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DETERMINATION OF PLUTONIUM BODY BURDENS FROM MEASUREMENTS OF DAILY URINE EXCRETION

by

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ABSTRACT

The original data from human experiments, as reported by Langham and others, have been re-analysed. The equations obtained from this analysis, which relate the body burden to the daily excretion in urine following an injection, are used in proposed mathematical models. In these models it is assumed that the release of plutonium into the body from the site of entry is continuous and decreasing with time. The results of calculations based on these models for both exponential and power function release of plutonium from the site of entry to the rest of the body are presented graphically.

Some results of measurements of plutonium in urine samples collected continuously from a small group of humans have been analysed. This analysis was carried out in order to investigate the type and magnitude of the biological variation in the amount of plutonium excreted in a urine sample.

Finally, programmes for the sampling of urinary excretion of plutonium are discussed in the light of the findings of this paper.

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5. Plot of the confidence factor against the number of amalgamated samples for three different confidence limits.

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1. Introduction

In the atomic energy industry a considerable amount of effort is expended in obtaining samples of urine and analysing them for plutonium. Interpretation of these measurements of plutonium in terms of body content is very difficult. Langham[1] used data obtained from human experiments to derive a simple power law equation to relate urinary excretion rate to body content. Many reports have been published in the literature (Langham[1] Healy[2] Sanders[3] Lawrence[4] Snyder[5] and Lister[6]) in which the equations derived by Langham were used to estimate body content in particular cases of plutonium contamination.

In the present paper mathematical models have been developed to represent the metabolism of plutonium and these are based on a re-assessment of the original human data from Langham[1]. The models take into account the fact that plutonium may be released continuously to the rest of the body from the site of entry which may be, for example, the lungs or a wound. This idea of slow continuous release to the body was first suggested by Healy[2] and in the present paper the original ideas have been developed and extended.

Hammond[7] noted that very large variations occurred in the daily urinary excretion of plutonium and new data are given on this biological variation in the present paper. These new data have been analysed by sampling and statistical techniques to determine the size and nature of the biological variation. This information has been used to determine the effect of combining two or more sequential samples in order to lower the biological uncertainty and increase the precision of the estimated value of the average excretion rate.

2. Excretion of plutonium in urine after intravenous injection

Many series of animal experiments, Schubert et al[8] Beliayev[9] Stover et al[10] and Lindenbaum et al[11], have been carried out in which plutonium citrate complexes were administered by injection. After a few days most of the injected plutonium was found to be located in the liver and bone. Immediately following the injection of plutonium citrate in these animal experiments the rate of excretion of plutonium in the urine was found to be high but it fell off rapidly during the first few days. This suggests that the initial excretion was probably plutonium in a citrate complex, similar to the injected material. After the first few days most of the plutonium citrate had been deposited in the bone, liver and other body organs or had become bound to protein in the blood and other body fluids and the rate of plutonium excretion in urine is reduced to a low level. The data for the rate of plutonium excretion in urine by humans following an injection of plutonium citrate, as described by Langham[1],

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have been re-analysed with the object of distinguishing between the initial rapid excretion rate of plutonium citrate and the much lower excretion rate of metabolised plutonium. From this analysis an equation was obtained which had two components as follows

$$Y_u(t) = 0.410 \exp(-0.67t) + 0.16t^{-0.68} \quad .. \quad .. \quad .. \text{(i)}$$

where $Y_u(t)$ is the percentage of the initially injected amount excreted per day on day t. This equation is plotted in Fig.1 on a log-log graph. The first component of this equation has a half-life of one day and accounts for the rapid excretion of about 0.6% of the injected amount and is probably unmetabolised plutonium citrate. The second component is a power function with an index slightly smaller than that given by Langham[1] i.e. 0.74 and this component is thought to represent metabolised plutonium excretion.

Data on the concentration of plutonium in blood following a plutonium citrate injection (Langham[12]) have been analysed and the following equation gave a reasonable fit to the data

$$B(t) = 4.3 \exp(-0.33t) + 0.105 \exp(-0.009t) \quad .. \quad .. \quad .. \text{(ii)}$$

where B(t) is the concentration of plutonium expressed as a percentage of the injected amount per litre of blood on day t after injection. The half lives of the two exponential components are two days and 80 days. The short half life component may be compared with the short half-life of the first component of the urinary excretion, in equation (i). This shows that the plutonium excretable through the kidney is initially decreasing with a half-life of one day whereas the amount of plutonium in the blood is decreasing with a two day half-life. This suggests that plutonium in blood is quickly becoming non-excretable through the kidney which agrees with experience from animal experiments where it is known that the injected plutonium citrate complex is rapidly converted into protein bound plutonium which cannot pass through the kidney.

