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COMPARATIVE METABOLISM OF RADIONUCLIDES IN MAMMALS—I

UPTAKE AND RETENTION OF ORALLY ADMINISTERED Zn^{65} BY FOUR MAMMALIAN SPECIES*

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Abstract—Uptake and retention of a single oral administration of $Zn^{65}Cl_2$ in mice, rats, dogs, and 4 human subjects were studied by whole-body counting methods. Retention functions for each species were accurately represented by multiple rate equations composed of three exponential terms. The average effective half-time of the longest component (which accounts for approximately 95 per cent of all the disintegrations occurring in the body) of the retention curve for man was 154 days with a range of 149–161 days. A parabolic relationship between species weight and equilibrium level for chronic exposure was derived and used to estimate Zn^{65} $(MPC)_w$ values for man. The average $(MPC)_w$ value (168 hr/week exposure) obtained directly from the human data by usual methods was 3.1×10^{-4} $\mu c/ml$ with a range of 1.7–4.7 $\times 10^{-4}$ $\mu c/ml$ compared with 2.4×10^{-4} $\mu c/ml$ when derived from interspecies correlation data.

INTRODUCTION

ZINC is known to be an essential trace element. It functions as a prosthetic group in enzymes concerned with proteolysis and with gaseous and cellular respiration. Zinc may also participate in erythropoiesis and in myelogenous bone marrow function.[1]

Although Zn^{65} is not a product of nuclear fission, it is produced by neutron activation of stable zinc in power reactors and nuclear detonations. Zn^{65} also appears to be produced as a contaminant in cyclotrons by the Cu^{65} $(d, 2n)Zn^{65}$ reaction. Trace amounts of this radionuclide have been detected in people and in foodstuffs from the Hanford area,[2,3] in animals from the vicinity of the Nevada Test Site,[4] in cyclotron workers at this and other laboratories,[5] in reactor workers,[6] and in human beings[7,8] and marine organisms[9,10] from the Marshall Islands. In addition to these geographically isolated cases, Zn^{65} has been detected in plankton and in fish from many areas of the Pacific Ocean[11–13] and in commercial food supplies.[14, 15]

Presence of Zn^{65} in food webs and in people as a contaminant from nuclear weapon tests, reactor effluents, and nuclear research operations motivated the present investigation. This report summarizes comparative metabolic data obtained from four mammalian species and presents an interspecies correlation as a possible basis for deriving, from laboratory animal data, certain parameters of radionuclide metabolism in man.

METHODS AND MATERIALS

Whole-body liquid scintillation counters were used to study uptake and retention of Zn^{65} by mice, rats, dogs and man. Radio-zinc was administered as a single dose of $Zn^{65}Cl_2$. Uptake and retention following oral administration were studied in all species. Additional groups of mice and rats were given Zn^{65} via intravenous injection to assess the validity of the common practice of using rate constants derived from intravenous studies to derive protection guides for radionuclide concentrations in food and in water. The number of animals used, their average ages and weights, routes of administration, and amounts of Zn^{65} administered are given in Table 1. Thirty minutes after

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Zn^{65} administration and at intervals thereafter, all animals were counted in 4π whole body liquid scintillation counters to determine initial Zn^{65} activity and its retention as a function of time. Mice and rats were counted in the Los Alamos Small Animal Counter (LASAC I), and dogs and people were counted in the Los Alamos Human Counter (Humco I). Both detectors have been described elsewhere.[16]

Counting standards for mice, rats, and dogs were prepared by diluting an amount of Zn^{65} equal to the administered dose with a weight of water equal to the average weight of the respective species. These standards were sealed in polyethylene containers and counted routinely throughout the experiments. Standards for human subjects consisted of aliquots of the administered $Zn^{65}Cl_2$ solution diluted to a volume of 1 gallon.

