADIATION PROTECTION GUIDES: INTERSPECIES CORRELATIONS*

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**Abstract**—Values recommended for maximum permissible concentration (MPC) of radionuclides in air and water and for retention by the body and its component tissues are commonly based on data obtained from acute tracer studies in rodents. Conceptually, however, conditions of chronic exposure for human subjects are embodied in MPC calculations. Unfortunately, studies on retention of many radionuclides by human subjects are impossible or impracticable, even though the development of ultrasensitive human counters represents a significant contribution to the problem. Metabolically speaking, a 70-kg mouse or rat is sometimes regarded as a standard man.

One approach to resolving this problem is to find interspecies correlations in radionuclide metabolism and ways of extrapolating to MPC values for man. During continuous ingestion of a constant amount of a material, an equilibrium level may be reached within the body. This level is predictable from acute administration studies. The integral of the effective retention function (limits of zero to infinity) is proportional to equilibrium level and has dimensions of multiples of the daily intake. The integral is also proportional to radiation dose.

Interspecies correlations of the form $E = aX^b$, which relate equilibrium levels ($E$) obtained for mice, rats, dogs, monkeys, and men to grams body weight ($X$), have been developed for tritium water (HTO), $^{22}$Na, $^{54}$Mn, $^{65}$Zn, $^{86}$Rb, $^{131}$I, and $^{137}$Cs. The proportionality constant $b$ differs for each element. In each case, values obtained directly from human studies agree well with values for man derived from the correlation. Equilibrium levels as a function of body surface, body weight, and metabolic rate using the power function (with and without the log transform) and a first-degree polynomial were also considered as models. The polynomial relating equilibrium level to body surface best describes cesium metabolism and accounts for shorter turnover times observed in children.

## INTRODUCTION

Radiation protection guides for human beings are sometimes based on data obtained not from man but from laboratory animals. The proper choice of species or, more properly, the applicability of data obtained from one animal to man is sometimes referred to as the "species problem". At least two avenues of investigation related to the field of radiation protection are concerned with this problem. The first is that of determining reparable and irreparable damage components following radiation exposure. The rate at which damage is repaired varies among species and tends to decrease as body weight increases.(1) The second, which we will consider in this paper, is that of estimating maximum permissible concentrations (MPC's) for various radionuclides.

One biological parameter used in calculating MPC values is the effective residence time for a specific radionuclide within the body or within a specific organ. More precisely, we want to know how much of a material will be present within the system when equilibrium conditions are reached between intake and excretion. Equilibrium levels are estimated from measurements of effective turnover of the

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element in question by using radionuclides or from a knowledge of the relation between daily intake (or output) and total body content of the stable species of the element.[2] Ideally, the necessary experimental data should be obtained from man, but this is not always practicable or prudent. Alternatively, metabolic correlations among mammalian species that relate the equilibrium body burden to some physiological parameter such as body weight can be used as a first approximation when human data are inadequate or totally lacking.[3-7] For convenience, the adaptation of the interspecies correlation, as used in this paper, to the ICRP method of calculating MPC values is presented in an appendix.

This report summarizes interspecies correlations established at our Laboratory for tritium, sodium, rubidium, cesium, zinc, iodine, and manganese. We also present several physiological parameters other than body weight as the basis of relating equilibrium burdens interspecifically. Factors that can shift the position of a given species within the correlation are also discussed.

## METHODS AND MATERIALS

The laboratory animals used in the studies reported here were RF strain mice, Sprague-Dawley strain rats, beagle hounds, and macaque monkeys. Female mice were used because of fighting among males; otherwise, attempts were made to use only male animals. The dogs and mice were selected from animals bred at our Laboratory; rats and monkeys were secured from commercial suppliers. Only mature animals in apparent good health were used. Rodents were approximately 90 days old before use. Dogs and monkeys must be 1½ to 2 years old. Two difficulties with rats are that growth continues and weight increases throughout the experimental period, and there is a high incidence of respiratory difficulty. We are now in the process of replacing the albino rat with a longer-lived rodent (*Mystromys albicaudatus*) that seems to be quite free from respiratory problems and that shows only a small weight change with age.

Commercial diets are used for all animals. Because the data reported here were collected over several years, several suppliers have been used. All species but monkeys are currently fed diets from a single supplier.* The animals are fed the rations *ad libitum* without dietary supplements. Water is always available.

Tritium water (HTO) was given orally (dog and man) or parenterally (mouse, rat, rabbit, monkey, and horse). For each species the volume of water containing the tritium was small compared to the volume of the body water reservoir. The total radiation dose delivered to the human subjects was of the order of 200 mrad, assuming homogeneous distribution of tritium throughout the body and using the observed effective half-life. At 2, 3, and 4 hr after administration and at appropriate subsequent times, the concentration of HTO was measured in pure water obtained from the blood of each species but man. Urine was the source of body fluid for human subjects.

At each blood sampling time, 20 $\mu$l of blood were drawn into a Sahli hemoglobin pipette from a small incision in the tail vein of rodents or from the marginal ear vein of rabbits and were immediately mixed with 1 ml of normal saline. After mixing and centrifugation, 0.5 ml of clear supernatant was pipetted into 24 ml of scintillator solution. One-ml aliquots of pure water were obtained from blood samples removed from dogs, monkeys, and horses and from urine samples voided by the human subjects by using a vacuum distillation procedure modified after Cooper *et al.*[8] To avoid any possible isotope fractionation effects, each sample was distilled to dryness. All samples were stored at 4°C for 1 hr prior to tritium assay in a scintillation detector. Composition of the scintillator solution and details of the assay are given elsewhere.[9] The tritium activity of each sample obtained from whole blood (mice, rats, and rabbits) was converted to $\mu$Ci/ml body water by multiplying by an appropriate dilution factor and correcting for the water content of blood at termination of the experiment. Blood water was measured in samples of whole blood dried to constant weight at 100°C.

In the other experiments reported here, gamma-emitting radionuclides were administered and assayed by means of whole-body (*in vivo*) counting techniques. Both the whole-body

* Wayne, Chicago, Illinois.

counting procedures for the $4\pi$ steradian geometry detectors (liquid scintillator variety) and the automatic data reduction and analytical methods have been reported in detail.[10, 11] Use of large-volume detectors reduces errors arising from translocation of the radionuclide within the animal during the experiment. For the gamma-emitting nuclides considered in this paper, the individual doses per animal were of the order of 1 $\mu$Ci or less.

