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THE ESTIMATION OF A BODY BURDEN OF PU FROM URINALYSIS DATA

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W. H. Langham has studied the excretion of Pu^{239} by adult humans over a period of 140 days following intravenous injection. By study of cases of occupational exposure, he has extended the period of study to as much as 5 to 6 years and shown that the excretion data may be fitted approximately by power functions. Specifically, he has given the functions

$$Y_u(t) = 0.0023\ t^{-0.77} \tag{1}$$

$$Y_f(t) = 0.0063\ t^{-1.09} \tag{2}$$

$$Y_{u+f}(t) = 0.0079\ t^{-0.94} \tag{3}$$

to approximate the urinary excretion, the fecal excretion, and the total excretion on the tth day following an intravenous injection of unit amount into the blood.[1,2,3] Using these formulae and his extensive experience with exposure to Pu, Langham has developed methods of predicting the body burden** of an individual on the basis of the urinary excretion data.

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*Operated by Union Carbide Corporation for the U. S. Atomic Energy Commission.

**More specifically, the bone burden since the method probably underestimates the lung burden.

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J. N. P. Lawrence has developed a computer code for the IBM 704 which embodies the principal features of Langham's method and gives results in general agreement with Langham's personal estimates. This paper develops an alternative method of treating the data and gives a preliminary discussion of the accuracy of the two methods. The influence of spurious data points or of insufficient data is indicated also.

Equations (1), (2), and (3) above presuppose a single injection. In order to treat the more general case of continuous exposure, it is necessary to consider the continuous case as the integral of the discrete case. This has been justified for a few elements in several studies. While no such study involving Pu is known, this procedure is that generally used in estimating body burdens and seems a necessary one in the present state of our knowledge. With this assumption, the urinary excretion on the $t^{\underline{th}}$ day of an exposure period beginning at time t = 0 is given by

$$U(t) = \int_0^t d\tau \, I(\tau) \, a(t-\tau)^{-\alpha} \qquad (4)$$

where $I(\tau)$ is the intake to blood on the $\tau^{\underline{th}}$ day, a = 0.0023, and $\alpha = 0.77$ in accordance with (1). The units of I may conveniently be taken as d/m/day and for U as d/m/24-hr sample.

Fractional retention of Pu on the $t^{\underline{th}}$ day following a single intravenous injection has been given[4] by

$$r(t) = bt^{-\beta} \qquad (5)$$

with b = 0.99 and $\beta = 0.01$. Applying the same principle of integrating the single dose formula to obtain the continuous case, one obtains the

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body burden q(t), or retention, on the $t^{\underline{th}}$ day following the beginning of exposure:

$$q(t) = \int_0^t d\tau\, I(\tau)\, b(t-\tau)^{-\beta}. \qquad (6)$$

With the above choice of units for I, q will be given in d/m.

Alternatively one may express the retention following a single intravenous injection as the difference of the intake and the total excretion. Using (3) one obtains

$$r(t) = 1 - \frac{C}{1-\gamma}\, t^{1-\gamma} \qquad (5')$$

with C = 0.0079 and γ = 0.94. Then the body burden q(t) on the $t^{\underline{th}}$ day following the beginning of a period of continuous exposure is given by

$$q(t) = \int_0^t d\tau\, I(\tau) \left[1 - \frac{C}{1-\gamma}\, (t-\tau)^{1-\gamma} \right]. \qquad (6')$$

Equations (4) and (6), or alternatively equations (4) and (6'), involve the functions q and I, which must be assumed to be largely unknown in most cases of exposure, and the function U, which is known in part, i.e., U is known to the extent that urinalysis data are available. The mathematical problem consists in expressing the unknown functions q and I in terms of the known or partially known function U.

The mathematical solution for q and I can be obtained elegantly by the use of the Laplace transform. Using a bar over a function to designate the transform of the function, the application of the Laplace transform to equations (4), (6), and (6') yields[5]

$$\bar{U}(s) = \bar{I}(s)\, a\Gamma\, (1-\alpha)\, s^{\alpha-1} \qquad (4^*)$$

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$$\bar{q}(s) = \bar{I}(s)\, b\Gamma\,(1-\beta)\, s^{\beta-1} \tag{6*}$$

$$\bar{q}(s) = \bar{I}(s)\left[s^{-1} - \frac{b\Gamma\,(2-\beta)\, s^{\beta-2}}{(1-\beta)}\right] \tag{6'*}$$

where Γ denotes the gamma function. Solving for $\bar{q}$ and $\bar{I}$, one obtains

$$\bar{q}(s) = \bar{U}(s)\, b\Gamma\,(1-\beta)\, s^{\beta-\alpha}/a\Gamma\,(1-\alpha) \tag{7*}$$

$$\bar{q}(s) = \bar{U}(s)\left[s^{-\alpha} - \frac{b\Gamma\,(2-\beta)\, s^{\beta-\alpha-1}}{1-\beta}\right]/a\Gamma\,(1-\alpha) \tag{7'*}$$

$$\bar{I}(s) = \bar{U}(s)\, s^{1-\alpha}/a\Gamma\,(1-\alpha) \tag{8*}$$

Taking inverse transforms yields

$$q(t) = \frac{b\Gamma\,(1-\beta)}{a\Gamma\,(1-\alpha)\,\Gamma\,(\alpha-\beta)}\int_0^t d\tau\, U(\tau)\,(t-\tau)^{\alpha-\beta-1} \tag{7}$$

$$q(t) = \frac{1}{a\Gamma\,(1-\alpha)\,\Gamma(\alpha)}\int_0^t d\tau\, U(\tau)\,(t-\tau)^{\alpha-1} + \\ - \frac{b\Gamma\,(2-\beta)}{a(1-\beta)\,\Gamma(1-\alpha)\,\Gamma(\alpha-\beta+1)}\int_0^t d\tau\, U(\tau)\,(t-\tau)^{\alpha-\beta}\, d\tau \tag{7'}$$

$$\int_0^t d\tau\, I(\tau) = \frac{1}{a\Gamma\,(1-\alpha)\,\Gamma(\alpha)}\int_0^t d\tau\, U(\tau)\,(t-\tau)^{\alpha-1}\,. \tag{8}$$

It will be noted that the solution for I does not yield an explicit formula for I but rather for its integral. The function I can then be recovered by differentiation, but for most practical purposes the accumulated intake may be of equal interest.