3. <u>Excretion after delayed release of plutonium to the blood</u>

Systemic contamination with plutonium may occur by retention in the lung following inhalation (Healy[2]), by direct absorption at the site of a wound (Hammond[7]), burn (Lister[6]) or other skin trauma (Wilson and Silker[13]). The rate of movement of plutonium from the site of entry depends on both the physico-chemical form of the plutonium and the physiological conditions at the site. For example, delayed movement from a wound site is indicated in data reported by Hammond[7] in which the excision of a sliver containing plutonium from the wound site some months

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after a puncture wound was accompanied by a significant drop in the urinary plutonium excretion. Healy[2] also reported data which indicated a delayed transfer of plutonium to the body from the lung. A full description of the mechanism of delayed transfer is not needed for the purposes of this paper; it is sufficient to assume that the radionuclide enters the blood according to some putative monotonic decreasing function of time I(t). If an amount q is initially retained at the site of entry then the amount released to the blood at a subsequent time t is q I(t). The daily excretion of plutonium Eu(t) is then

$$Eu(t) = q \int_0^t I(\tau) \; Yu \; (t - \tau) \; d\tau \qquad .. \; .. \; .. \; (iii)$$

where $Y_u(t)$ is the power function component of equation (i).

Various particular functions may be substituted for the completely general monotonic decreasing function I(t). The two elementary functions that have been considered in this paper are: a simple negative exponential function and a power function of negative index. The exponential function represents the simplest type of release mechanism in which the rate of release is a constant fraction of the quantity present. This function may be thought to represent an over-simplification of the actual release mechanisms and so the power function was also used. The power function may be considered to represent approximately a set of exponential functions of both decreasing fraction and decreasing release rate. However, it should be emphasised that the two functions were chosen for mathematical convenience rather than with any special knowledge of the biological mechanisms of release.

The function given above, equation (iii), was solved, for the simple single exponential function with half lives of the transfer mechanism of 1, 10, 25, 50, 80, 120, 365, 500 and 1000 days. The results obtained are shown graphed on a log-log scale in Fig. 2. For comparison, the power function component of equation (i) is shown drawn with a broken line in this figure. The values of the function (iii) were also obtained when the transfer from the site of entry was assumed to be a power function. The chosen representative values of the index were

-2.000, -1.231, -1.177, -1.151, -1.137, -1.126, -1.105, -1.100 and -1.091,

the choice being based somewhat arbitrarily on the criterion that half the retained amount would be transferred to the blood in times similar to those chosen for the exponential function. In order to illustrate the power function release in more detail Table I has been compiled.

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Table I

Time taken to transfer various amounts of the initially retained plutonium from the site of entry to the blood for several values of the index of the power function

Index b	Time taken to transfer		Percent transferred after 50 years %
	half (days)	three quarters (days)	
2.000	1	2	100
1.231	10	202	91
1.177	25	1,260	84
1.151	50	5,000	80
1.137	80	12,400	76
1.126	120	30,000	73
1.105	365	271,000	67
1.100	500	524,300	65
1.091	1000	2,065,000	62

This table shows that although the half period for release has been chosen to be the same for both exponential and power functions the release rate becomes much slower for the power function at times longer than the half period. This is illustrated by the values in column 3 which give the time required to release to the blood three-quarters of the initial intake. The last column shows the amount release during 50 years. For example, the power function of index -1.177 is chosen to give a release to the blood of half the initial intake in 25 days but the time taken to release three-quarters of the initial intake is 1260 days and even after 50 years 16% of the original intake is still present at or near the site of entry. Hence, a practical consequence of the use of the power function to represent a release to the blood is that some of the intake is permanently retained at or near the site of entry into the body.

Fig. 3 shows the curves obtained by integration of equation (iii) with the general release function represented by a power function with the indices as given in Table I. In these calculations the total amount retained at the site of entry, all of which will be theoretically allowed to eventually enter the blood, is 0.04 μc. This is the ICRP [14] maximum permissible body burden of plutonium referred to bone as the critical organ.

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The following general points may be made about the two families of curves given in Figs. 2 and 3

(a) The predicted initial excretion rate for all the curves in Fig. 2 is less than would be expected on the basis of the excretion equation given by Langham[1].

(b) All the curves in Fig. 2 predict that the urine excretion rate will reach a maximum value at some time after intake which depends on the assumed half-life of the exponential release. The longer the half life the greater the time after intake that the peak is reached.

(c) All the curves in Fig. 2 converge on the power function component of equation (i) at long times after intake.

(d) The curves in Fig. 3 predict a lower initial excretion rate than the power function component of equation (i) but in contrast to the curves in Fig. 2 they reach a peak within one or two days of the intake.

(e) The curves in Fig. 2 are all significantly non-linear on the log-log plot throughout the period of 10,000 days whilst the curves in Fig. 3 rapidly become linear in appearance. From about 10 days after the initial intake the apparent indices of the excretion curves in Fig. 3 range from about 0.59 to 0.65.

The curves in Figs. 2 and 3 have no real foundation because the mechanisms of transfer from the site of entry are not understood. However, it is certain that delayed release does occur in some cases as shown by the data of Healy[2] and Hammond[7] previously referred to. If a monotonically decreasing release function is applicable and this might be considered the most readily acceptable of all the assumptions made in these calculations then some general conclusions can be inferred from the shape of the curves. The most important general conclusion is that the initial rate of excretion of plutonium in urine is expected to be more dependent on the rate of release from the site of entry than on the amount of plutonium at the site. Hence measurements of plutonium in urine made shortly after intake are probably less reliable in terms of estimating the body content than measurements made at long intervals after intake. Unfortunately the original data from the human experiments for excretion of plutonium following a plutonium citrate injection is least reliable at periods beyond one year.