Whole-body retention data were coded for analysis by an IBM Model 704 computer which was programmed to perform iterative least square calculations.[17] Coding procedures called for retention values (Y) at each time (t) and estimated intercept and rate parameters of the retention function. Each value of Y was weighted statistically by a factor proportional to $1/Y$. Computer analysis eliminates subjectiveness inherent to graphic analysis of retention data composed of several exponential functions.

Excreta were collected and measured to check accuracy of retention measurements by determining material balance and to compare measured excretion rate with the derivative of the retention function. Twenty-four hour urinary and fecal samples were collected from all species and diluted with a volume of water equal to the volume of the appropriate standard. Samples and standards were counted under the same geometric conditions. Human fecal samples were sealed in No. 2 tin cans containing formalin, and their measured activities were normalized also to an appropriate standard.

Studies using rats were carried out to demonstrate the time variation of Zn^{65} tissue distribution. Thirty-two adult male animals were given single oral doses of 1.2 μc Zn^{65} as the chloride and counted individually in the whole-body animal counter immediately after administration and just prior to sacrifice. Groups of 4 rats each were sacrificed at 4 hr and at 2, 8, 15, 30, 45, 60 and 112 days after Zn^{65} administration. At sacrifice, γ-activity of liver, gastrointestinal tract, testes, pelt, carcass and remainder was measured in the same geometry used to count the whole animal. The remainder consisted of the accessory sex organs, blood, fat and visceral organs. The carcass (the remains of the animal after visceral organs and pelt had been removed) consisted mainly of skeleton, muscle and some fat. After measurement, the carcass was autoclaved and skeleton and balance of carcass (primarily muscle) were separated and measured individually. Zn^{65} activity of individual tissues and organs at time of sacrifice was expressed as per cent of administered dose.

Table 1. Number of animals, age, weight and dose conditions for the study of Zn^{65} uptake and retention in 4 mammalian species

Species	Route	No.	Age at t_0	Weight ($\bar{x}$)	Dose (μ_c)	Last measurement (days)
Mice	Oral	12	58 days	17.0 g	0.5	90
Mice	I.V.	12	46 days	15.5 g	0.5	137
Rats	Oral	6	78 days	266.0 g	1.0	164
Rats	I.V.	6	85 days	289.0 g	1.0	135
Dogs	Oral	3	777 days	10.9 kg	2.0	540
HMZn-1*	Oral		29 years	72.0 kg	1.0	664
HMZn-2	Oral		48 years	56.8 kg	0.6	579
HFZn-3	Oral		31 years	72.7 kg	0.8	431
HMZn-4	Oral		45 years	70.2 kg	0.8	416

* The code for designating human subjects indicates species, sex, nuclide, and case number (e.g. the third subject receiving zinc was a female, whereas subjects 1, 2, and 4 were males).

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RESULTS

Data showing retention of orally administered Zn^{65} by mice, rats, dogs and man are presented in Fig. 1. The points represent observed average retention values expressed as per cent of administered dose as a function of time after ingestion. These data were analyzed by a computer programmed to give multiple-rate functions having the general form,

$$R_t = \sum_{i=1}^{n} [a_i \, e^{-k_i t}] \qquad (1)$$

where R_t is the whole-body retention on any day t, a_i and k_i are intercept and rate constants, respectively, and e is the base of natural logarithms. Units of R_t and a are per cent of administered dose, and k is expressed in reciprocal days. Since retention decreases with time, t is negative.

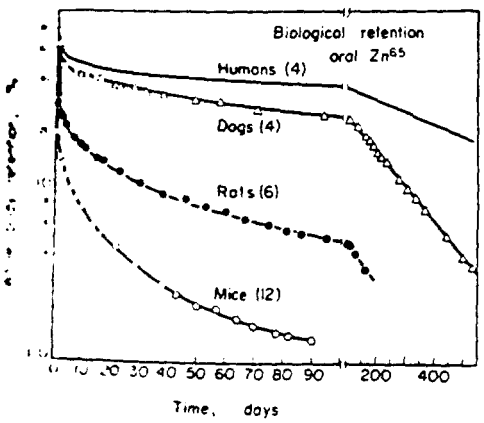

FIG. 1. Retention of orally administered Zn^{65} by 4 mammalian species.