## RESULTS AND DISCUSSION

### *Tritiated water (HTO)*

Retention of HTO (per ml body water) was described for each species by a simple exponential function,

$$R_t = a \exp(-kt), \quad (1)$$

in which $a$ is the initial concentration of HTO in the body water, $k$ is the rate constant in reciprocal days, and $t$ is days. The rate constant is related to biological half-life ($T_b$) and average residence time ($\tau$) for a hydrogen atom within the body by the following:

$$k = \frac{\ln 2}{T_b} = \frac{1}{\tau}. \quad (2)$$

Values of $T_b$ ranged from average values of 1.1 days for mice to 9.5 days for human subjects. These data were presented in detail elsewhere.[4]

Figure 1 shows an interspecific correlation between log of daily water loss and log of body weight for seven species. Average daily water turnover was calculated from $k$ and body water reservoir volume ($W$) for the individual animals comprising the sample. $W$ was determined by the dilution principle using the intercept $a$ of eq. (1) as the equilibrium specific activity of $^3H$ in body water during early mixing.

One can calculate total daily water turnover from a knowledge of the size and turnover of the exchangeable water pool. The derivative of the retention function, which corresponds to excretion rate, is:

$$-\frac{dR_t}{dt} = a(k) \exp(-kt). \quad (3)$$

If the volume of the body water pool ($W$) is substituted for the tritium concentration in eq. (3), one can then determine the instantaneous rate of water loss by setting $t$ equal to zero as follows:

$$-\frac{dR_t}{dt} = W \cdot (k). \quad (4)$$

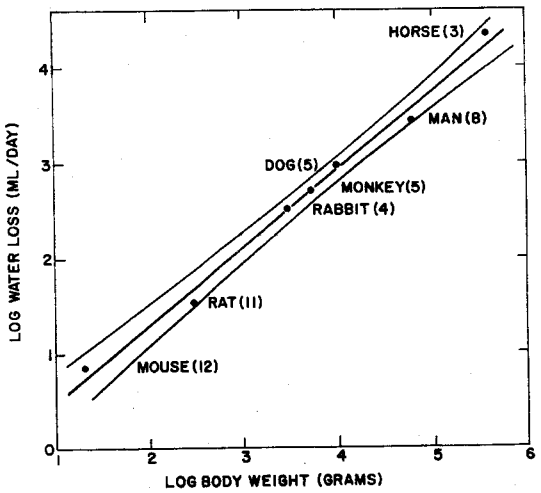


FIG. 1. Interspecies correlation between log daily water loss and log body weight (in g) for 7 mammalian species. The regression equation is: log water loss = $-0.4188 + 0.8180 \log X$.

The regression line, which was fit by the least-squares method, and the 95% confidence limits are given. The correlation coefficient ($r$) between the variables is 0.993. The regression equation is:

$$\log \text{water loss} = -0.4188 + 0.8180 \log X, \quad (5)$$

and the standard error of the slope constant ($S_b$) is $\pm 0.0129$. A value of $\pm 0.122$ was obtained for the standard error of estimate ($S_e$) for the regression line.

It is clear from the value of parameters $r$, $S_e$, and $S_b$ that a high degree of confidence may be placed on the regression equation relating body water turnover to body weight. The value of the slope constant indicates that body water turnover is proportional to the 0.82 power of body weight. Relative to body weight, larger mammals have a slower turnover of body water than smaller ones.

Figure 2 shows the equilibrium factor ($E$) for tritium water as a parabolic function of

body weight (in g) for 12 mice, 12 rats, 4 rabbits, 5 dogs, 5 monkeys, and 8 human subjects. Age, sex, body weight, and equilibrium factor are given in Table 1 for each human subject. Using a parabolic model (i.e. $y = ax^b$), the best computer fit to the 46 data points is:

$$E = 1.24\ X^{0.2057}. \tag{6}$$

As indicated by the exponent, $E$ increases not in direct proportion to body weight but as the 0.2057 power of body weight. As shown in the appendix, $E$ is equal to the mean residence time for the atom within the body. Thus, because retention of tritium water by the body is a monotonic process (for all practical purposes), the ordinate values in Fig. 2 are equivalent to mean residence times, $\left(\frac{T_b}{\ln 2}\right)$. Values of $E$ tend to increase with age as well as with body weight for the human subjects. All 3 subjects aged 16 or younger fall below the curve. Of the 5 adults, all but 1 fall above the curve. If we solve eq. (6) for $7 \times 10^4$ g, we obtain a value of 12.35 for $E$, which corresponds to a $T_b$ value of 8.6 days. From data given in Table 1 we can calculate a mean $T_b$ value of 8.4 days for all 8 subjects. For the 5 adults, with an average body weight of $6.7 \times 10^4$ g, the average experimentally determined $T_b$ was 9.5 days.

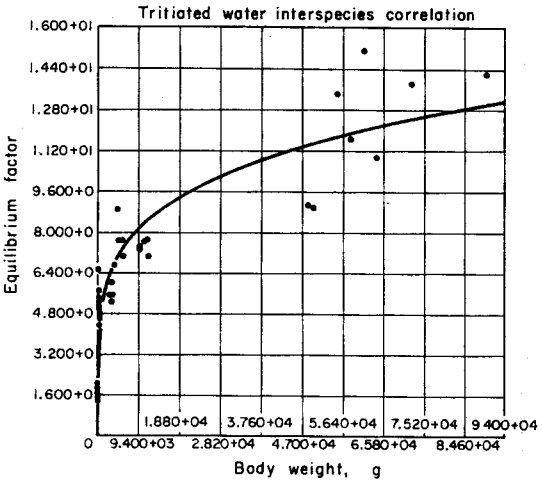


FIG. 2. Interspecies correlation between equilibrium factor ($E$) and body weight (in g) for mice, rats, rabbits, monkeys, dogs, and men given tritium water. The regression equation is: $E = 1.24\ X^{0.2057}$.

Figure 3 shows equilibrium values obtained from the individual animals plotted as a function of body surface. The best computer fit to the data points is:

$$E = 10.42\ X^{0.2818}. \tag{7}$$

As in eq. (6), no logarithmic transformation of the variables was made prior to fitting the data. Equilibrium factor $E$ is proportional to body surface (in $m^2$) raised to the 0.28 power. The intercept (10.42) is the value of $E$ when body surface is 1 $m^2$. However, as can be seen in Fig. 3, when body surface becomes very small, $E$

*Table 1. Age, Sex, Weight, and Equilibrium Factor (E) for Human Subjects given Tritium Water by Mouth*

| Subject No. | Sex | Age (yr) | Weight (kg) | $E$* |
|---|---|---|---|---|
| 1 | M | 43 | 72.3 | 13.82 |
| 2 | M | 14 | 64.1 | 10.94 |
| 3 | M | 10 | 49.5 | 8.93 |
| 4 | M | 24 | 61.2 | 15.12 |
| 5 | M | 23 | 89.8 | 14.11 |
| 6 | F | 16 | 48.2 | 9.07 |
| 7 | F | 36 | 58.2 | 11.66 |
| 8 | F | 45 | 55.0 | 13.39 |

* Multiples of the daily intake.

