Similarity Ratios and Patterns in Retention of
Trace Substances*

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RECEIVED BY DTIC JUN 1 1971

Introduction

One of the major problems facing all biologists is the extrapolation of results to species other than those observed in laboratory and/or field studies. Environmental pollution and the subsequent food-chain passage of substances presents a particularly difficult aspect of this problem. The myriad of possible organisms and interactions makes analysis using usual step-by-step methods nearly impossible. Obviously, underlying relationships of "similarity" among species could greatly reduce the time and effort necessary to predict the ultimate fate of pollutants, at least for large segments of food chains.

Eberhardt (1969) has shown that the prospects for developing similarity ratios for nuclide retention data are encouraging. The purpose of this paper is to extend his results using additional nuclides, to propose additional areas for further study, and to discuss results in relation to present-day concerns for environmental pollution.

Assumptions and Data Employed

Eberhardt (1969) has discussed the concepts of allometry and similarity in addition to the mathematical derivation for the expression of nuclide retention or body burden as a sum of exponentials. Only the basic ideas will be repeated here.

*This paper is based on work performed under United States Atomic Energy Commission Contract AT(45-1)-1830.

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It has been demonstrated by Brody (1945) and Kleiber (1961) that metabolic functions or growth of various organs (Y) can be related to body mass (W) by the expression

$$Y = \alpha W^{\beta}. \quad (1)$$

Even though considerable interest has been evident in determining β in equation 1, Brody (1945) argues that a value of 0.75 should be adequate for most purposes. Stahl (1962, 1965) deals in great length with dimensionless numbers to relate ratios of various metabolic functions to organ size or body mass.

Since nuclide retention should be a function of metabolism then it or indirect measures should also follow some power law. Eberhardt (1967) and Hakonson (1967) have successfully related long component half-times for Cesium-137 in humans and Cesium-134 in mule deer to body weight by power functions (power coefficients of .66 and .75, respectively). Others, including the senior author, using Cesium-137 in rodents (unpublished data) have been unable to demonstrate any significant relationship. Reasons could include precision of measurements, lack of wide ranges of body weight, or selection of either a highly uncorrelated or extremely variable metabolic parameter. Eberhardt and Nakatani (1968) point out that selection of animals with wide weight ranges complicate things further because of higher metabolic rates in younger animals. However, many laboratory studies are carried out using animals of uniform weight thus allowing no evaluation of the possible correlations. ~~Intraspecies relationships are useful but generalized findings must come from interspecies comparisons.~~

Considerably less controversy exists when interspecies comparisons between measures of retention and body weight have been made. Table 1 summarizes

the estimates of α and β in equation 1 (labeled a and b) from papers selected as representative. Many other examples are in the literature; these were chosen because of constant modes of isotope administration and their constant method of expressing results. However, the markedly different characteristics of the isotopes and inter- and intraspecies body weights employed by these workers are illustrated in Tables 2 and 3.

A noticeable feature evident from Table 1 is the failure of any of the observed slopes (b's) to be very near the postulated value of 0.75 or any other common value. Eberhardt (1969) has proposed that this latter observation could be due to the wide range of interspecies relative to intraspecies body weights. The data of Richmond et. al. (1961) were used to illustrate the unlikelihood that the postulated value of 0.75 or any other constant value can be determined. These workers used effective equilibrium level; i.e. the amount of a unit dose which is retained under a chronic regimen of Cesium-137 feeding. Their calculated values were obtained by integrating an observed exponential retention function from $t = 0 \rightarrow \infty$ (% of injected dose; whole body counts) with physical decay considered. Since we were interested only in unit effective biological ^{equilibrium level} ~~retention~~ we ignored the decay constant and divided the coefficient of each exponential term by 100. However, since cesium has a 30 year physical half-life, our results deviate only slightly from Richmond et. al. (1961) for effective retention. ^{equilibrium level.}