Formulae (7), (7'), and (8) require that U be given as a continuous function of the time. In practice, the urinalysis data will be available only at certain discrete times when the individual submitted a sample.

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Thus the actual urinalysis data must be regarded as a sampling of the values of the function U, and in computing formulae (7), (7'), and (8) it is necessary to interpolate the values of U from the urinalysis data of the individual. There are many ways of doing this, and some methods may be more appropriate than others in certain cases. For example, if an individual is known to have a high exposure on a certain date, the data should not be "smoothed" or averaged to remove a sharp increase in urinary output. However, it might be useful to smooth the data over periods where sporadic intakes of large amounts are not considered likely. Clearly, any decision to alter or treat the data must be based on a close study of the exposure situation.

Codes for the IBM 7090 have been prepared which calculate the formulae (7), (7'), and (8). The input consists of the sample dates (day, month, year) and the sample values (d/m/24-hr sample), as well as identification of the case and the time when the body burden is to be estimated. The code converts the dates into days following the beginning of the exposure period, taking the first sample date as 0. Thus the data are converted into the form (t_i, C_i) $i = 1,2,\ldots,n$ where n is the number of sample values, t_i is the number of days following the beginning of the sample record when the sample value C_i was observed, and t is the day on which the body burden or total intake is required. The code uses linear interpolation to estimate U for values between successive sample dates. Thus

$$C = C_i + m_i (\tau - t_i)$$

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for

$$t_i \leq \tau \leq t_{i+1}$$

with

$$m_i = (C_{i+1}-C_i)/(t_{i+1}-t_i).$$

Equation (7) then becomes

$$q(t) = \frac{b\Gamma(1-\beta)}{a\Gamma(1-\alpha)\Gamma(\alpha-\beta)} \sum_{j=1}^{n-1} \frac{C_j t_{j+1} - C_{j+1} t_j + (C_{j+1}-C_j)\, t}{t_{j+1} - t_j}$$

$$\left[\frac{(t-t_j)^{\alpha-\beta} - (t-t_{j+1})^{\alpha-\beta}}{\alpha - \beta}\right] - \frac{b\Gamma(1-\beta)}{a\Gamma(1-\alpha)\Gamma(\alpha-\beta)} \times$$

$$\sum_{j=1}^{n-1} m_j \left[\frac{(t-t_j)^{\alpha-\beta+1} - (t-t_{j+1})^{\alpha-\beta+1}}{\alpha - \beta + 1}\right]$$

and analagous expressions for (7') and (8) may be written down directly by substitution for U./~~These are~~ These are the expressions which have been coded for the IBM 7090.

Unfortunately there is little in the way of precise data which can be used as a check on the accuracy of the method. Fig. 1 illustrates the effect of truncation on the data. Urinalysis data corresponding to a hypothetical case of a single intake at time t = 35 days were computed for 200 additional days. The accumulated intake was computed taking data points at intervals of 30 days, 20 days, 10 days, and 5 days. Ideally the accumulated intake should be zero before day 35 and one thereafter, and the various approximations illustrate the effect of truncation on the data.

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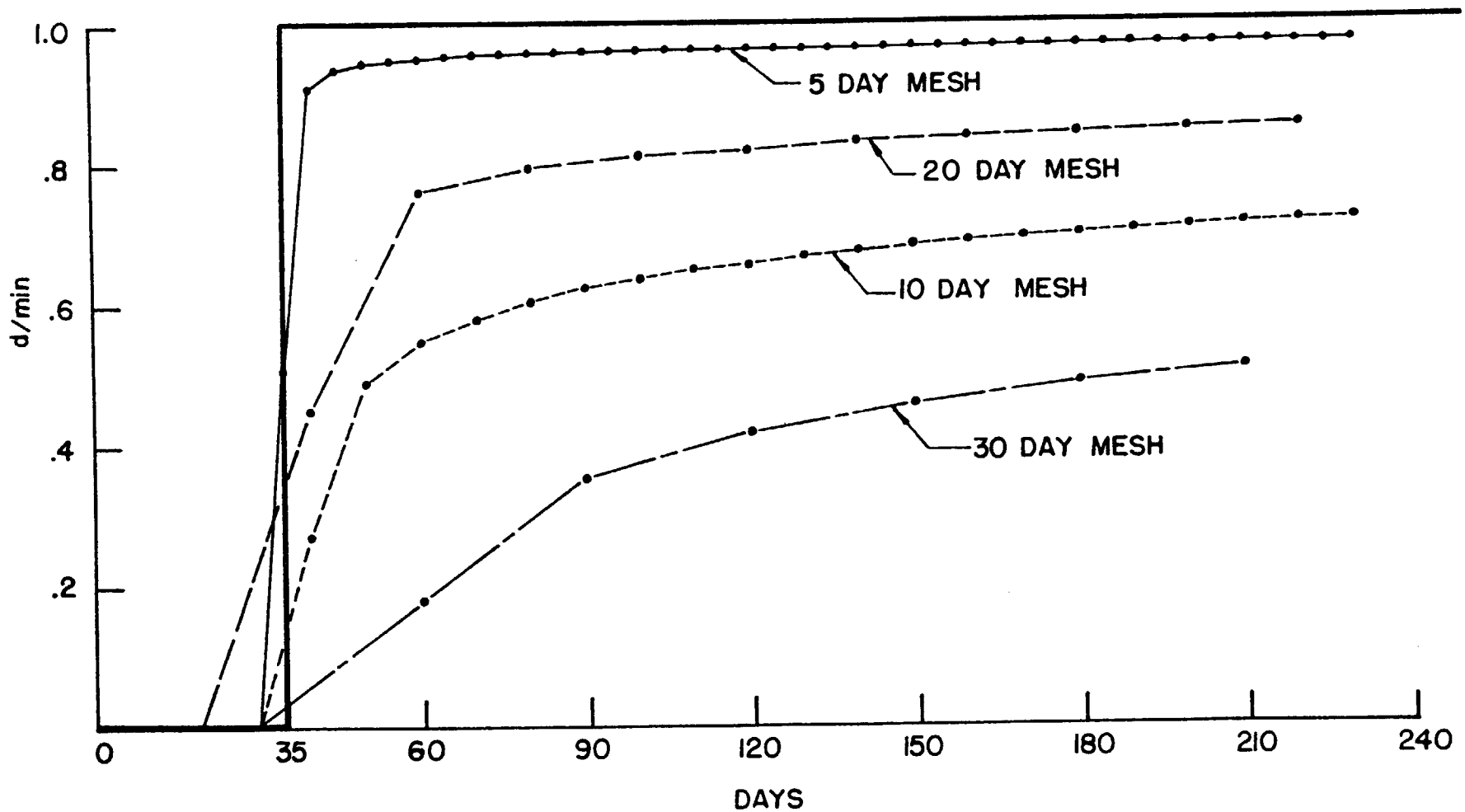