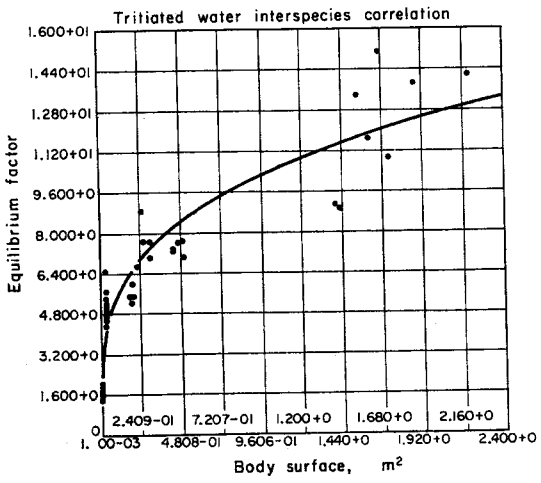


FIG. 3. Interspecies correlation between equilibrium factor ($E$) and body surface (in $m^2$) for mice, rats, rabbits, monkeys, dogs, and men given tritium water. The regression equation is: $E = 10.42\ X^{0.2818}$.

approaches zero. An interspecific relation derived by von Schelling[12] was used to convert body weight to body surface.

Equilibrium factors shown in Figs. 2 and 3 were also fit as a function of several physiological parameters in the normal plane using a first-degree polynomial. The computer-obtained regression equations that correlate $E$ with body weight, body surface, and metabolic rate are given in Table 2. Body surface and metabolic rate were calculated from the body weight of each animal using the equations of von Schelling[12] and Brody.[13]

The average $(MPC)_w$ value for continuous intake, calculated from equilibrium factors obtained from the eight human subjects (Table 1), was $8 \times 10^{-2}$ μCi $^3H$/ml, as compared with a value of $5 \times 10^{-2}$ now listed by the ICRP.[2] If one substitutes a value of $7 \times 10^4$ g in the interspecies correlation based on grams body weight (eq. 6), the resultant equilibrium factor ($E$) is 11.15. The value of $(MPC)_w$ is then calculated by substituting $E$ in the equation,

$$(MPC)_w = \frac{q}{E \cdot S}, \qquad (8)$$

where $q$ is $2 \times 10^3$ μCi and $S$ is 2200 ml/day (see eqs. (A1) to (A4) in the appendix).

If human data were not available, the interspecies correlation and subsequent $(MPC)_w$ estimation would be based on the data obtained solely from laboratory animals. Table 3 gives regression equations for $E$ as a function of body weight and body surface with and without data from the human subjects. All values of $E$ and $(MPC)_w$ are reasonably similar. Data extrapolated from animals to man yield essentially the same values of $E$ and $(MPC)_w$ as those obtained from the correlation that includes the human data.

*Cesium*

Figure 4 shows the interspecies relation between $E$ and body weight (in g) for 74 animals (21 mice, 35 rats, 4 monkeys, 7 dogs, and 7 human subjects) given radiocesium. Table 4 gives age, weight, and equilibrium factor for

*Table 2. Interspecies Correlation between Equilibrium Factor ($E$) and Several Physiological Parameters for Mice, Rats, Rabbits, Dogs, Monkeys, and Men given Tritiated Water by Mouth*

| Independent variable ($X$) | Interspecies correlation | Correlation coefficient |
|---|---|---|
| Body weight (g) | $4.30 + 0.00013\ X$ | 0.574 |
| Body surface ($m^2$) | $3.91 + 5.22\ X$ | 0.679 |
| Metabolic rate (cal/day) | $3.92 + 0.006\ X$ | 0.677 |

*Table 3. Comparison of Equilibrium Factor ($E$) and $(MPC)_w$ Values for Tritium Water in Man using Interspecies Correlations of the Form $E = aX^b$ with and without Data from Human Subjects*

| Independent variable ($X$) | Interspecies correlation | $E$* | $(MPC)_w$ ($\mu$Ci/ml) |
|---|---|---|---|
| Body weight (g)† | $1.24\ X^{0.2057}$ | 11.15 | $8.1 \times 10^{-2}$ |
| Body weight (g)‡ | $1.43\ X^{0.1861}$ | 11.40 | $7.9 \times 10^{-2}$ |
| Body surface ($m^2$)† | $10.42\ X^{0.2818}$ | 12.31 | $7.4 \times 10^{-2}$ |
| Body surface ($m^2$)‡ | $9.75\ X^{0.2549}$ | 11.32 | $8.0 \times 10^{-2}$ |
| ICRP[2] | — | — | $5.0 \times 10^{-2}$ |
| From 7 human subjects** | — | — | $8.0 \times 10^{-2}$ |

* Value of interspecies correlation calculated for a person with a body weight of $7 \times 10^4$ g or a body surface of 1.8 $m^2$.
† Man included in the derivation of the interspecies correlation.
‡ Man omitted from the derivation of the interspecies correlation.
** Using observed turnover values in equation used by the ICRP.[2]
See eq. (A1) in the appendix.

each male subject. The best computer fit to the data given in Fig. 4 is:

$$E = 0.23\ X^{0.5914}. \quad (9)$$

Thus, $E$ varies as the 0.5914 power of body weight. The exponent indicates a closer proportionality between $E$ and body weight for cesium than in the case of tritium water (eq. 6). Equation (9) also predicts a value of 0.23 for $E$ when body weight is 1 g. No logarithmic transformation of the variables was made prior to fitting the data.

*Table 4. Age, Weight, and Equilibrium Factor ($E$) for Male Human Subjects given Radiocesium by Mouth*

| Subject No. | Age (yr) | Weight (kg) | $E$* |
|---|---|---|---|
| 1 | 33 | 81.8 | 133.30 |
| 2 | 35 | 77.3 | 164.60 |
| 3 | 37 | 57.0 | 144.09 |
| 4 | 27 | 68.2 | 187.26 |
| 5 | 28 | 75.4 | 191.05 |
| 6 | 34 | 70.3 | 217.98 |
| 7 | 53 | 61.2 | 161.96 |

*Multiples of the daily intake.

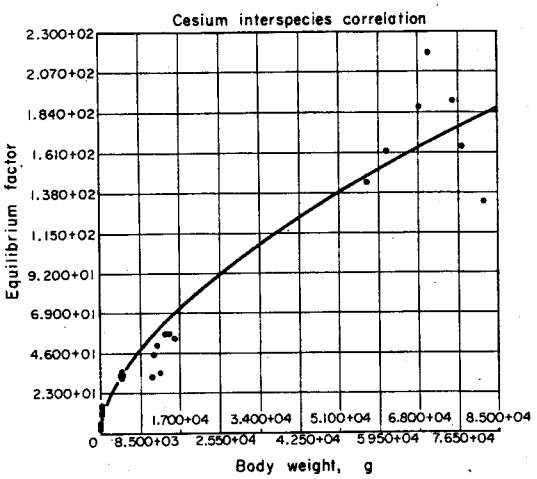


FIG. 4. Interspecies correlation between equilibrium factor ($E$) and body weight (in g) for mice, rats, monkeys, dogs, and men given radioactive cesium. The regression equation is: $E = 0.23\ X^{0.5914}$.