Table 2 gives the computer-derived biological retention functions for Zn^{65} in mice, rats, dogs and 4 human subjects. The equations and measured retention values are plotted in Fig. 1 for mice, rats and dogs. The representative curve for the human subjects, which is shown merely for purposes of comparison with the other species, was obtained from the unweighted averages of the retention parameters given in Table 2. Effective retention functions (Eff. R_t) may be derived form the following expression:

$$\text{Eff. } R_t = \sum_{i=1}^{n} [a_i \, e^{-(k_i+\lambda)t}] \qquad (2)$$

in which λ is the physical decay constant for Zn^{65}, and other terms are the same as given in equation (1). Also, the area under each effective retention function from t_0 to t_∞ is given by the sum of the integrals $\int_0^\infty a_i \, e^{-(k_i+\lambda)t} dt$ and is as follows:

$$\text{total area} = \sum_{i=1}^{n} \left[\frac{a_i}{(k_i + \lambda)} \right]. \qquad (3)$$

Table 3 gives parameters of the effective retention functions for each species and the effective area under each component.

Observed and calculated retention of Zn^{65} by rats following oral administration is tabulated in Table 4. Column 1 shows the time of measurement in days. For these times, column 2 shows the average observed retention and column 3 shows the average retention derived from the computer analysis. Column 4 shows the average retention derived from an equation in which the smaller rate constants (k_2 and k_3) were taken from the computer-derived retention

Table 2. Biological retention functions of orally administered Zn^{65} for 4 mammalian species

Species	No. animals	Retention function
Mice	12	$R_t^* = 86.82\, e^{-2.3421t} + 11.19\, e^{-0.0572t} + 1.84\, e^{-0.0048t}$
Rats	6	$R_t = 77.01\, e^{-1.4672t} + 13.83\, e^{-0.0447t} + 8.84\, e^{-0.0063t}$
Dogs	3	$R_t = 51.63\, e^{-1.2208t} + 10.06\, e^{-0.0743t} + 38.74\, e^{-0.0045t}$
Man (HMZn-1)		$R_t = 38.50\, e^{-2.5201t} + 11.36\, e^{-0.1549t} + 50.15\, e^{-0.00164t}$
Man (HMZn-2)		$R_t = 9.26\, e^{-0.7452t} + 24.37\, e^{-0.0277t} + 66.63\, e^{-0.00145t}$
Man (HMZn-3)		$R_t = 61.26\, e^{-0.5807t} + 7.79\, e^{-0.0268t} + 35.63\, e^{-0.00175t}$
Man (HMZn-4)		$R_t = 71.87\, e^{-1.1645t} + 4.80\, e^{-0.0797t} + 26.13\, e^{-0.00179t}$

* $R_t = \sum_{i=1}^{n} [a_i e^{-k_i t}]$, when t is in days. These values were derived by IBM-704 computer.

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Table 3. Parameters of the components of effective retention functions for Zn^{65} administered orally to 4 mammalian species*