Fig. 1. EFFECT OF TRUNCATION ON ESTIMATED INTAKE

Fig. 2 illustrates the same effect, but the unit single intake has been placed at day 30 so as to coincide with one of the sample dates. Figs. 3 and 4 show the estimated body burdens at various times for these two cases as compared with the theoretical body burden predicted by 4. It will be noted that the position between sample dates of a single intake may have considerable effect on the result. The reason for this can be inferred from Figs. 5 and 6. The dotted lines show the data used by the computer. This differs considerably, in some cases, from the solid curves which represent the hypothetical case from which the sample values were selected. This effect and a remedial programming technique are under study also. Finally, it should be borne in mind that this is only a check on the mathematical treatment of the problem and does not test the validity of the biological assumptions.

Table I contains estimates of body burden for 26 individuals* by Langham, by the PUQFUA code, and by PUQUAP and PUQUAE. Since PUQFUA postulates a single intake 15 days prior to the first sample date, the PUQUAP and PUQUAE estimates are shown with and without this assumption. When this assumption is made, the first actual data point has been extrapolated back by formula (1) to obtain a data point for this first day. As will be noted, there is broad agreement of the estimates. The last entry E822 is the case reported by Langham,[6] and in this case the additional estimate is from the autopsy data.

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*Langham selected these cases as being some for which the body burden is considered to be best known.

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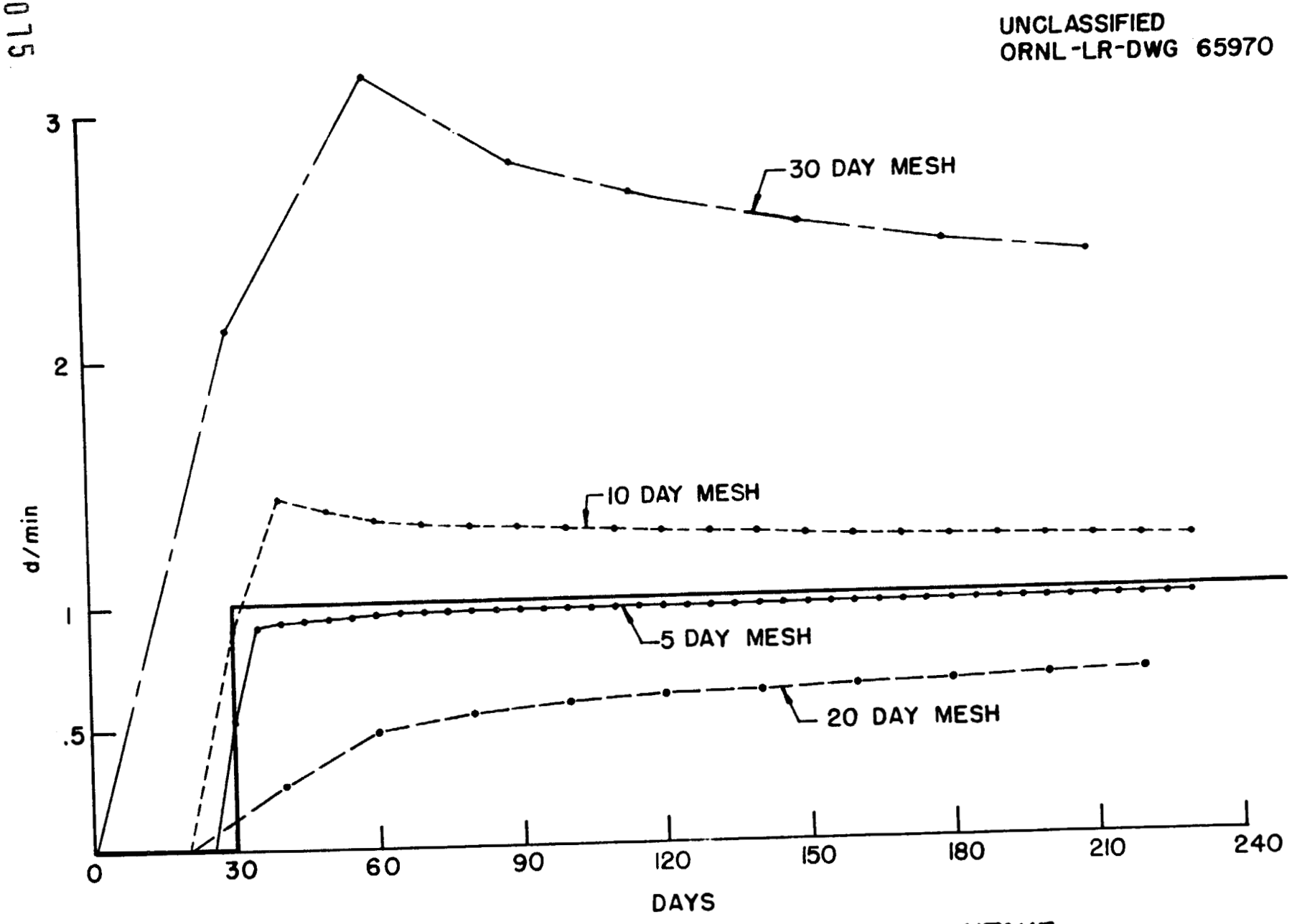