Figure 5 shows the interspecies relation between $E$ and body surface (in $m^2$) for the same animals. In this case, the best computer-derived regression equation is:

$$E = 97.35\ X^{0.8618}. \quad (10)$$

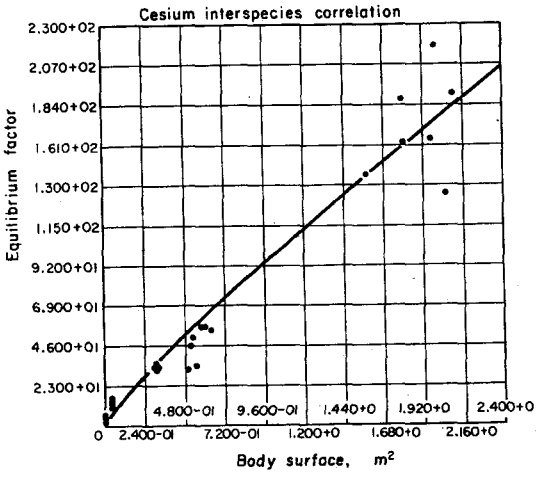


FIG. 5. Interspecies correlation between equilibrium factor ($E$) and body surface (in $m^2$) for mice, rats, monkeys, dogs, and men given radioactive cesium. The regression equation is: $E = 97.34\ X^{0.8518}$.

The coefficient indicates a value of 97.35 for $E$ when body surface is unity. Figure 5 shows, however, that for body surfaces approaching zero, $E$ approaches zero.

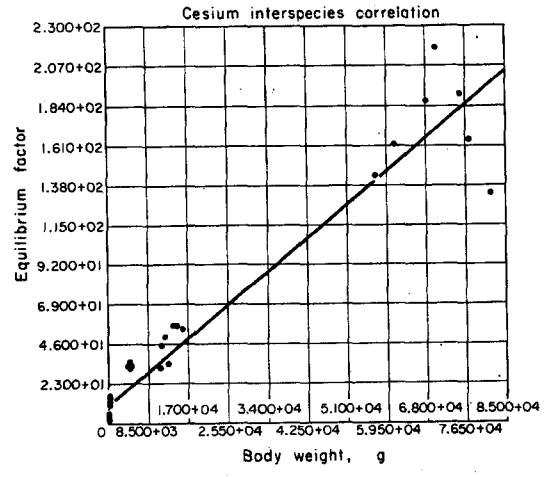


FIG. 6. Interspecies correlation between equilibrium factor ($E$) and body weight (in g) for mice, rats, monkeys, dogs, and men given radioactive cesium. The regression equation is: $E = 10.88 + 0.0023\ X$.

The cesium data were also fit using a first-degree polynomial. Figure 6 shows the interspecies correlation between $E$ and grams body weight. The best computer-derived fit is:

$$E = 10.88 + 0.0023\ X, \qquad (11)$$

with a correlation coefficient of 0.962.

If $E$ is fit as a function of body surface (Fig. 7), the best regression equation is:

$$E = 6.64 + 85.59\ X, \qquad (12)$$

with a correlation coefficient of 0.981.

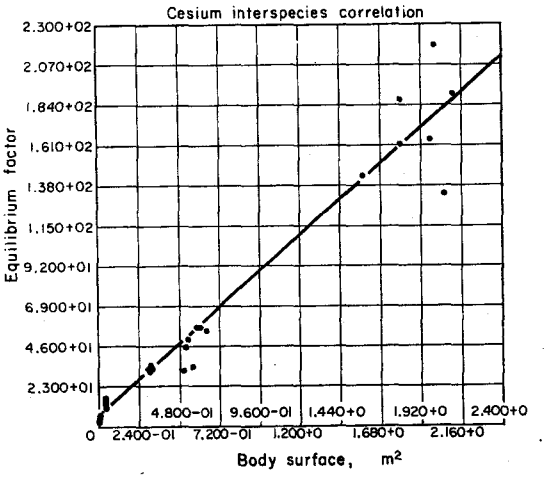


FIG. 7. Interspecies correlation between equilibrium factor ($E$) and body surface (in $m^2$) for mice, rats, monkeys, dogs, and men given radioactive cesium. The regression equation is: $E = 6.64 + 85.59\ X$.

Table 5 compares $(MPC)_w$ values obtained from the 7 human subjects with the value currently listed by the ICRP.[2] The average value obtained from our sample is about one-third that recommended by the ICRP. Values for $(MPC)_w$, calculated from interspecies correlations shown by Figs. 4 through 7, are in each case $0.8 \times 10^{-4}$ $\mu$Ci $^{137}$Cs/ml. Values of $7 \times 10^4$ g, or 1.8 $m^2$, are used in solving the regression equations for $E$. The value of $(MPC)_w$ is then calculated by substituting $E$ in eq. (8) (see also eqs. (A1) to (A4) in appendix). The respective values of $q$ and $S$ are 30 $\mu$Ci and 2200 ml/day.

*Table 5. Maximum Permissible Concentration of $^{137}Cs$ in Water [$(MPC)_w$] for Continuous Exposure when the Whole Body is considered as the Critical Organ*

| Source of value | $(MPC)_w$* ($\mu$Ci/ml) |
|---|---|
| ICRP[3] | $2.0 \times 10^{-4}$ |
| Subject 1 | $0.9 \times 10^{-4}$ |
| Subject 2 | $0.7 \times 10^{-4}$ |
| Subject 3 | $0.8 \times 10^{-4}$ |
| Subject 4 | $0.6 \times 10^{-4}$ |
| Subject 5 | $0.7 \times 10^{-4}$ |
| Subject 6 | $0.6 \times 10^{-4}$ |
| Subject 7 | $0.8 \times 10^{-4}$ |
| Average $T$ for 7 subjects | $0.7 \times 10^{-4}$ |

$$*(MPC)_w = \frac{3.15 \times 10^{-4}\, q \cdot f_2}{T \cdot f_w[1 - \exp(-0.693t/T)]},$$

where $q$ equals 30 $\mu$Ci, $f_2$ and $f_w$ both equal 1, $t$ equals 50 yr, and effective half-life ($T$) is determined individually for each subject.

Table 6 shows values of $E$ and $(MPC)_w$ calculated for a standard man (i.e. $7 \times 10^4$ g or 1.8 m$^2$) from interspecies correlations. When man is not included in the correlation, an equilibrium level of 87 or 83 is calculated, depending on the choice of body weight or surface as the independent variable. When man is included in the data used to calculate the correlation, the calculated equilibrium levels are higher by about a factor of 2, and the resulting $(MPC)_w$ values are reduced by a factor of 2. Extrapolation to man results in underestimating $E$ and overestimating $(MPC)_w$. When a first-degree polynomial is used (Table 7), extrapolation to man on the basis of body weight results in an overestimation of $E$; the reverse is true when body surface is used as the independent variable. Good agreement exists between interspecies correlations based on body surface in Table 7, whether human data are included ($E = 161$) or excluded ($E = 142$). The average value for $E$ obtained from the 7 human retention studies is 171.