4. Sources of uncertainty in the measurement of the urinary excretion rate of plutonium

One of the principle objections to the interpretation of a single measurement of urinary excretion of plutonium is the existence of a

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typically large uncertainty. There are four important sources of uncertainty in any measurement which are as follows

(a) the biological variation in the daily amount of plutonium excreted

(b) the determination of a 24-hour sample of urine

(c) the quantitative chemical analysis of urine for small amounts of metabolised plutonium

(d) the background contamination level.

By far the largest of these uncertainties is the biological variation and, for the purposes of this paper, the others may be neglected by comparison. The reasons for this biological variation which are quite frequently of the order of a factor of 10 or more are not known. However, Hammond[7] suggested that they might be due to temporary kidney damage because he found a large variation of the order of 200 in the excretion rate in an individual six weeks after intake was accompanied by albumin in the urine. To obtain some information about the type and size of this biological variation a study was made of the urinary excretion rate in a few workers who had been involved in the processing of plutonium at some previous time. An almost continuous urine collection for the normal working week was instituted for these men. Those workers whose urine record showed no statistically significant curvilinear trend in urine excretion during the period of the investigation were selected for inclusion in this study.

Frequency histograms of the data were formed for each of the selected individuals. Typically all these were found to be positively skew and of the log normal type. The raw data were then subjected to a logarithmic transformation, normalised to a transformed mean excretion rate of 1pc per day and then amalgamated into a single histogram. Other such histograms were developed by adding the raw data sequentially in pairs, trios and tetrads for each individual. Hence four histograms were obtained, the first is shown in Fig. 4. A log normal curve was fitted to the raw data shown in Fig. 4 and this shows that the histogram departs slightly from the curve. This slight departure was due to the presence of more extremely large values than would be expected in this type of distribution. It was felt that this excess of large values indicates the presence of significant contamination in a very small percentage of urine samples. Following a discussion of Cramer's[17], it is possible to suppose the size of a daily excretion of plutonium to be the net result of a number of small independent influences acting in an ordered sequence upon an initial amount. If the influence of any one factor is proportional to the instantaneous amount of the plutonium the distribution of the eventually excreted amount will be log normal. However, an exact biological interpretation of this distribution

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is not possible at present and is not necessary for the purposes of this paper. There was some evidence, not statistically significant in the sample under investigation in the current work, which suggests that the individual raw data could be regarded as a stationary Markov process with an error-component. However, if this auto-correlation is ignored the exact frequency distribution formed by sequentially adding urine samples can be theoretically calculated. Unfortunately, in practice, the definite integrals formed proved intractable to the current writers. Nevertheless, the central limit theorem suggests that continued amalgamation of this sort would result in frequency distributions that were increasingly nearer to the Gaussian form. The four frequency distributions found were plotted cumulatively on log-probability graph paper and the extent of the confidence limits determined for the levels of probabilities of 90%, 95% and 99%. These confidence limits can be expressed as a factor by which the median value must be multiplied to get the upper confidence limit and divided to get the lower confidence limit. In Fig. 5 this factor was plotted against the number of raw data added sequentially for the three different confidence limits. The shape of these curves may serve as a guide to the advantages of amalgamating sequential urinary excretion data in order to minimise the biological error associated with a single urine sample. It can be seen that for the reasonable assurance of 95% confidence there is a decrease of just over one of this factor if two consecutive samples are collected whilst for the far more restricted case of 99% confidence there is still a great advantage in the collection of three or more consecutive samples before analysing a conveniently sized aliquot for plutonium content. Furthermore, the curves in Fig. 5 suggest that 10 or more sequential samples might have to be added together before the 90% confidence factor approaches the value 2.

5. Programmes for sampling the daily excretion of plutonium in urine

Following the discussions and results obtained in the previous sections of this paper some consideration is now given to sampling programmes for determining the urinary excretion rate of plutonium. There are clearly two situations, each of which requires a sampling programme. The first is that following a known accidental intake and the second is that where workers are routinely engaged in laboratories and factories processing plutonium. These situations will be considered separately.

(a) Sampling following a known accidental intake

The curves shown in Figs. 2 and 3 indicate that the rate of urinary excretion of plutonium varies rapidly during the first few weeks after intake. The manner in which the urinary excretion varies will depend on the mode of entry of the plutonium into the

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body and the mechanisms by which it is released into the rest of the body. In order to establish this initial rapidly varying excretion pattern the most comprehensive sampling programme should be instituted immediately the accidental intake is recognised. It should be noted, however, that whilst the data on the urinary excretion of plutonium obtained during this initial period will not necessarily be of great value in ultimately assessing the body content it might give valuable information about the rate of transfer of the plutonium from the site of entry to the rest of the body. The body content may be more reliably estimated from excretion measurements made at longer times after intake. However, it has been emphasised in section 4 that a large biological uncertainty is associated with each single measurement of plutonium excreted in 24 hours and therefore to lessen the effect of this uncertainty some sequential collection of urine over several days is essential.