Fig. 2. EFFECT OF TRUNCATION ON ESTIMATED INTAKE

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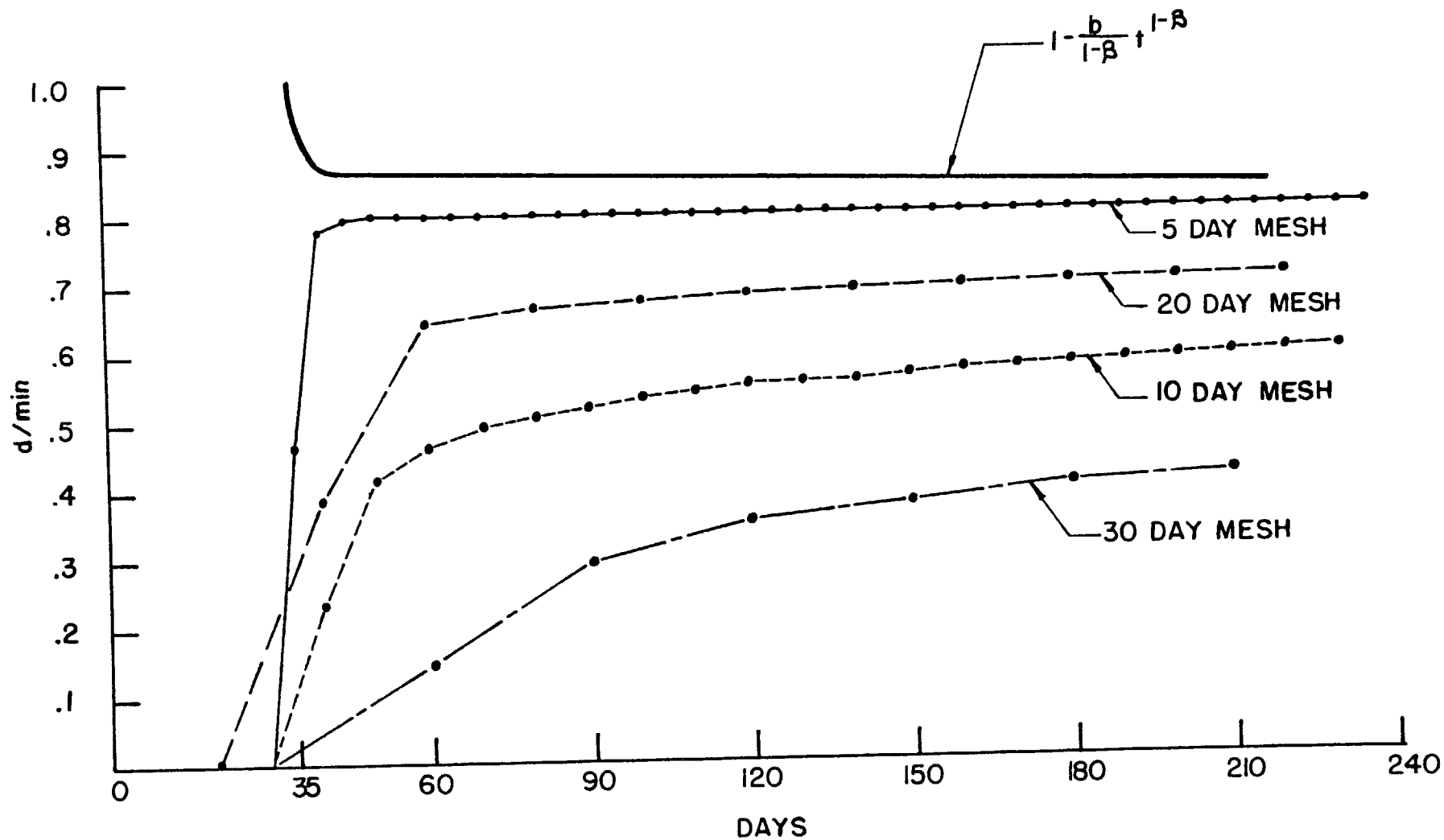

Fig. 3. EFFECT OF TRUNCATION ON ESTIMATED BODY BURDEN

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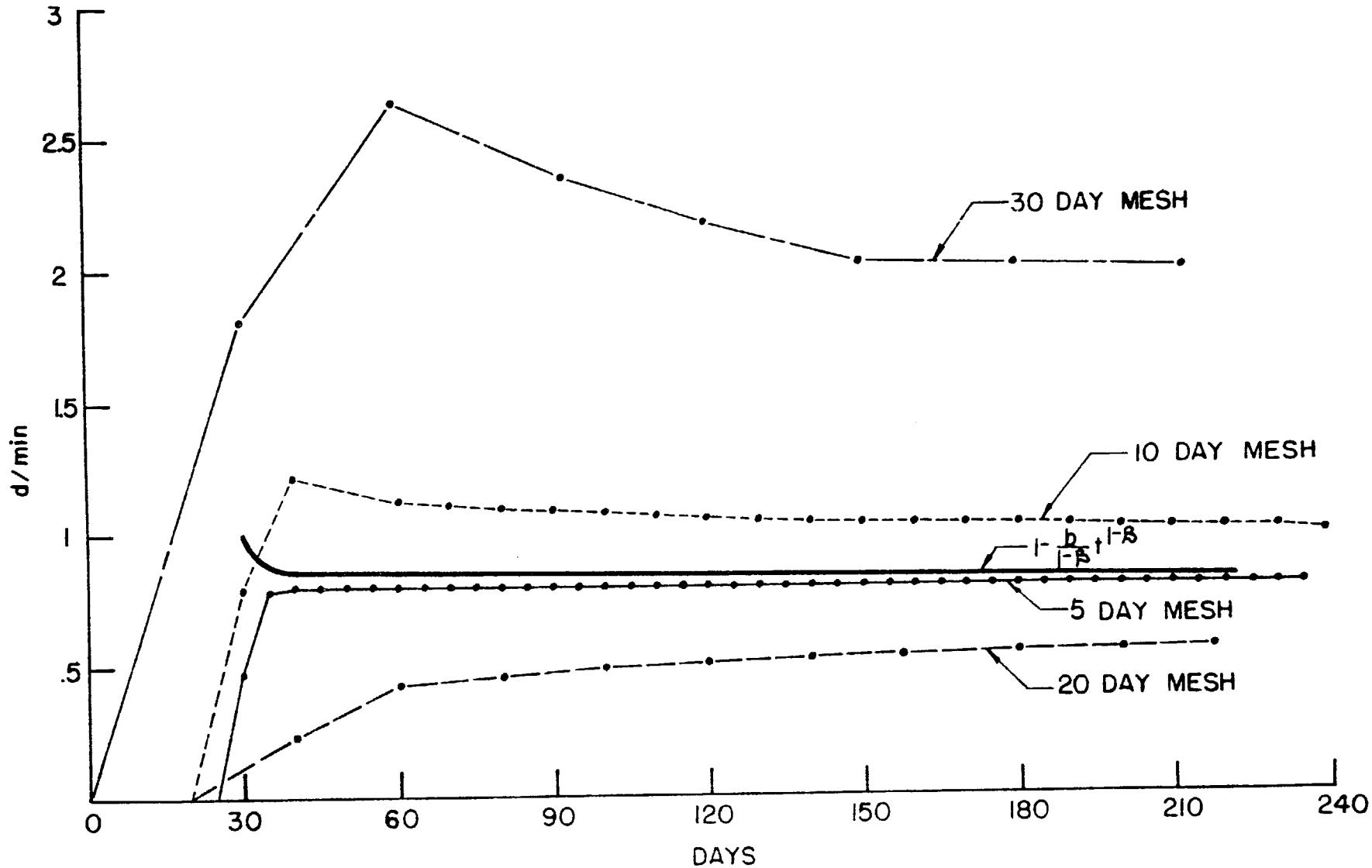