Species		a (%)	T (days)	$k + \lambda$ (days^{-1})	Area (% days†)	Area (% of total)
Mice	1	86.82	0.30	2.3449	37.5	8.09
	2	11.19	11.55	0.0600	186.4	40.22
	3	1.84	91.18	0.0076	239.6	51.69
Rats	1	77.01	0.47	1.4700	52.4	4.01
	2	13.83	14.56	0.0476	290.7	22.23
	3	8.84	75.33	0.0092	964.8	73.77
Dogs	1	51.63	0.57	1.2237	42.0	0.77
	2	10.06	8.98	0.0772	130.0	2.38
	3	38.74	94.93	0.0073	5292.0	96.84
Man (HMZn-1)	1	38.50	0.27	2.5230	16.0	0.14
	2	11.36	4.39	0.1577	72.0	0.64
	3	50.15	154.37	0.0045	11,167.0	99.22
Man (HMZn-2)	1	9.26	0.93	0.7481	13.0	0.08
	2	24.37	22.66	0.0306	797.0	4.89
	3	66.63	161.04	0.0043	15,480.0	95.03
Man (HFZn-3)	1	61.26	1.19	0.5835	105.0	1.29
	2	7.79	23.41	0.0296	263.0	3.23
	3	35.63	151.27	0.0046	7,776.0	95.48
Man (HMZn-4)	1	71.87	0.59	1.1673	61.0	1.07
	2	4.80	8.40	0.0825	58.0	1.01
	3	26.13	149.98	0.0046	5,654.0	97.93

* Effective retention function, Eff. $R_t = \sum_{i=1}^{n} [a_i e^{(-k_i+\lambda)t}]$.

† Total area under Eff. $R_t = \sum_{i=1}^{n} \left[\frac{a_i}{(k_i + \lambda)}\right]$.

equation obtained from intravenous administration experiments. The good agreement shown between columns 2 and 3 indicates an adequate mathematical description of the observed data. Also, the agreement between columns 2 and 4 suggests that retention of assimilated Zn^{65} is not influenced by the route of administration. Although the computation is given only for Zn^{65} retention by rats, similar results were obtained when oral and intravenous retention data for mice were analysed and compared in the same way.

Urinary and fecal samples were collected from all animals and were measured separately, after which the results were summed for each species and each collection period. Fecal excretion constituted the principal mode of Zn^{65} elimination for all 4 species. The average per cent of administered dose excreted per day in urine plus feces was compared with the first derivative of the biological retention function,

$$\frac{dR_t}{dt} = \sum_{i=1}^{n} [-k_i a_i e^{-k_i t}] \qquad (4)$$

in which $\frac{dR_t}{dt}$ is the rate of change of retention or total excretion rate. A comparison of $\frac{dR_t}{dt}$ for dogs with the observed average Zn^{65} urinary plus fecal elimination rate following oral administration is shown in Fig. 2. The whole-body activity on day 11 plus the total activity excreted to that time accounted for 96 per cent of the total administered activity. Material balance of Zn^{65} was comparable for the other species.

Data showing average Zn^{65} content of various tissues and organs of the rat as a function

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Table 4. Comparison of observed and calculated retention of Zn^{65} by rats following oral administration

Time (days)	Retention observed after oral administration (% of dose)	Retention calculated from oral data* (% of dose)	Oral retention calculated from intravenous data† (% of dose)
0	100.00	100.00	99.69
1	38.99	38.90	39.77
2	25.54	26.11	25.48
3	24.06	22.84	21.72
4	21.93	21.49	20.41
7	18.43	19.00	18.59
9	16.96	17.65	17.60
11	16.26	16.47	16.71
15	14.26	14.51	15.12
17	13.96	13.70	14.41
23	11.94	11.77	12.59
30	10.47	10.21	10.93
38	8.99	8.98	9.49
46	8.40	8.10	8.38
53	7.76	7.51	7.62
60	7.26	7.02	7.00
67	6.55	6.60	6.49
75	6.05	6.18	5.99
81	5.64	5.89	5.67
86	5.44	5.66	5.43
95	5.13	5.29	5.05
102	4.78	5.02	4.79
109	4.69	4.76	4.55
128	4.27	4.14	3.99
164	3.46	3.17	3.15

* Derived from computer analysis.

† Calculated by substituting last 2 rate constants derived from intravenous data into equation for oral retention.

of time after oral administration are presented in Fig. 3 in which per cent of administered dose is plotted on a log scale against a linear scale of time in days.