(b) Sampling of workers routinely engaged in plutonium processing

Normally measurements of plutonium in the air and on the surfaces in the working areas of laboratories and factories processing plutonium should give early warning of any release of plutonium into the environment. Hence, sampling of the urine of workers engaged in routine processing is carried out to ensure that no intakes of plutonium have occurred which were undetected by the environmental sampling. In fact, if plutonium is unexpectedly found in the urine of the workers it is an indication that the environmental monitoring devices have not been adequate. The object of a sampling programme is, therefore, to ascertain whether the urinary excretion rate of plutonium by a worker is above or below a certain level known here as the warning level. Further discussion of the value chosen as the warning level is not essential in this paper and, indeed, is outside its scope. It is only necessary to state that if the urinary excretion rate is above this level some action must be taken by the management. It is clear from the discussion in section 4 that the degree of biological variation is such that a single measurement could, by chance, be spuriously above the warning level whilst the actual median excretion at that time was below the warning level. This could lead to the unnecessary instigation of special procedures such as taking the worker away from contact with plutonium and carrying out a programme of intensive sampling for plutonium in his urine. Such procedures carried out unnecessarily could be both uneconomic for management and unsatisfactory for the worker. In order to decrease the possibility of a single measurement being spuriously above the warning level every effort should be made to obtain the best estimate of the plutonium excretion rate. This can be done by collecting sequential samples of urine over

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a week or even longer periods. Thus a sampling programme based on the collection of a single 24 hour urinary excretion at, say, monthly intervals might be less satisfactory for both management and men than a programme based on less frequent collection of a much larger quantity of urine.

6. Conclusions

The mathematical models developed in sections 2 and 3 of this paper culminating in the theoretically idealised functions for the urinary excretion rate of plutonium, as shown in Figs. 2 and 3, have been following limitations,

(a) the models are based, as indeed all similar work must be based, upon the biological data from the small series of human experiments reported by Langham[1], and

(b) the aptness of the models is limited by the assumption that the movement of the plutonium from the site of entry to the rest of the body can be represented by a monotonic decreasing function of time.

The first limitation will not be overcome until more human data become available from planned experiments or from relating measurements of plutonium content in body organs obtained at autopsy with plutonium in urine measurements made during life. The second limitation will gradually be overcome as a greater understanding is gained of the mechanisms of plutonium transport from the site of entry to the rest of the body. In the meantime, the two monotonically decreasing functions of time chosen to represent release from the site of entry to the rest of the body may serve to indicate how the expected urinary excretion rate may differ from that obtained in the human experiments where a solution of plutonium in a citrate complex was injected.

In section 4, the biological variation in the daily plutonium excretion was analysed and its influence on the planning of a programme of urine sampling was discussed in section 5. No attempt has been made to explain this biological variation but obviously more work is required on the mechanisms of plutonium excretion which might throw some light on this problem.