Fig. 4. EFFECT OF TRUNCATION ON ESTIMATED BODY BURDEN

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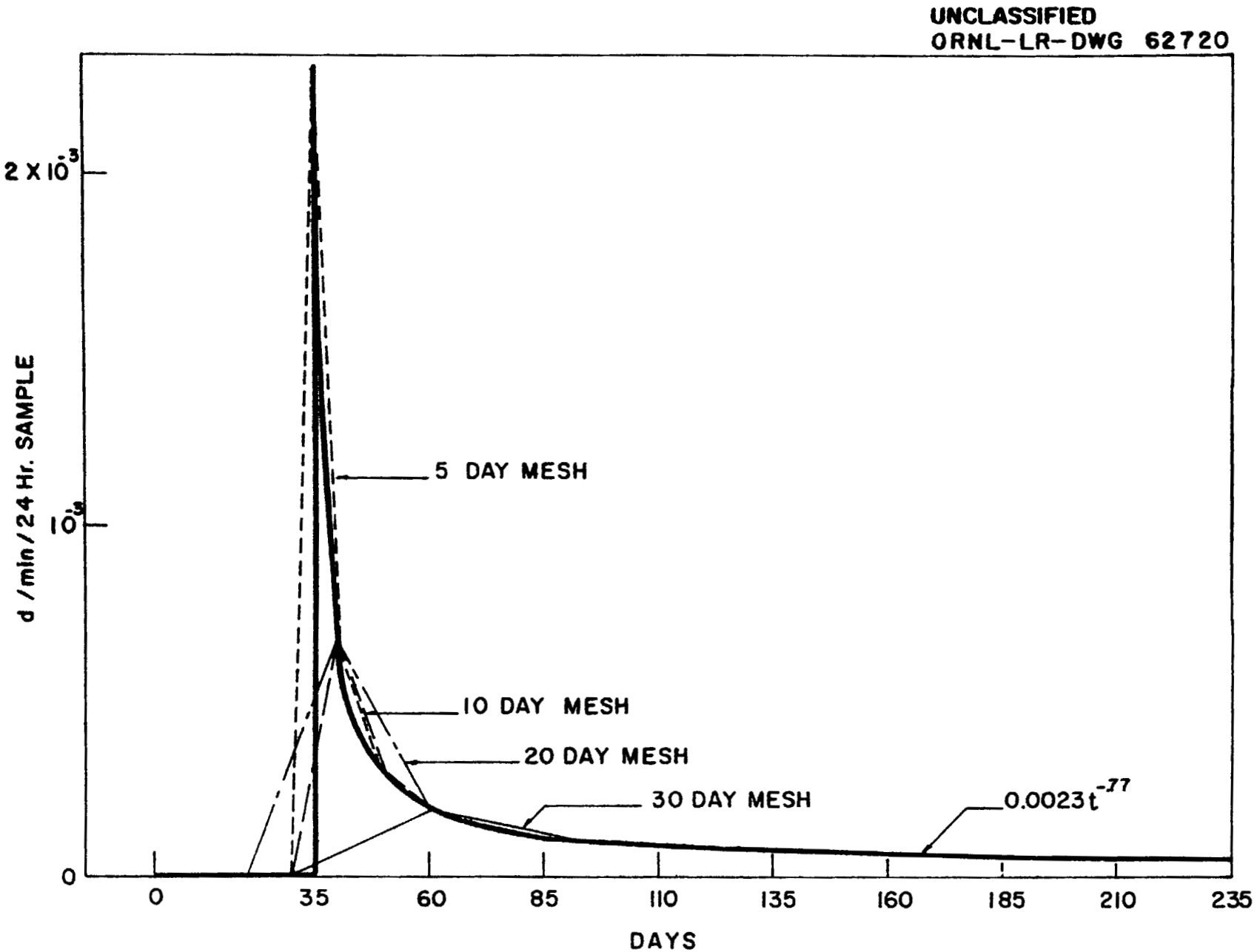