For predictive purposes, the interspecies correlation of the form $E = a + bX$, where $X$ is body surface in m$^2$, yields equilibrium values for man that agree best with human experimental data.

Figure 8 shows the interspecies relation between $E$ and basal metabolic rate for the radiocesium data. The best computer fit to the data is:

$$E = 0.44\, X^{0.8062}, \qquad (13)$$

in which $X$ is calories/day. The basal metabolic rate was calculated from each animal's body weight according to Brody.[13] The relation between $E$ and specific metabolic rate (calories/g body weight · day) is given in Fig. 9. The computer-derived equation,

$$E = 48.37\, X^{-2.2233}, \qquad (14)$$

*Table 6. Comparison of Equilibrium Factor ($E$) and $(MPC)_w$ Values for $^{137}Cs$ in Man using Interspecies Correlations of the Form $E = aX^b$ with and without Data from Human Subjects*

| Independent variable ($X$) | Interspecies correlation | $E$* | $(MPC)_w$ ($\mu$Ci/ml) |
|---|---|---|---|
| Body weight (g)† | $0.23\, X^{0.5914}$ | 167 | $0.8 \times 10^{-4}$ |
| Body weight (g)‡ | $1.66\, X^{0.3550}$ | 87 | $1.6 \times 10^{-4}$ |
| Body surface (m$^2$)† | $97.35\, X^{0.8518}$ | 161 | $0.8 \times 10^{-4}$ |
| Body surface (m$^2$)‡ | $63.81\, X^{0.5100}$ | 83 | $1.6 \times 10^{-4}$ |

* Value of interspecies correlation calculated for a person with a body weight of $7 \times 10^4$ g or a body surface of 1.8 m$^2$.
† Man included in the derivation of the interspecies correlation.
‡ Man omitted from the derivation of the interspecies correlation.

*Table 7. Comparison of Equilibrium Factor ($E$) and $(MPC)_w$ Values for $^{137}Cs$ in Man using Interspecies Correlation of the form $E = a + bX$ with and without Data from Human Subjects*

| Independent variable ($X$) | Interspecies correlation | $E$* | $(MPC)_w$ ($\mu$Ci/ml) |
|---|---|---|---|
| Body weight (g)† | $10.88 + 0.0023\ X$ | 172 | $0.8 \times 10^{-4}$ |
| Body weight (g)‡ | $9.37 + 0.0031\ X$ | 226 | $0.6 \times 10^{-4}$ |
| Body surface ($m^2$)† | $6.64 + 85.59\ X$ | 161 | $0.9 \times 10^{-4}$ |
| Body surface ($m^2$)‡ | $7.47 + 74.84\ X$ | 142 | $1.0 \times 10^{-4}$ |

* Value of interspecies correlation calculated for a person with a body weight of $7 \times 10^4$ g or a body surface of 1.8 $m^2$.
† Man included in the derivation of the interspecies correlation.
‡ Man omitted in the derivation of the interspecies correlation.

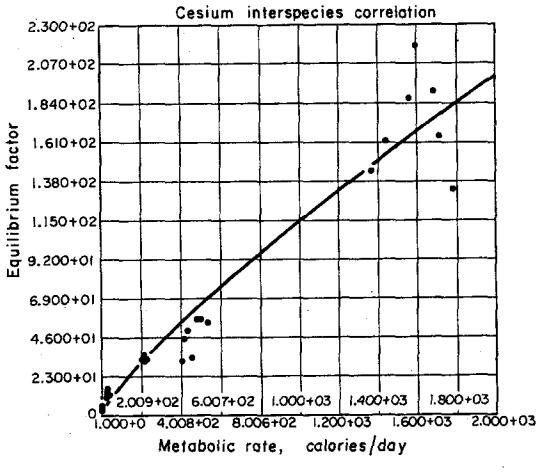


FIG. 8. Interspecies correlation between equilibrium factor ($E$) and metabolic rate (in calories/day) for mice, rats, monkeys, dogs, and men given radiocesium. The regression equation is: $E = 0.44\ X^{0.8062}$.

indicates that $E$ decreases as specific metabolic rate increases. Smaller animals produce more calories/g body weight · day as the result of a higher metabolic rate. Therefore, at least for many elements which are not deposited in nonlabile pools such as bone matrix, equilibrium levels are at least partially determined by metabolic rate. Higher metabolic rates result in faster biological turnover and in lower equilibrium burdens. Consequently, one would predict faster turnover of these materials in the young of one species as compared with adults with lower metabolic rates. Recent studies indicate that this is true for cesium.[14, 15] The Federal Radiation Council uses a value of 30 days as the biological half-life of $^{137}Cs$ in infants.[16]

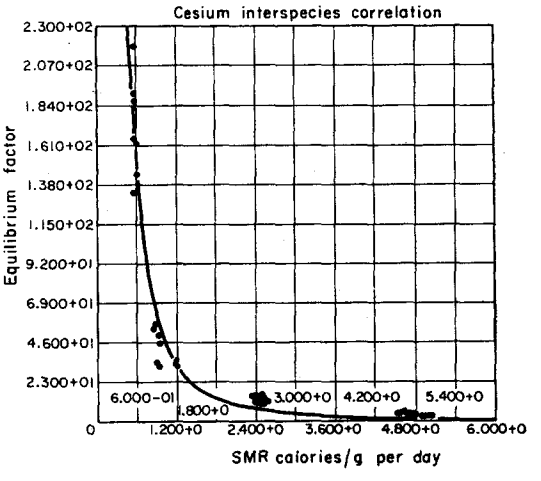


FIG. 9. Interspecies correlation between equilibrium factor ($E$) and specific metabolic rate (in calories/day/g) for mice, rats, monkeys, dogs, and men given radiocesium. The regression equation is: $E = 48.37\ X^{-2.2233}$.