We assumed that b in equation 1 was in fact 0.75 and estimated "a" for their data using

$$\frac{1}{n} \cdot \sum \frac{y}{w^{0.75}} = "a" \text{ with several groups of similar data or } \frac{y}{w^{0.75}} = "a" \quad (2)$$

for a single group of data where y is biological equilibrium level. Substituting the possible weight extremes for each species and the calculated "a" values

in equation 2 gave us the end points for each of the species lines illustrated in Figure 1 (i.e. biological equilibrium level for the extreme body weights at the calculated "a" values). Subsequently we fit a power function of the form $y = a X^b$ to the observed biological equilibrium levels and observed body weight values. Obviously, the estimates for a and b, (these estimates could be called c and d for clarity), 0.87 and 0.44 respectively, could theoretically assume many values (in this case 0.44 is not nearly = 0.75) based on where the mean animal weight occurred for each species and the precision of any individual experiment. The reader can repeat the calculations for a different assumed coefficient less than 0.75 and obtain similar although less extreme results.

Since various workers have failed to obtain a common metabolic weight coefficient for different isotopes (b's in Table 1) and because the possibilities are meager at best for precise estimates in the case of a single isotope (Figure 1) we have investigated the possibility of an interspecies analysis for all isotopes based on metabolic body size and estimates of "a" in equation 1.

Results

We estimated "a" (in equation 2) for each isotope and species given in the references in Table 1. Both biological equilibrium level and calculated long component half-time (days) were used as dependent variables for each species and isotope. These calculated "similarity values" are illustrated in Figures 2-5. Ratio estimates of b in

$$y = bx \quad (3)$$

were calculated as

$$b = \frac{1}{n} \sum \frac{y}{x} \quad (4)$$

(Turner, 1960) for the figures because our experience indicates that nuclide retention and excretion data is well represented by the γ distribution.

However, the estimate

$$b = \frac{\sum y}{\sum x} \quad (5)$$

is often used when the Poisson distribution of y for a given x is assumed. Since x and/or y are variables with unknown distributions, additional work should be done and a great deal more data evaluated before precise estimates are obtained. Both estimates and their respective standard errors are shown in Table 4 for many of the possible interspecies comparisons. If the smallest error of an estimate for b is used as a criterion, no appreciable difference is evident within a comparison. Although these elements may serve different physiological functions there is a pronounced similarity ratio shown in each of Figures 2-4. When biological half-time was employed as the dependent variable to calculate "a" the resulting interspecies similarity ratios were not nearly as clear, Figure 5. Other half-time comparisons, not illustrated, were much poorer. We believe that this result should not be surprising because biological equilibrium level is computed using the complete exponential retention function while long component half-time describes only a portion of the metabolic fate of nuclides which, while important in radiation protection, probably are not always representative of overall radiometabolism. Moreover, the latter measure in no way allows for the size (or amount) of nuclide available for excretion from a presumed pool. Of course, these two factors vary depending on the species and nuclide considered.

Eberhardt (1969) has used similar data for the rat and mouse and four nuclides in a "similarity" comparison with humans. Portions of his data are shown in Figure ~~6~~ along with additional data for silver and manganese

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comparing the former species. No important change in the ratio estimate is evident thus supporting the concept of similarity and its utility. The ratio estimates shown in Table 4 (either method) offer another intriguing possibility. When the ratio estimates for mice vs. dogs, monkeys, or man are computed they are strikingly similar. Data for rats follow a similar pattern as does dog vs. monkey or man. At this point we are not sure whether this observation has any profound meaning or is an artifact.

Discussion

The possible ultimate uses for an analysis such as this are either as a method for predicting expected biological equilibrium level for a larger organism, or as a beginning step for predicting the fate of substances in food chains. In the former case, biological equilibrium level for humans could be calculated from rats or mice for a substance of interest by computing "a" for rats, reading off (predicting) "a" for humans and then calculating equilibrium level using equation 2 and a body weight for humans. Such a procedure could thus circumvent the laborious testing of many species and compounds. It is, in effect, another idea for "extrapolating to man."

An extension to more general food chain analysis would be predicated on demonstrations that many more substances (pesticides, mercury, etc.) and species could be incorporated into our postulated "Similarity Ratio." If rates of loss and uptake through a food chain are of major interest, then metabolic measures other than the one used here (biological equilibrium level) could be investigated.