Fig. 5. EXCRETION DATA AND TRUNCATION FOR INPUT TO CODE

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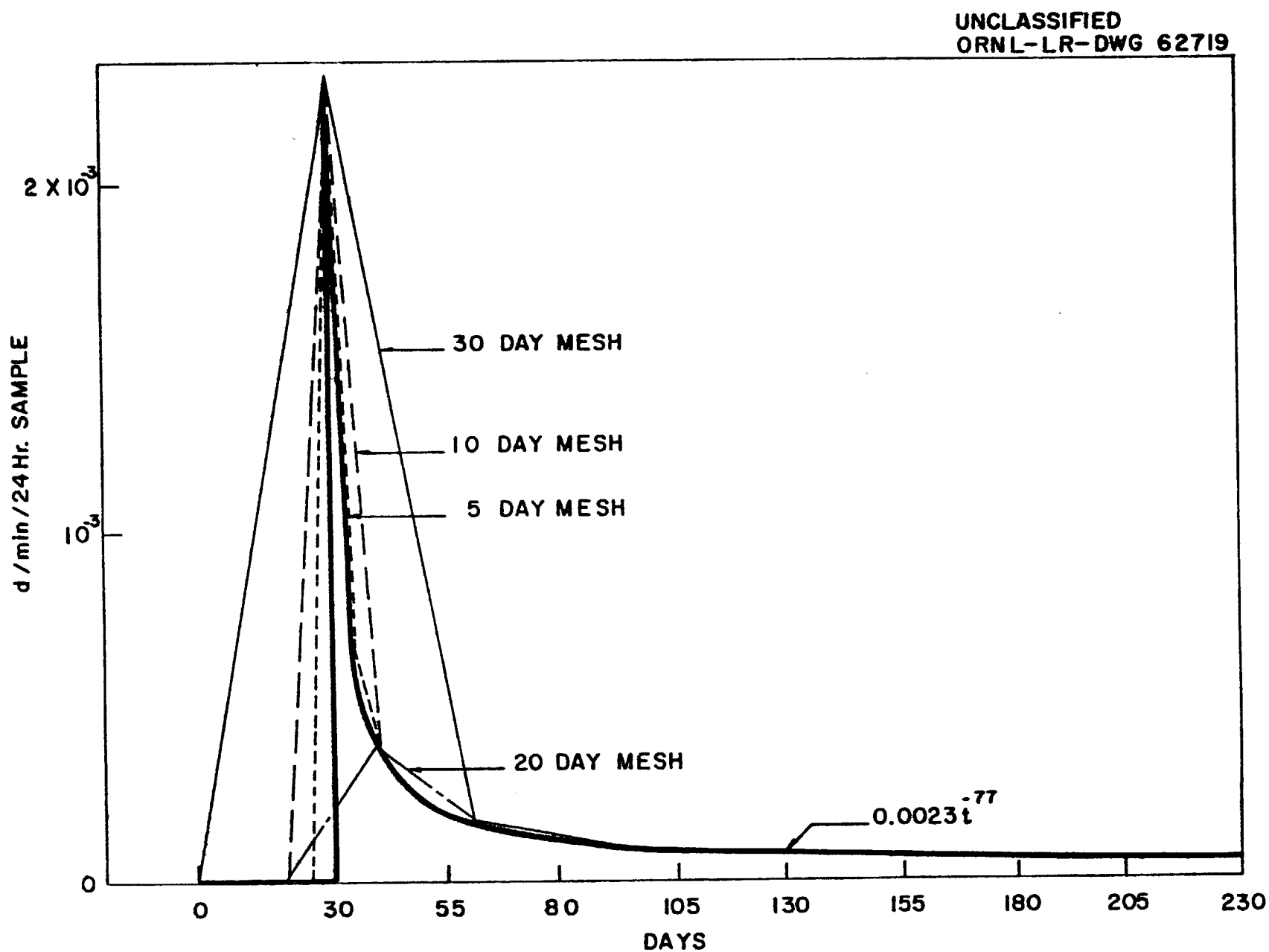

Fig. 6. EXCRETION DATA AND TRUNCATION FOR INPUT TO CODE

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Table I. COMPARISON OF Pu BODY BURDEN ESTIMATES

CODE	LANGHAM	PUQFUA	PUQFUA INVALIDATED SAMPLES	PUQUAP[1]	PUQUAP[2]	PUQUAE[1]	PUQUAE[2]
C135	.08	.1382	16	.0882	.1002	.0758	.0861
D334	.07	.1336	2	.1002	.1058	.0872	.0921
D711	.07	.1375	1	.0901	.1312	.0785	.1142
G717	.06	.0732	2	.1340	.1488	.1168	.1297
D63	.06	.1137	0	.0702	.0769	.0611	.0670
E36	.06	.0797	1	.0739	.0784	.0644	.0683
C397	.05	.0294	5	.0454	.0456	.0390	.0391
D501	.04	.0552	2	.0376	.0407	.0328	.0355
F664	.04	.0934	0	.0511	.0540	.0445	.0471
G716	.04	.0350	1	.0242	.0407	.0211	.0355
E742	.03	.0579	2	.0490	.0539	.0427	.0469
D775	.02	.0250	5	.0231	.0284	.0201	.0246
D182	.02	.0233	1	.0179	.0296	.0156	.0258
G524	.02	.0227	2	.0177	.0254	.0154	.0221
E629	.02	.0277	1	.0165	.0256	.0144	.0223
E390	.02	.0174	1	.0173	.0201	.0151	.0175
D791	.02	.0278	2	.0205	.0230	.0178	.0200
D591	.02	.0398	1	.0213	.0235	.0186	.0205
D205	.02	.0397	0	.0156	.0192	.0136	.0168
C137	.02	.0286	17	.0350	.0350	.0300	.0300
F634	.01	.0418	0	.0478	.0478	.0413	.0413
E252	.01	.0233	2	.0173	.0174	.0150	.0151
F412	.006	.0112	2	.0103	.0119	.0090	.0104
D670	.006	.0020	2	.0179	.0219	.0156	.0191
C365	.006	.0114	10	.0090	.0157	.0077	.0135
E822	.032	.0186	20	.0296	.0299	.0255	.0257
E822	.0175*						

1. ASSUMES EXPOSURE BEGINS ON DATE OF FIRST SAMPLE.

2. ASSUMES EXPOSURE BEGINS 15 DAYS BEFORE DATE OF FIRST SAMPLE WITH URINE COUNT PREDICTED BY EXCRETION FORMULA.

* BODY BURDEN ESTIMATE FROM AUTOPSY.

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Since case E822 is the only case where the body burden is determined by autopsy, a special study of the data was made in an effort to understand why PUQUAP and PUQUAE gave larger estimates than the autopsy value might indicate, while PUQFUA gave an estimate in close agreement. The urinalysis data of case E822 are shown in Fig. 7, and the connecting lines indicate the interpolated data used by PUQUAP and PUQUAE. It is evident that two of the highest values occurred after periods of 230 and 233 days during which no other sample was taken. The linear interpolation results in attributing high urinary excretion values over an extended period in each case. In actuality, no data are available for this period. To test the influence of this assumption of linearity on the estimate, the code was rerun after insertion of two additional fictitious data points at days 2062 and 2522, attributing to these the excretion values 0.701 and 0 in line with the preceding sample value. Using this modification, the estimated body burden of E822 was 0.0206 by PUQUAP and 0.0177 by PUQUAE. These are well in line with the actual value. Fig. 8 shows the accumulated growth of body burden as estimated by PUQUAP and PUQUAE without any modification of the data. Fig. 9 shows the effect of the modification for PUQUAE. This in no sense justifies the use of such a procedure* but does indicate that the higher estimates were due to the effect of the linear interpolation scheme applied over such an extended period and not to the high values themselves. It was found on examination that PUQFUA also rejected these

*In subsequent discussion with Lawrence, he has indicated that after study of the working record he feels there may be some justification for the assumption that the urinary excretion of E822 was not high for most of these two periods of time.