Acknowledgements

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References

1. LANGHAM, W.H. Brit. J. Radiol. Suppl. No.7 (1957) 95-113.

2. HEALY, J.W. Amer. Ind. Hyg. Atly. 18 (1957) 261-266.

3. SANDERS, S.M. Arch. Env. Hlth. 2 (1961) 474-483.

4. LAWRENCE, J.N.P. Health Phys. 8 (1962) 61-66.

5. SNYDER, W.S. Health Phys. 8 (1962) 767-772.

6. LISTER, B.A.J., MORGAN, A., and SHERWOOD, R.J. AERE R 4064 (1962).

7. HAMMOND, S.E. AEC R & D Report WASH 1023 (1959) 84-100.

8. SCHUBERT, J., FRIED, J.F., ROSENTHAL, M.W., and LINDENBAUM, A. Rad. Res. 15 (1961) 220-226.

9. BELIAYEV, Yu A. Med. Radiol. 4 (1959) 45-51.

10. STOVER, B.J., ATHERTON, D.R., and KELLER, N. Rad. Res. 10 (1959) 130-147.

11. LINDENBAUM, A., MARKLEY, J.F., and ROSENTHAL, M.W. Health Phys. 8 (1962) 695-697.

12. LANGHAM, W.H. Health Phys. 2 (1959) 172-185.

13. WILSON, R.H., and SILKER, W.B. HW 66309 (1960).

14. ICRP Publication 2 Report of Committee II on Permissible Dose for Internal Radiation (1959).

15. CRAMER, H. Mathematical Methods of Statistics. Princeton University Press, Princeton (1946).

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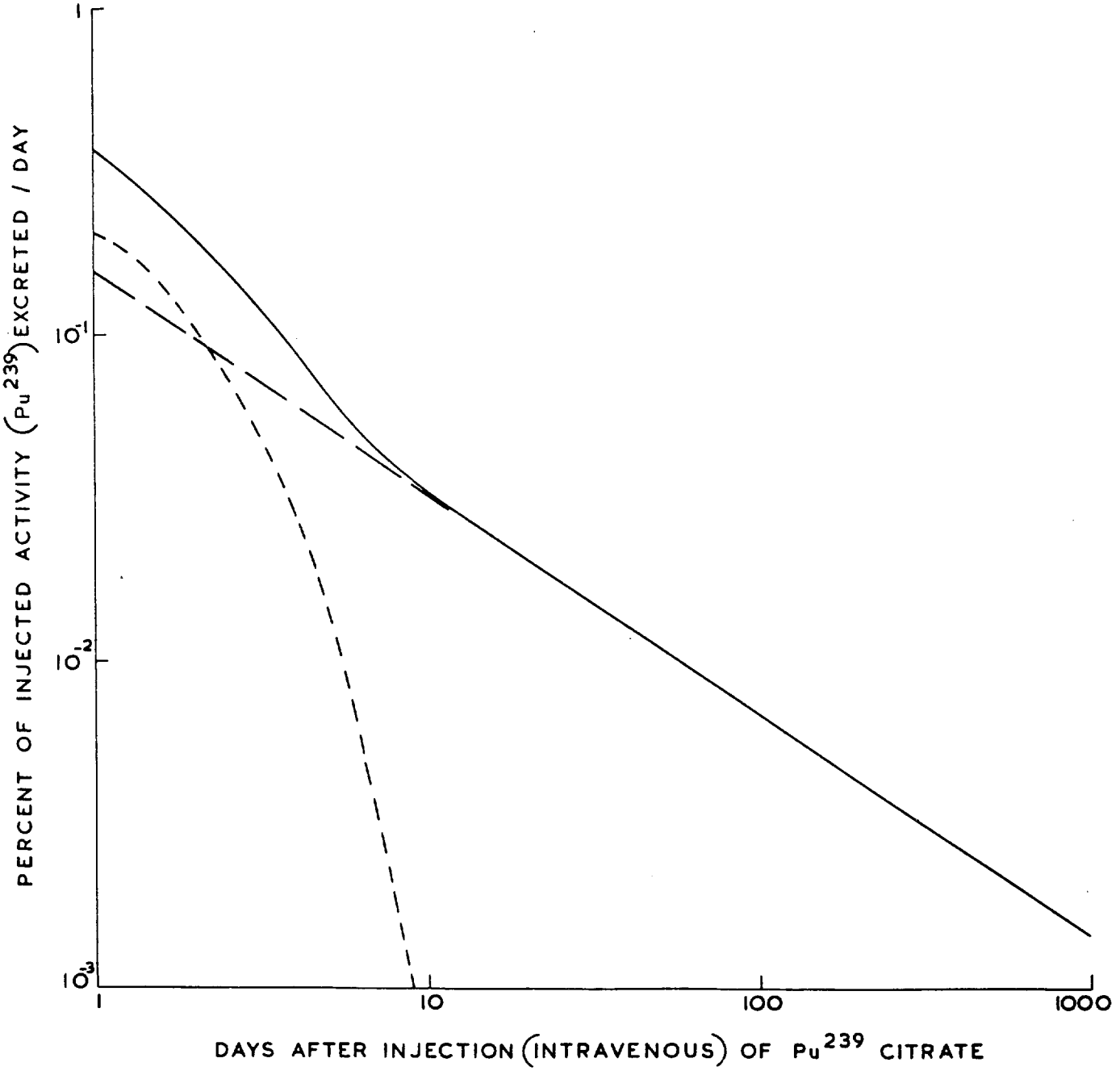

SM/52-12 Fig. 1

Log-log plot of $Y_u(t) = 0.41 \exp(-0.67t) + 0.16t^{-0.68}$ where $Y_u(t)$ is the percentage of the initially injected amount excreted per day, on day t. This equation was found to give the best fit to the human data, Langham[1]. The two components of the equation are illustrated by broken lines.