DISCUSSION

Biological retention of Zn^{65}

Data for biological retention of orally administered Zn^{65} in mice, rats, dogs and man are accurately represented by multiple rate equations consisting of three exponential terms (Table 2). Deviations of the observed retention values from the calculated lines are quite small (Fig. 1). Individual components of the retention functions probably represent three gross rates of loss from a number of sites where zinc is bound by more than one mechanism rather than by loss from specific tissues or organs acting as separate compartments. It seems unlikely that additional components will be required to describe retention of Zn^{65} at times greater than those observed, since the human and dog data did not deviate from linearity after 100 days.

Effective retention of Zn^{65}

Effective retention functions in the four species were calculated from the biological retention data by intoducing the radiological decay constant for Zn^{65} (equation 2). The areas under the effective retention functions (equation 3) are proportional to the total number of Zn^{65} disintegrations occurring in the body and are, therefore, related to radiation dose. Evaluation of the integral from t_0 to t_∞

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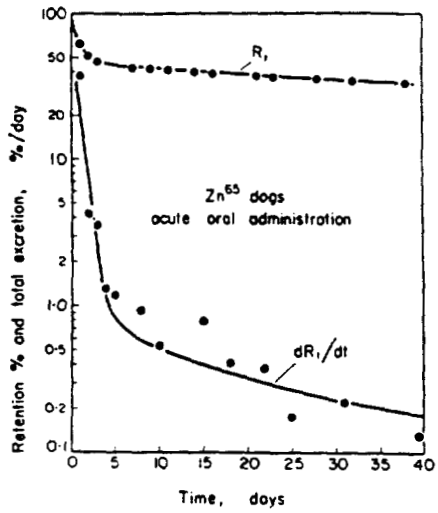

FIG. 2. Retention and excretion of orally administered Zn^{65} by dogs.

for each term of the retention equation gives the contribution of each component to total area (equation 3) and to total dose. The summed integrals also afford a prediction of the whole-body equilibrium level, in multiples of daily intake, under conditions of chronic exposure to a constant level of Zn^{65} intake. The average effective half-time of the third and last component of the retention equation for man is approximately 154 days. If equilibrium conditions were established in man under constant chronic exposure conditions, about 95–99 per cent of the Zn^{65} disintegrations

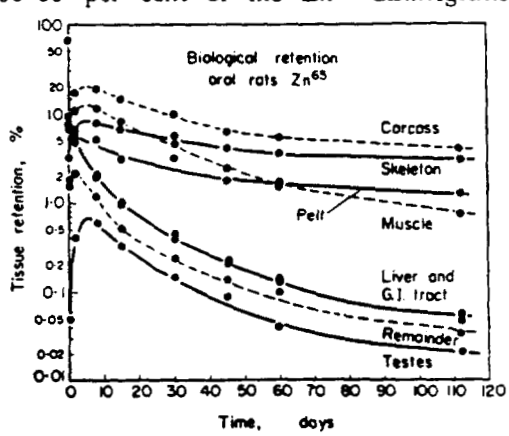

FIG. 3. Average Zn^{65} content of rat tissues as a function of time after oral administration of $Zn^{65}Cl_2$.

occurring in the body would be contributed by this component. Based on a 154-day half-time, an equilibrium level of about 112 times the daily intake could be established in man in about 1000 days. Miller and Steingraber[7] reported an effective half-time of 110 days for Zn^{65} in the Marshallese subjects exposed during the nuclear weapon test series in 1954. The 194 day effective half-time recommended by the ICRP[18] is based on measurements of the elimination rate of stable zinc.