At this point we should examine some of the factors that can alter the position of a species within the correlation. First, any agent that affects metabolic rate may influence the turnover and change the equilibrium factor. Included in this category are environmental temperature, age, and certain drugs. A second factor is diet. Simple exchange of the tracer with its stable form or with a physiologically similar element appears to govern turnover for some elements. Increasing water intake, therefore, will accelerate tritium turnover. Also, increasing the intake of potassium will accelerate the loss of cesium, which has similar physiochemical properties. A third factor is that of

*Zinc*

Zinc, unlike tritium and cesium, is not completely absorbed from the gastrointestinal tract. Figure 10 shows the interspecies correlation relating log $E$ to log body weight (in g) for $^{65}$Zn given orally to 12 mice, 6 rats, 3 dogs, and 4 human subjects. The regression line calculated from the average $E$ value for the mice, rats, and dogs is:

$$\log E = 0.1903 + 0.3833 \log X. \quad (15)$$

The rather large range for the human data is due mainly to differences in gastrointestinal absorption rather than to differences in turn-

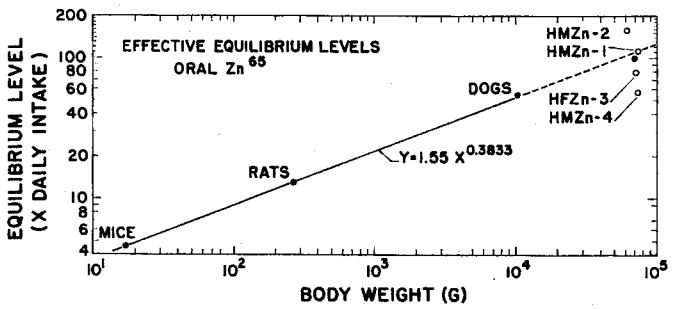


FIG. 10. Interspecies correlation between equilibrium factor ($E$) and body weight (in g) for mice, rats, dogs, and men given $^{65}$Zn. The regression equation is: $\log E = 0.1903 + 0.3833 \log W$.

specific binding agents. For example, certain natural foodstuffs act as ion exchangers in the lumen of the gut, thereby preventing initial absorption or recycling across the gut wall.[17, 18] Specific ion binding within the gut is the basis of recent work in which ferric ferrocyanide was used to reduce radiocesium burdens in animals and man.[19-21] The equilibrium level can be reduced by 60% in the rat by ferric ferrocyanide feeding.[20]

The fibrous, potassium-rich food consumed by cows probably acts to accelerate cesium turnover. It is known that the biological half-life for cesium in cows[22] and in goats,[23] both ruminants, is shorter than would be expected on a body weight basis. In both species fecal loss exceeds urinary loss for cesium; the reverse is true for nonruminant mammals.

over. The effective retention parameters obtained for the human subjects were used to calculate $(MPC)_w$ values for continuous occupational exposure using the basic equation from the ICRP Report of Subcommittee II (eq. A1). Values of 60 $\mu$Ci and unity were used for $q$ and $f_2$, respectively. The effective half-life of the last component of the retention function was used for $T$, and its intercept was used for $f_w$. Values for the 4 subjects were 2.4, 1.7, 3.4, and 4.7 $\times 10^{-4}$ $\mu$Ci $^{65}$Zn/ml. Although zinc is concentrated largely in bone, the range of its hard electromagnetic radiation makes assumption of the whole body as the critical organ reasonable. An $(MPC)_w$ value of 2.4 $\times 10^{-4}$ $\mu$Ci/ml was calculated for $^{65}$Zn using values of 60 $\mu$Ci for $q$, 112 for $E$, and 2200 ml for $S$. Details of this work are available.[5]

*Iodine*

The interspecific correlations for orally ingested iodine are given in Fig. 11 for biological retention of non-radioactive iodine and for effective retention of $^{131}I$. It is apparent that biological retention data afford a more accurate extrapolation to measured human values than effective retention. If equilibrium levels are, in fact, a function of metabolic rates, the relation between biological equilibrium levels and body weights follows. Short-lived isotopes tend to decrease the value of the slope constants of the interspecies relation derived from biological retention data. Nevertheless, it is the effective retention that is of interest in estimating MPC values for any particular radionuclide. Extrapolation of the $^{131}I$ effective retention data to $7 \times 10^4$ g body weight gave a value of 4.7 for $E$, whereas human retention data gave a value of 2.4. If the human data are used to establish the interspecific relation, then the value for $E$ for $7 \times 10^4$ g is 3.4.

These values of $E$ are derived from whole-body retention data. Although the thyroid is the critical organ for $^{131}I$, whole-body retention is paralleled by thyroid retention and may be used as an approximation of thyroid retention. $(MPC)_w$ may then be calculated from

$$(MPC)_w = \frac{q f_2}{f_w E S}, \tag{16}$$

where $E$ and $S$ have the same meaning as in eq. (8), $f_2$ is the fraction in the organ of reference of that in the total body, and $f_w$ is the fraction of that ingested that is retained in the critical organ: 0.2 and 0.3, respectively.[2] The value of $q$ is 0.7.[2] Values for $(MPC)_w$ were $4.5 \times 10^{-5}$, $6.3 \times 10^{-5}$, and $8.8 \times 10^{-5}$ $\mu$Ci $^{131}I$/ml, respectively, when $E$ values of 4.7, 3.4, and 2.4 are used in eq. (16). The value now listed by the ICRP, $2.0 \times 10^{-5}$, agrees best with that obtained from the interspecies extrapolation to man given in Fig. 11. These data are available in more detail.[6]

*Manganese*

The relation between body weight and $E$ for 12 mice, 9 rats, 3 monkeys, and 4 dogs is shown in Fig. 12. The data were derived from

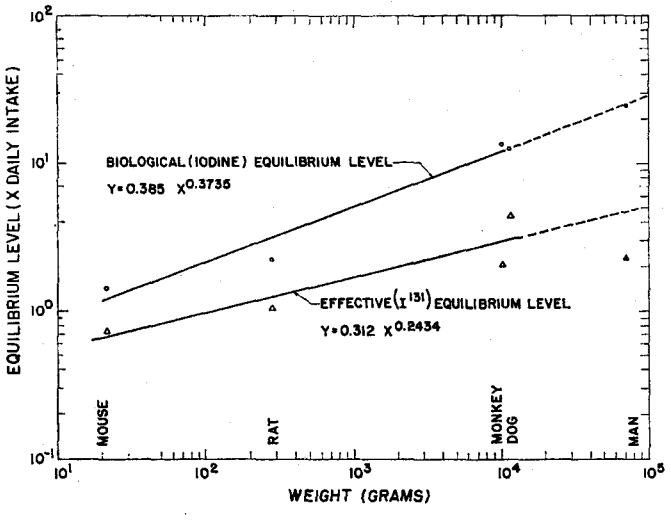


FIG. 11. Interspecies correlation between equilibrium factor ($E$) and body weight (in g) for mice, rats, monkeys, dogs, and men given $^{131}I$. The regression equations are:

$$\log E = -0.4145 + 0.2434 \log X \text{ (for } ^{131}I)$$

and

$$\log E = -0.5059 + 0.3735 \log X \text{ (for stable iodine).}$$

whole-body retention measurements following a single oral dose of $^{54}$Mn. Details of this work appear elsewhere.[7] Extrapolation of the data shown in Fig. 12 to $7 \times 10^4$ g body weight gives a value of 2.8 as an estimate of $E$ for man. The value for $q$, when the whole body is considered to be the critical organ, is 40 $\mu$Ci.[2] Using 2200 ml as the daily water intake ($S$) and substituting both values in eq. (8), a value of $6 \times 10^{-3}$ $\mu$Ci/ml as the $(MPC)_w$ for continuous intake of $^{54}$Mn is obtained. This agrees well