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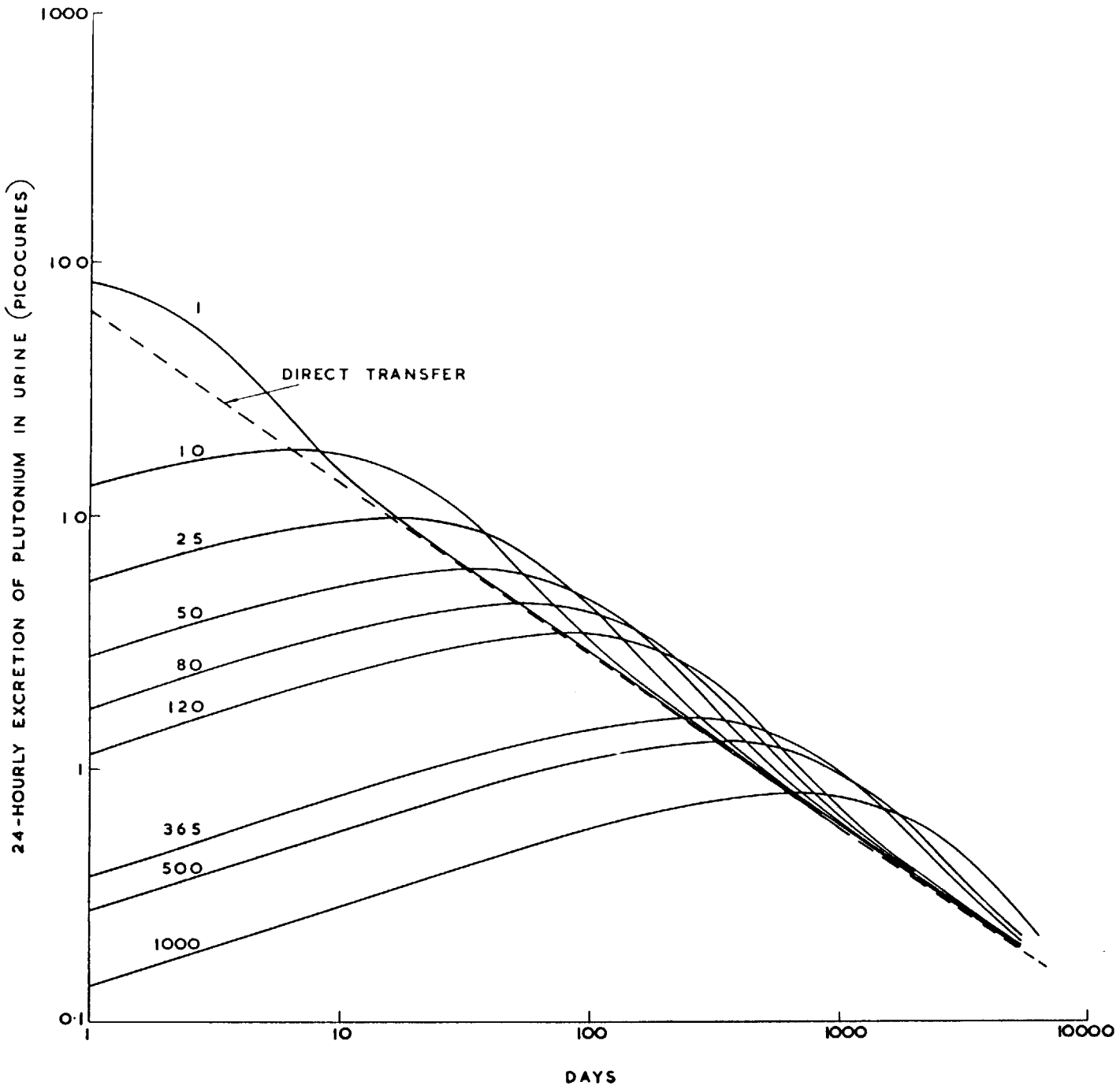

SM/52-12 Fig. 2

Log-log plot of the predicted daily urinary excretion rate of plutonium assuming an exponential release of plutonium to the rest of the body from the site of entry. Curves are given for half-lives of the exponential release function ranging from 1 to 1000 days.