Interspecies correlations in Zn^{65} metabolism

Cursory inspection of the parameters of the biological and effective retention functions suggests the possibility of some relationship between Zn^{65} metabolism and species size. The constants in the last terms of the equations

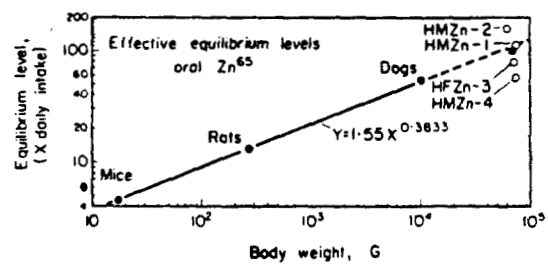

FIG. 4. Interspecies correlation between Zn^{65} equilibrium level and body weight. Regression line is based on mice, rats and dogs. Open circles represent experimentally determined values for human subjects.

show that more of the dose is retained for longer time as the size of the species increases. Likewise, the first terms indicate an inverse relationship between size and amount of Zn^{65} lost from the body at the fastest rate. Excreta analyses show that this rapid loss is largely via feces and is probably related to passage of unabsorbed Zn^{65} through the gastrointestinal tract. Although some material may be absorbed and re-excreted into the gut at early times, the administered dose minus the intercept of the first component of the retention function is assumed to be proportional to gastrointestinal absorption or uptake. The family of curves shown in Fig. 1 are a result, therefore, of combined effects of greater gastrointestinal absorption and decreased rate of excretion with increasing species weight.

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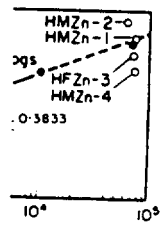
An interspecific correlation between species weight and equilibrium level (derived from the areas under the effective retention functions) is shown in Fig. 4. Least squares analysis of the log transformation of equilibrium level and body weight gives,



$$\log A = 0.1903 + 0.3833 \log W,$$

or

$$A = 1.55\ W^{0.3833} \tag{5}$$

in which A is the equilibrium level in multiples of the daily intake, and W is species weight in grams. Gastrointestinal absorption also tends to increase with species weight.

For purposes of establishing interspecies correlations between biological parameters and body weight, the model of choice should be one containing only biological parameters. Using such a model the equilibrium level for stable zinc in man, extrapolated from smaller species, is about 190 times the daily intake. This value is about two-thirds the average value obtained for the human subjects. However, the radioactive decay factor must be introduced to calculate dose or to estimate radiation protection criteria. Thus, it is felt that the correlation as given in equation (5) has more practical usefulness to the health physicist.

A parabolic interspecies correlation between species weight and daily turnover of tritium water has been observed also.[19] Such correlations can be used to supplement sparse human data for derivation of radiation protection guides. ADOLPH[20] has pointed out many parabolic relationships among the anatomical and physiological constitutions of mammals and their body weights. It is quite possible that certain metabolic parameters such as uptake and retention may conform to similar relationships.

Zn^{65} *retention after oral and intravenous administration*

Although it was possible to measure Zn^{65} whole-body retention in rats and mice for reasonably long times after oral administration, Zn^{65} was also administered intravenously to these species to assess feasibility of substituting rate constants derived from intravenous administration in oral retention equations. Table 4 shows that such procedures may be valid and useful in studying retention of radionuclides which are not readily absorbed from the gastrointestinal tract and yield extremely limited retention data because of very low counting rates. Similar studies comparing retention of Sr^{85} and Ba^{133} in rats after both oral and intraperitoneal administration also validate the practice of substituting rate constants from intravenous data after normalization for oral uptake.

Excretion of Zn^{65} *after oral administration*

The good agreement found between measured daily excretion of Zn^{65} and the derivative of the retention function for dogs (Fig. 2) illustrates the accuracy and convenience of whole-body counting methods for the study of radioisotope metabolism. Activity levels of excreta samples soon fall to less than 1 per cent of the administered dose and present problems in measurement. The advantages of whole-body counting, when compared with excretion analyses for determination of retention functions (apparent in Fig. 2), include greater accuracy, less emphasis on excreta collections, and ability to make measurements of activity at longer times after administration. Agreement between total excretion and whole-body retention was equally good in mice, rats, and human subjects. Most of the Zn^{65} was excreted in the feces. It should be possible, therefore, to estimate fairly accurately the body burden of contaminated subjects solely from fecal analyses, if reliable estimates of the retention functions and date of exposure are available.