We have done some preliminary work which indicates that the biological equilibrium level for the last component of retention function, and for readily absorbable nuclides (Table 3), yields similarity ratios nearly the same as those in figures 2-4.

It does seem possible that measures of loss rate and/or pool size could lead directly to estimated of kinetic value in food chain models even though the data in figure 5 show that the prospects using long component half-times alone are not attractive.

The foregoing possibility, while plausible, ignores^e the very real additional problems found in any ecosystem analysis^A. These range from age, as related to metabolism through growth, weight changes due to environmental and physiological factors, age-specific mortality rates, and the like. Eberhardt (1969) advocates combining both the dynamics of population and the kinetics of food chains to account for some of these difficulties.

Summary

We have attempted to show that the methods of similarity and allometry are applicable over a wide range of non-ruminant mammalian species and radionuclides. The analysis presented here has lead us to speculate that there are prospects of much wider applicability than to the behavior of isotopes in biological systems alone.

- NOT FOR DEBIT
1. Brody, S.A., 1945. "Bioenergetics and Growth". New York: Reinhold.
 2. Eberhardt, L.L., 1967.
Health Physics 13: 88.
 3. Eberhardt, L.L., and R. E. Nakatani, 1968.
Jour. Fisheries Res. Board Canada. 25: 591-
 4. Eberhardt, L.L. 1969. Similarity, ^{LC}Allometry, and Food Chains. ^{LC LC}J. Theoret. Biol., 24: 43-55.
 5. Fujita, M., Iwamoto, J., and M. Kondo, 1966.
Health Physics, 12: 1237⁺
 6. Furchner, J.E. and C. R. Richmond, 1963. Comparative metabolism of radioisotopes in mammals. II Retention of iodine ¹³¹ by four mammalian species. Health Physics 9: 277-282. ry-
 7. Furchner, J.E., Richmond, C.R., and G. E. Drake, 1966. Comparative metabolism of radionuclides in mammals. III Retention of ⁵⁴Manganese - 54 in the mouse, rat, monkey, and dog. Health Physics 12: 1415-1423.
 8. Furchner, J.E., Richmond, C.R., and G. A. Drake, 1968. Comparative metabolism of ^{110m}radionuclides in mammals. IV. Retention of Silver - 110m in the mouse, rat, monkey, and dog. Health Physics, 15: 505-514.
 9. Hakonson, T.E., 1967. M.S. Thesis, Colorado State University, (Mimeo).
 10. Kleiber, M., 1961. "The Fire of Life". New York: Wiley.
 11. Richmond, C.R., Furchner, J.E., and W.H. Langham, 1961. Estimation of maximum permissible concentrations of radioisotopes in water (MPC)_w from interspecies correlations. II. Comparison of estimated and measured values for cesium - 137. ^{137M}Los Alamos Scientific Report, LAMS-2627, 175-182.

References continued

12. Richmond, C.R., Furchner, J.E. Trafton, G.A., and W.H. Langham, 1962. Comparative metabolism of radionuclides in mammals. I. Uptake and retention of orally administered $Zn-65$ by four mammalian species. *Health Physics*. 8: 481-489.
13. Stahl, W.R., 1962,
Science 137: 205
14. Stahl, W.R., 1965,
Science 150: 1039

ESTIMATES OF THE COEFFICIENTS IN $y = aW^b$
FOR THE DATA USED¹

<u>Isotope</u>	<u>a</u>	<u>b</u>	<u>Source</u>
Cesium-137	0.80	0.46	Richmond et.al. (1961)
Zinc-65	1.55	0.38	Richmond et.al. (1962)
Iodine-131	0.36	0.37	Furchner & Richmond (1963)
Potassium-40	0.45	0.45	Fujita et.al. (1966)
Manganese	0.22	0.23	Furchner et.al. (1966)
Silver-110m	0.10	0.28	Furchner et. al. (1968)