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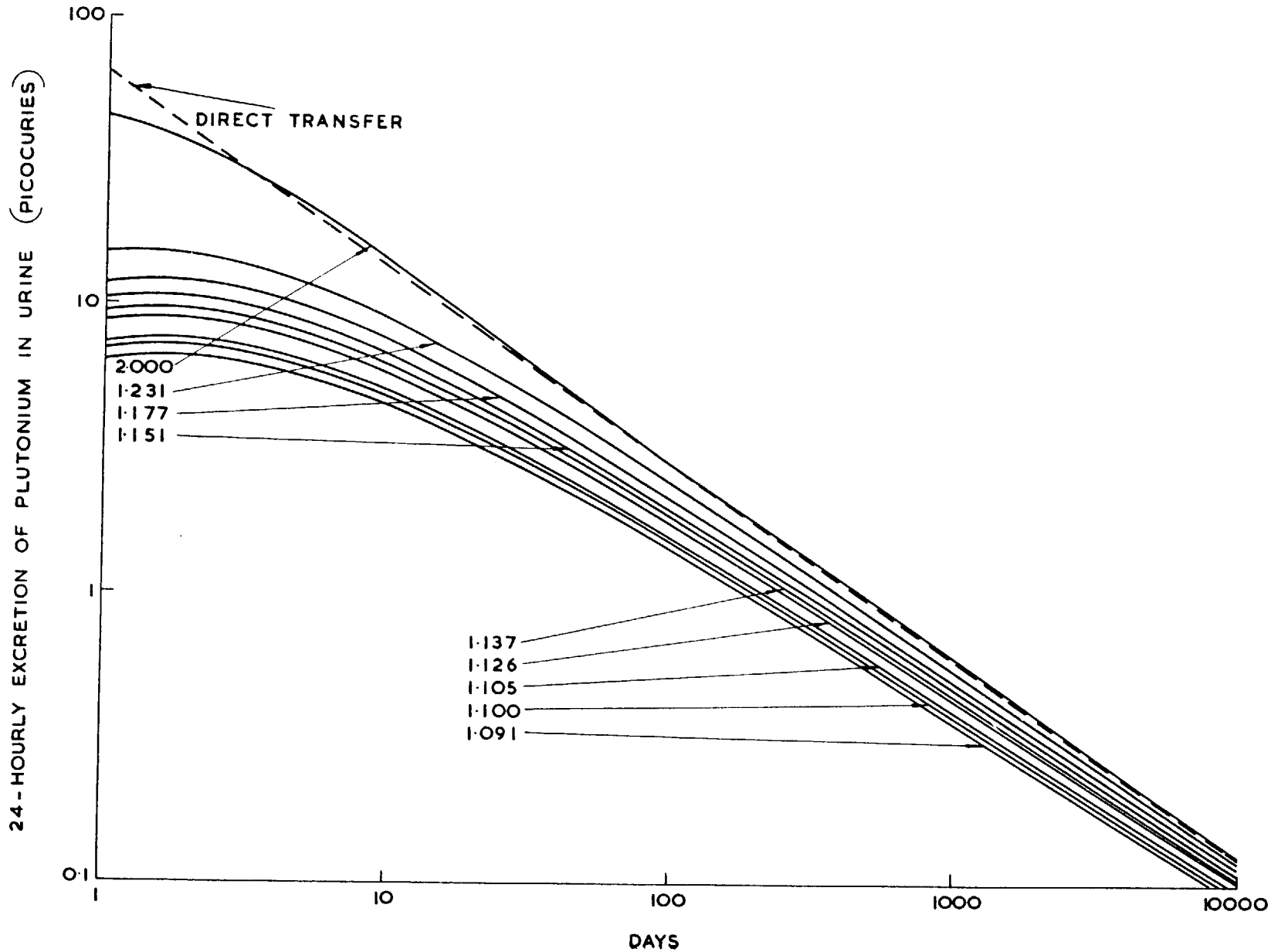

SM/52-12 Fig. 3

Log-log plot of the predicted daily urinary excretion rates of plutonium assuming a power law release of plutonium to the rest of the body from the site of entry. Curves are given for values of the index of the power law release function as shown in Table I.

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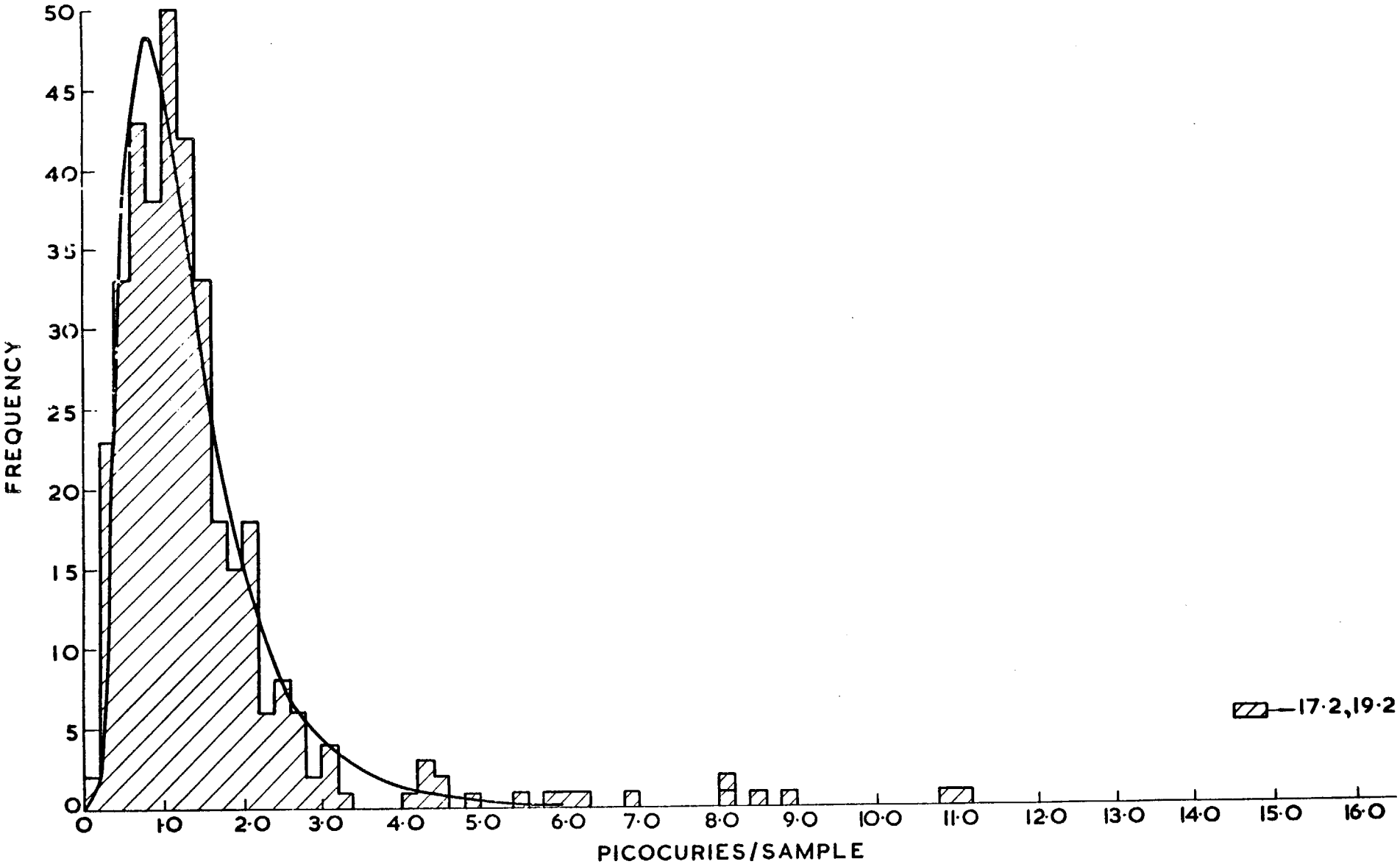