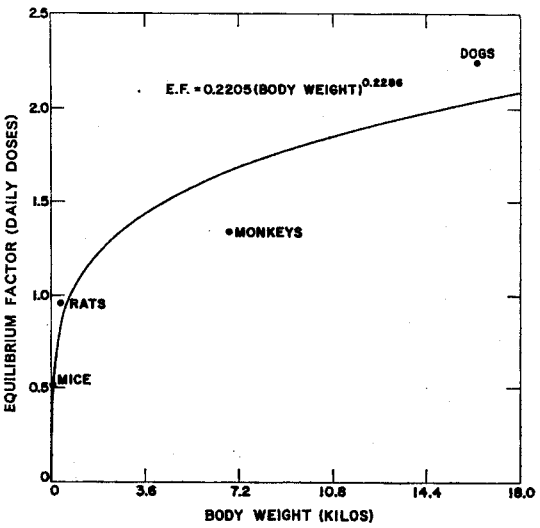


FIG. 12. Interspecies correlation between equilibrium factor ($E$) and body weight (in kg) for mice, rats, monkeys, and dogs given $^{54}$Mn. The regression equation is:

$$E = 0.22 + 0.2286 \log W.$$

with the value of $8 \times 10^{-3}$ currently listed by the ICRP.[2]

*Sodium*

The interspecies relation between the log of biological half-life and log of body surface (in $m^2$) for 12 mice, 6 rats, 4 dogs, 4 monkeys, and 3 human subjects was reported in 1958.[3] This method of presenting the data was complicated by the presence of three components in the curve describing retention by the whole body. Later,[24] log $E$ was related to grams body weight by the following equation:

$$\log E = 0.1139 + 0.2400 \log X. \quad (17)$$

The value of $E$, calculated from the human data, was 17.85. From eq. (17) a value of 18.91 can be calculated for a $7 \times 10^4$-g man. The calculated MPC value using $E$ values of either 17.85 or 18.91 is approximately $2.6 \times 10^{-4}$ $\mu$Ci $^{22}$Na/ml, and agrees well with the $4.0 \times 10^{-4}$ currently listed by the ICRP[2] for the whole body.

*Rubidium*

Preliminary results for $^{86}$Rb were given elsewhere.[24] In general, $E$ increased as body weight increased in a manner similar to that observed for cesium.

*Strontium*

Analysis of our experimental data for $^{85}$Sr and $^{90}$Sr given to five mammalian species is incomplete. However, the reader is directed to recent work by Fujita and Iwamoto[25] in which long-term retention of strontium in humans is predicted from small-animal experimental data. These authors, who also noted species similarities in retention patterns, suggest that retention patterns obtained from small animals are "epitomes" of human retention patterns.

## USE OF HUMAN DATA IN CALCULATING MPC VALUES

Liden,[26] in a summary of cesium metabolism, noted that biological half-lives reported from Finland, Sweden, and Russia are clustered in the 50- to 80-day range, while values from England fall into the 80- to 110-day range and German values average 140 days. The scatter of values reported from the United States is large, but most fall into the 100- to 130-day range. Liden speculates that perhaps real differences in cesium metabolism exist for people living and working in various parts of the world as the result of differences in climate, dietary habits, working habits, etc. For example, Eskimos in the Anaktuvuk Pass, Alaska area, have resting metabolic rates (room air 35°C) that average about 35% higher than non-Eskimos.[27] The results of this paper indicate that the observed variation may be at least in part due to differences in metabolic rate. These

observations suggest a consideration of *which* human data, if available, should be used to calculate radiation protection guides such as MPC values. Perhaps extrapolations to man on the basis of interspecies correlations can also supply estimates of variability one might expect to find for human subjects because of variables such as metabolic rate.


## SUMMARY

Whole-body retention data obtained from mice, rats, monkeys, dogs, and in some cases men were used to calculate equilibrium factors ($E$) for continuous intake of tritium water (HTO) $^{137}$Cs, $^{65}$Zn, $^{131}$I, $^{54}$Mn, $^{22}$Na, and $^{86}$Rb. This was done by integrating the effective retention functions obtained experimentally between the limits of zero and infinity. The values of $E$ for the different species were then fit as a function of grams body weight, m$^2$ body surface, or metabolic rate in calories/day. Maximum permissible concentrations for continuous intake $(MPC)_w$ were then calculated using the proper value for man in the interspecies correlation.

For tritium water and radiocesium, both of which distribute throughout the entire body, $(MPC)_w$ values calculated from the interspecies correlations agreed extremely well with data obtained directly from human subjects. A comparison of linear and parabolic models was also made for HTO and radiocesium. Either model gave good fits to the experimental data. For predictive purposes, however, the parbolic model is best for HTO data and the linear model is best for radiocesium data. Metabolic rate provides the best independent variable for correlations for both HTO and radiocesium.

Interspecies correlations are also given in varying detail for $^{65}$Zn, $^{131}$I, $^{54}$Mn, $^{22}$Na, and $^{86}$Rb. Zinc and iodine are good examples for materials which do not distribute throughout the entire body. The parabolic model, with log transformation of the variables, was used. In each case, predicted values of $E$ for man agreed well with observed or reported values.

The partial dependence of turnover and, therefore, $E$ on metabolic rate helps to explain shorter turnover times observed for radiocesium in children as compared with adults, as well as suggested latitudinal differences in reported turnover times.