Distribution of Zn^{65} *in tissues and organs of the rat*

The data in Fig. 3 show that loss of Zn^{65} from various tissues and organs of the rat is governed by more than one rate process. Peak tissue concentrations were reached within 5 days after oral administration, and kinetics of loss were similar for all tissues other than bone and pelt. Bone and pelt hold Zn^{65} more tenaciously than do other tissues, and together they account for the fraction of administered dose which is lost from the rat at the slowest rate (Table 3). Others have found the highest Zn^{65} tissue concentrations in bone and hair of cattle[2] and rats.[21] It seems reasonable to assume that

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radiozinc in tissues and organs of man would follow, at least qualitatively, the same general distribution pattern as observed in other species.

Radiation protection guides for Zn^{65}

The parameters of the effective retention function of Zn^{65} in man (Table 3) may be used to estimate the maximum permissible concentration for Zn^{65} in water or in food $(MPC)_w$ during continuous occupational exposure using the following basic equation taken from the *ICRP Report of Subcommittee II*:[18]

$$(MPC)_w = \frac{3.15 \times 10^{-4}\, q f_2}{T f_w\,(1 - e^{-0.693\, t/T})} \qquad (6)$$

in which q (the maximum permissible body burden) is 60 μc, f_2 (fraction of radionuclide in the critical organ of that in the total body) is unity, T is the effective half-time of the last component of the retention function, f_w is the intercept value for the third component of the retention function, and t is 50 years. Values for the 4 subjects are 2.4, 1.7, 3.4 and 4.7 $\times 10^{-4}$ μc Zn^{65}/ml, respectively. The average value is 3.1 $\times 10^{-4}$. Although Zn^{65} is concentrated largely in bone, the range of its hard electromagnetic radiation makes assumption of the whole body as the critical organ reasonable. Use of the parameters of the entire retention function in the denominator of equation (6) instead of those for the third term only makes essentially no difference in the calculated values for $(MPC)_w$. When the whole body is taken as the critical organ, the $(MPC)_w$ for continuous exposure may be estimated from the interspecies correlation data shown in Fig. 4, using,

$$(MPC)_w = \frac{q}{ES}$$

where q is 60 μc, E is the equilibrium level (112 times the daily intake) for man under conditions of constant chronic exposures, and S is 2200 ml (the daily water intake). Calculated in this manner, the $(MPC)_w$ of Zn^{65} for 40 and 168 hr/week exposure is 7 $\times 10^{-4}$ and 2.4 $\times 10^{-4}$ μc/ml, respectively. These values are approximately one-fourth of those recommended by the NCRP and ICRP.

SUMMARY

Retention of $Zn^{65}Cl_2$ in mice, rats, dogs and man following acute oral administration was measured using whole-body counting methods. Retention functions for all species were described by the sum of three exponential components. The average effective half-time of Zn^{65} in 4 human subjects was 154 days with a range of 149–161 days. The equation $A = 155X^{0.3833}$ relates area under the effective retention functions of the various species to body weight. This parabolic relationship between Zn^{65} uptake and retention and the body weight suggests that the allometric relationships among various physiological and anatomic parameters and body size may be reflected also in mineral metabolism.

Distribution studies of Zn^{65} in rats sho that its loss from various organs and tissues governed by more than one rate proces After oral administration, peak tissue concentrations are reached within 5 days. Bone and pelt together account for essentially al Zn^{65} making up the longest component of th retention function.

Using human data and the whole body a the critical organ, the average $(MPC)_w$ value for Zn^{65} for conditions of continuous occ pational exposure was estimated to be 3.1 10^{-4} μc/ml. The comparable value derive from the interspecies correlation was 2.4 10^{-4} μc/ml.

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