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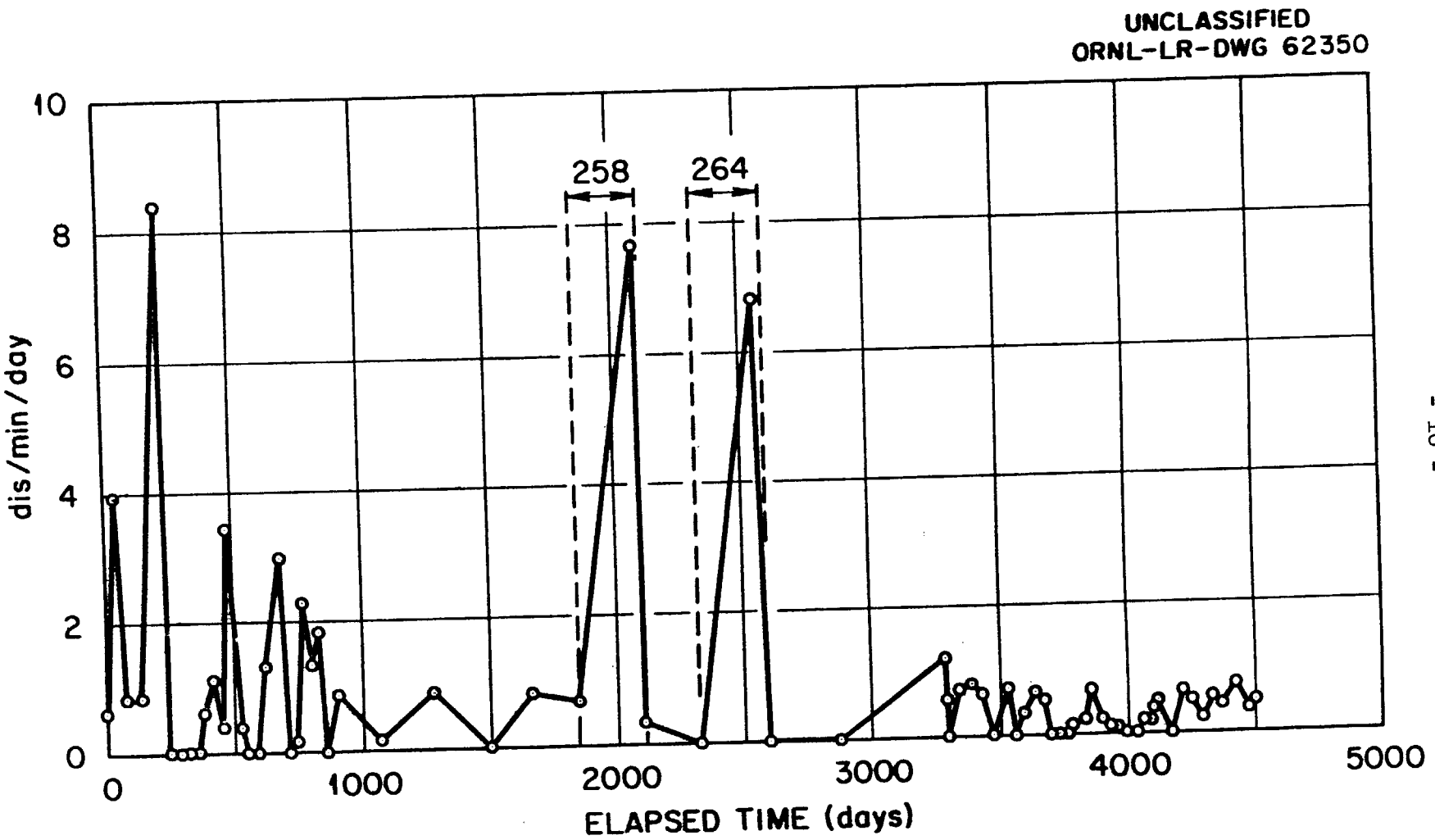

Fig. 7. Urinalysis Data of Case E822.