## REFERENCES


1. S. M. Michaelson and L. T. Odland. *Radiation Res.* **16,** 281 (1962).
2. International Committee on Radiation Protection. Report of Committee II on Permissible Dose for Internal Radiation (1959). *Health Phys.* **3** (1960).
3. C. R. Richmond. *Los Alamos Scientific Laboratory Report* LA-2207 (1958).
4. C. R. Richmond, W. H. Langham and T. T. Trujillo. *J. Cell. Comp. Physiol.* **59,** 45 (1962).
5. C. R. Richmond, J. E. Furchner, G. A. Trafton and W. H. Langham. *Health Phys.* **8,** 481 (1962).
6. J. E. Furchner and C. R. Richmond. *Health Phys.* **9,** 277 (1963).
7. J. E. Furchner, C. R. Richmond and G. A. Drake. *Health Phys.* **12,** 1415 (1966).
8. J. A. D. Cooper, N. S. Radin and C. Borden. *J. Lab. Clin. Med.* **52,** 129 (1958).
9. W. H. Langham, W. J. Eversole, F. N. Hayes and T. T. Trujillo. *J. Lab. Clin. Med.* **47,** 819 (1956).
10. C. R. Richmond, J. E. Furchner, P. N. Dean and P. McWilliams. *Health Phys.* **10,** 3 (1964).
11. P. N. Dean and C. R. Richmond. *Radioisotope Sample Measurement and Techniques in Medicine and Biology*, pp. 139–168. IAEA, Vienna, 1966.
12. H. von Schelling. *Ann. N.Y. Acad. Sci.* **56,** 1143 (1954).
13. S. Brody. *Bioenergetics and Growth.* Reinhold, New York (1945).
14. J. K. Miettinen, A. Jokelainen, P. Roine, K. Liden and Y. Naversen. *Ann. Acad. Sci. Fennicae.* Ser. AII, Chemica No. 120 (1963).
15. L. G. Bengtsson, Y. Naversen and K. G. Svensson. *Assessment of Radioactivity in Man*, Vol. II, pp. 21–32. IAEA, Vienna (1964).
16. Federal Radiation Council. *Background Material for the Development of Radiation Protection Standards*, p. 26, Report No. 7, Government Printing Office, Washington, D.C. (1965).
17. F. R. Mraz and H. Patrick. *Proc. Soc. Exp. Biol. Med.* **94,** 409 (1957).
18. F. R. Mraz and H. Patrick. *J. Nutrition* **61,** 535 (1957).
19. V. Nigrovic. *Int. J. Radiation Biol.* **7,** 307 (1965).
20. C. R. Richmond and D. E. Bunde. *Proc. Soc. Exp. Biol. Med.* **121,** 664 (1966).
21. K. Madshus, A. Stromme, F. Bohne and V. Nigrovic. *Int. J. Radiation Biol.* **10,** 519 (1966).
22. S. L. Hood and C. L. Comar. *Arch. Biochem. Biophys.* **25,** 423 (1953).
23. R. H. Wasserman, C. L. Comar and A. R. Twardock. *Int. J. Radiation Biol.* **4,** 299 (1962).
24. C. R. Richmond. *Los Alamos Scientific Laboratory Report* LAMS-2445, pp. 71–79 (1960).

25. M. FUJITA and J. IWAMOTO. *Health Phys.* **11,** 271 (1965).
26. K. LIDEN. *Assessment of Radioactivity in Man,* Vol. II, pp. 33–40. IAEA, Vienna, 1964.
27. D. W. RENNIE, B. G. COVINO, M. R. BLAIR and K. RODAHL. *J. Appl. Physiol.* **17,** 326 (1962).
28. C. R. RICHMOND, J. E. FURCHNER and G. A. TRAFTON. *Health Phys.* **7,** 219 (1962).

## APPENDIX

An equilibrium level will be established within an organism for any physiologically soluble element that is ingested at a constant rate for a sufficiently long time. This point of metabolic homeostasis is one at which the RBE dose rate to the critical organ* reaches a maximum value for that particular radionuclide intake level. Prior to reaching equilibrium, daily intake of the radionuclide exceeds daily output; after reaching equilibrium, intake and output are essentially equal. The time required to reach equilibrium is determined by the parameters that describe retention of the radionuclide by the organism. Therefore, the maximum permissible body burden ($q$) is that quantity of a radionuclide that will deliver the permissible RBE dose rate to the critical organ. Likewise, a maximum permissible concentration (MPC) for an ingested radionuclide is the amount per day that will result in the critical organ receiving the permissible RBE dose rate when equilibrium conditions are reached.

If we know values for $q$ and for effective half-life ($T$), then MPC of a radionuclide in water (for a 40-hr work week) can be estimated as follows:

$$(MPC)_w = \frac{9.2 \times 10^{-4}\, q\, f_2}{T f_w\, [1 - \exp - (0.693t/T)]}, \quad \text{(A1)}$$

as given in eq. (8) of ref. 2. The quantities $f_w$ and $f_2$ are fractionation constants which become unity if, for simplicity, we consider the whole body as being the critical organ. The numerical constant in the numerator is obtained by dividing ln 2 by 750 (the latter assumed to represent the effective daily water intake). Thus, the step preceding eq. (8), in the derivation of the MPC equation,[2] is:

$$(MPC)_w = \frac{0.693\, q\, f_2}{T \cdot S \cdot f_w\, [1 - \exp - (0.693t/T)]}. \quad \text{(A2)}$$

* As defined in ref. 2.

For continuous exposure, the daily intake ($S$) is 2200 ml and the numerical constant in eq. (A1) becomes $3.15 \times 10^{-4}$.

At equilibrium, for cases where the whole body is the critical organ, eq. (A1) reduces to:

$$(MPC)_w = \frac{0.693\, q}{T \cdot S\, [1 - 0]}. \quad \text{(A3)}$$

At this point, we can substitute a factor (equilibrium factor $E$) for $T/0.693$ in eq. (A3):

$$(MPC)_w = \frac{q}{E \cdot S}. \quad \text{(A4)}$$

Re-arrangement of eq. (A4) is as follows:

$$q = (MPC)_w \cdot E \cdot S, \quad \text{(A5)}$$

which indicates that the maximum permissible body burden ($q$) is equal to the product of the maximum permissible radionuclide concentration ($\mu$Ci/ml), the volume ingested daily (ml/day), and an equilibrium factor. For eq. (A5) to be dimensionally correct, $E$ must have dimensions of days. $E$ can be obtained by integrating between the limits of zero and infinity, the effective retention function ($R_t$) which describes retention by human subjects following a single intake of the radionuclide:

$$E = \int_0^\infty (R_t)\, dt. \quad \text{(A6)}$$

Reference 28 describes this step in more detail.

The equilibrium factor is proportional to the area bounded by the retention function and has the dimension of dependent variable times days. $E$ can also be estimated for humans by extrapolating similar values obtained from laboratory animals on the basis of some physiological parameter such as body weight or surface.

The equilibrium factor is calculated for single administration tracer experiments as follows. Let us assume a single daily intake ($I$) of a radionuclide that is subsequently lost from the body in an exponential manner governed by the rate constant $k$. Then retention at any time ($R_t$) is:

$$R_t = I \exp(-kt), \quad \text{(A7)}$$

and, by integration,

$$\int_1^2 (R_t)\,dt = I\int_1^2 \exp(-kt)\,dt$$

$$= -\frac{I}{k}\left[e^{-kt_2} - e^{-kt_1}\right]$$

$$= \frac{I}{k}\left[e^{-kt_1} - e^{-kt_2}\right].$$

If limits 1 and 2 are zero and infinity, respectively,

$$\int_0^\infty (R_t)\,dt = \frac{I}{k}[1 - 0]. \qquad \text{(A8)}$$

Because the mean residence time ($\tau$) for the average atom is the reciprocal of the rate constant, eq. (A8) becomes:

$$\int_0^\infty (R_t)\,dt = I\tau = E. \qquad \text{(A9)}$$

Thus, the dimensions of $E$ become days if $I$ is considered one daily intake. Therefore, the equilibrium factor ($E$) as substituted in eq. (A4), is the mean time that the atoms under study remain within the body.

Equation (A4) is not limited to conditions where the whole body is considered to be the critical organ. However, it is imperative to use an equilibrium factor that relates to the same critical organ as does $q$ (see ref. 28 for more detail).