1. y = effective equilibrium level

AVERAGE BODY WEIGHTS (Kg) OF SPECIES STUDIED¹

<u>Isotope</u>	<u>Species</u>				
	<u>Dogs</u>	<u>Mice</u>	<u>Rats</u>	<u>Monkeys</u>	<u>Man</u>
Zn-65	10.9	.0162	.2775	-	67.9
Cs-137	6.2	.0550	.3850	5.7	70.0 ²
I-131	11.8	.0204	.3100	4.6	71.1
K-40	-	.0370	.3150	-	57.8
Ag-110m	13.3	.0265	.3550	6.8	-
Mn-54 m	6.85	.0245	.3370	16.5	-

1. Means represent averages of 1 - 3 groups of several (up to 12) animals.

2. Assumed value.

SOME CHARACTERISTICS OF THE ISOTOPES STUDIED

<u>Isotope</u>	<u>Physical Half Time</u>	<u>Relative Absorption of Oral Dose ¹</u>	<u>Biological Half-Time (Days²)</u>	<u>Effective H. (Days)</u>
Zn-65 _m	245 days	Moderate	110-478	75-154
Cs-137	30 years	High	4-147	4-147
I-131	8.1 days	High	11-80	4-7
K-40 & Stable	9+ years	High	33-55 ³	-
Ag-110m	249 days	Low	39-105	34-75
Mn-54 _m	310 days	Low	87-277	68-146

1. Species dependent.

2. Long component; range for all species.

3. As stated by Fujita et.al. (1966).

COMPARISONS OF TWO RATIO ESTIMATES OF b IN $Y = bx$

Comparison	N	Ratio Estimates		Standard Error of Estimates	
		1	2	1	2
Mouse vs Rat	6	.334	.363	.054	.052
vs Dog	5	.083	.099	.010	.009
vs Monkey	4	.080	.130	.037	.037
vs Man	4	.085	.089	.019	.014
Rat vs Mouse	6	3.09	2.58	.453	.499
vs Dog	5	.274	.270	.028	.033
vs Monkey	4	.235	.312	.071	.040
vs Man	4	.237	.214	.040	.055
Dog vs Mouse	5	12.1	10.1	1.58	1.06
vs Rat	5	3.83	3.70	.440	.490
vs Monkey	4	.943	1.47	.319	.243
vs Man	3	.760	.850	.158	.072
Monkey vs Mouse	4	23.452	7.71	9.75	3.69
vs Rat	4	6.222	3.20	2.36	.730
vs Dog	4	1.579	0.680	.546	.182
Man. vs Mouse	4	15.449	11.24	5.70	2.66
vs Rat	4	4.58	4.15	.777	.514
vs Dog	3	1.41	1.17	.331	.162

$$1 \quad b = \frac{\sum x}{\sum y} \times \frac{1}{n}$$

$$2 \quad b = \frac{\sum x}{\sum y}$$

of $y = a w$ using weight extremes for
several species.

Figure 2

Similarity Ratio for B. E. L. mic rat dogs

Figure 3

Similarity ratios for Biol eg. L. 3 species
to monkeys

Figure 4

Simil Ratio for 3 species comp to humans.

Fig 5

Simil Ratios for Biol Half time
Monkeys

Fig 6

Sim Ratios Biol eg. Level
comparative study of data

Fig 1

PLOTS OF $Y = \alpha W^{.75}$ USING WEIGHT EXTREMES FOR SEVERAL SPECIES

"SIMILARITY RATIOS" FOR BIOLOGICAL EQUILIBRIUM LEVEL MICE, RATS, AND DOGS

Fig 3

"SIMILARITY RATIOS" FOR BIOLOGICAL EQUILIBRIUM LEVEL 3 SPECIES COMPARED TO MONKEYS

"SIMILARITY RATIOS" FOR BIOLOGICAL EQUILIBRIUM LEVEL 3 SPECIES COMPARED TO HUMANS

FIG 5
 "SIMILARITY RATIOS" FOR BIOLOGICAL HALF TIME

Fig 6

"SIMILARITY RATIOS" FOR BIOLOGICAL EQUILIBRIUM LEVEL