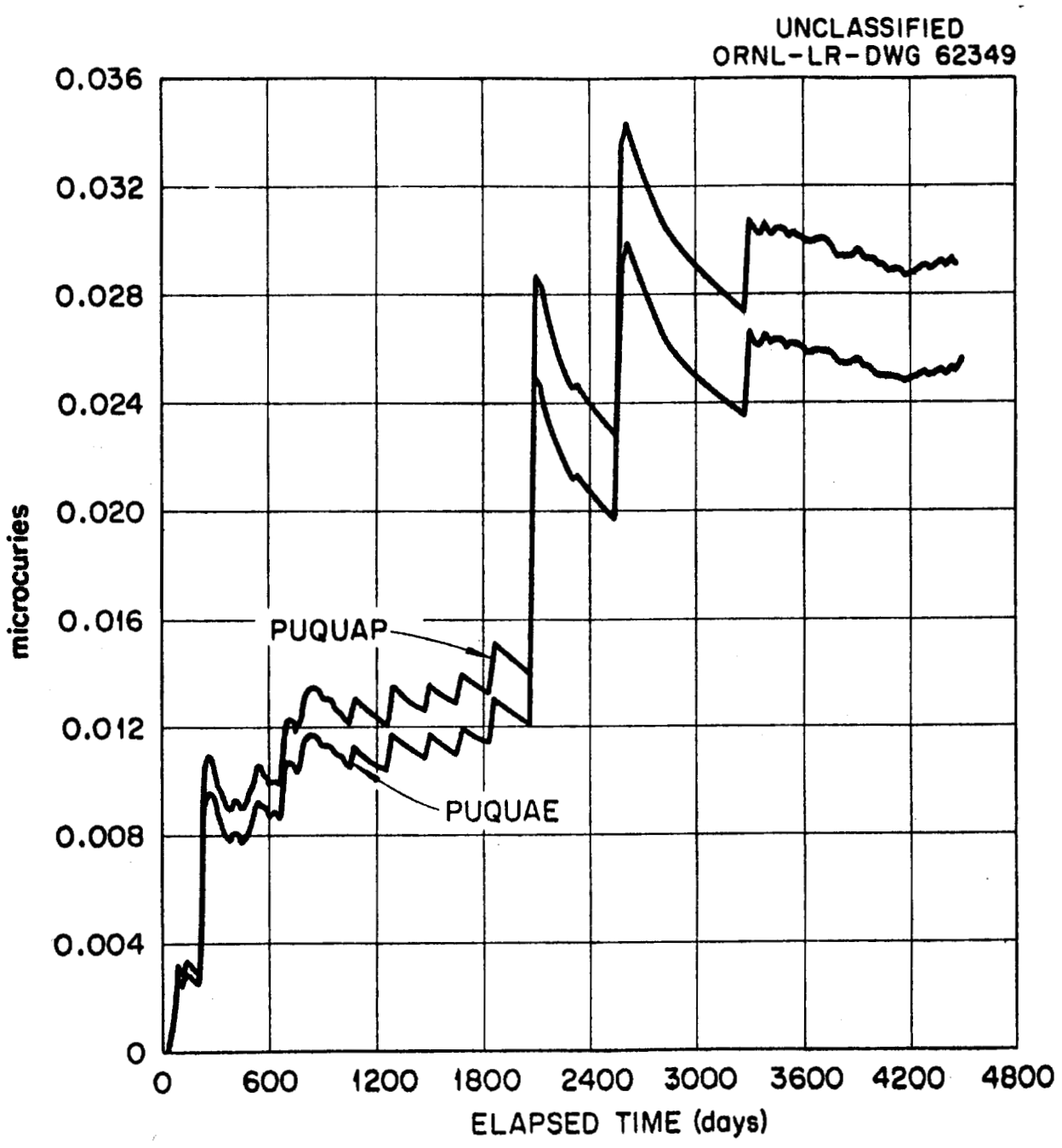

Fig. 8. Estimated Growth of Body Burden of Case E822.

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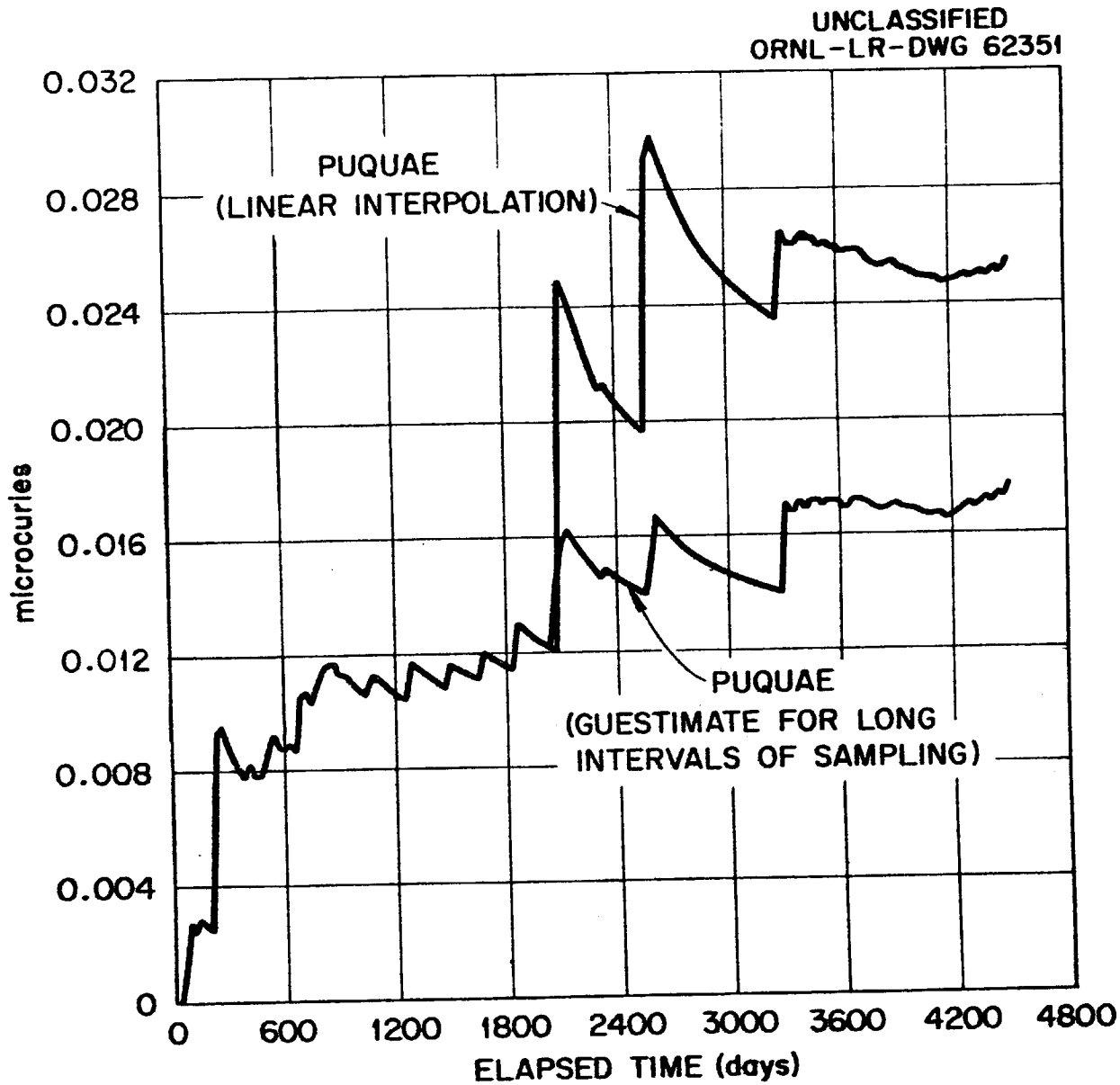

Fig. 9. Two Estimates of Body Burden Case E822.

data points. This example indicates the great importance of adequate urinalysis data, because such extensive periods where some assumptions must be made may introduce a large uncertainty in the estimate.

There are many aspects of the problem which call for further exploration. It is evident that $I(\tau)$ represents the intake into the blood and not ingestion or inhalation of the material. Thus there is no apparent inconsistency in $I(\tau)$ being positive even though the individual is not currently exposed. The material may be feeding into the blood from the lung or from other body tissues. This phenomenon of a rather high urinary excretion rate of an individual removed from exposure is frequently observed in cases of occupational exposure. It would be valuable to have carefully controlled animal experiments which would provide interpretation of this phenomenon. In fact, it seems important that the methodology used in these codes be thoroughly explored and that similar methods be developed for other isotopes if this is feasible.

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