SM/52-12 Fig. 4

Histogram of 357 measurements of plutonium in urine samples normalised for each individual to 1pc per sample and amalgamated. The full line represents a log-normal curve found to give the best fit to the data.

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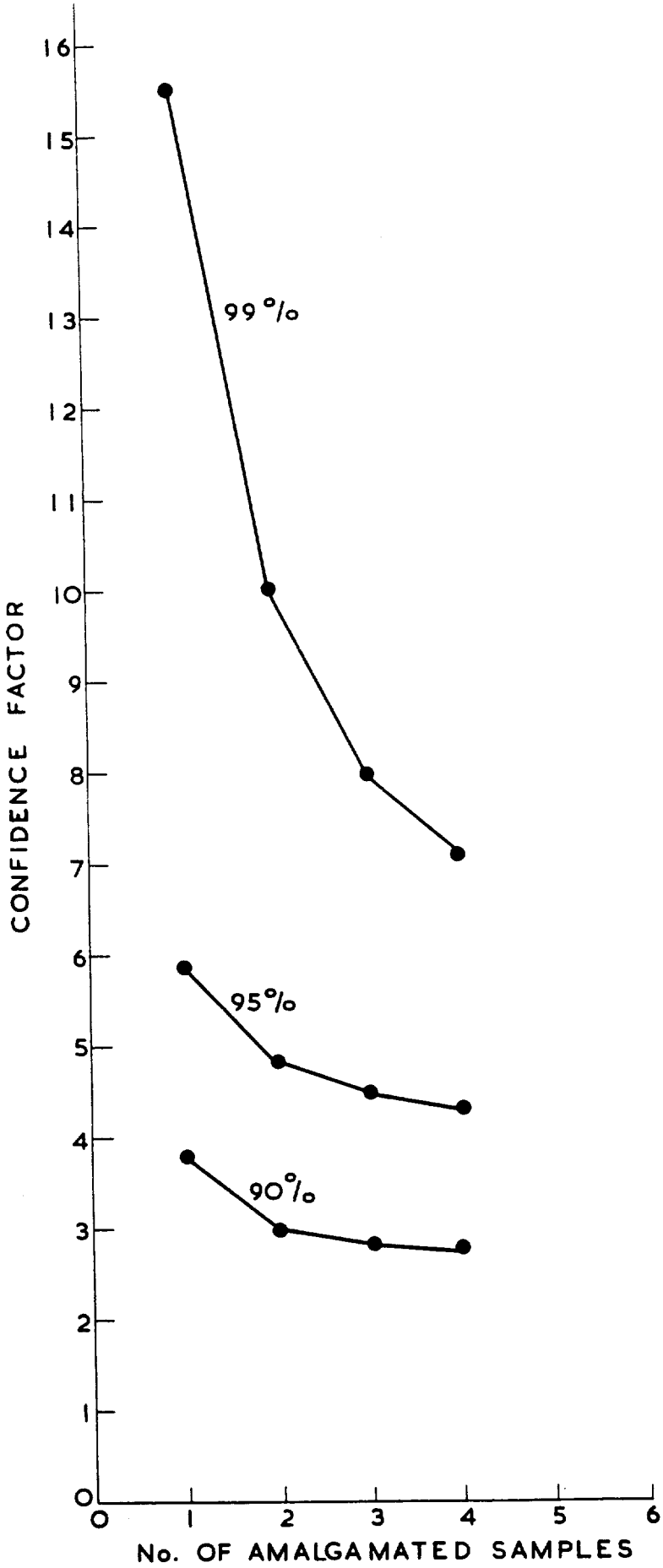

SM/52-12 Fig. 5

Plot of the confidence factor against the number of amalgamated samples for three different confidence limits. For example, in twenty single urine samples the curve for 95% confidence indicates that on the average a measurement of plutonium in one sample would be a factor of six different from the median measured value of plutonium in a large number of samples.

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