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HUMAN THYROID UPTAKE AND BODILY ELIMINATION OF I^{131} FOR THE CASE OF SINGLE AND CONTINUAL INGESTION OF BOUND IODINE IN RESIN-TREATED MILK

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Abstract—Five human volunteers ingested resin-treated milk containing protein-bound I^{131} for periods of time ranging from 1 to 63 days and in amounts ranging from 0.15 to 92 mc.

In the first experiment all subjects ingested daily dosages of I^{131} for periods ranging from 4 to 63 days. Thyroid uptake was measured by γ-ray scintillation countings of all subjects. Urinary excretion was measured on two subjects, one of which was followed for 67 days.

In a second experiment, two subjects ingested a single dose each. Thyroid uptake and urinary excretion were measured as in the first experiment. Extrapolations are made from the single-intake data to the case of continuous intake and are compared with the daily intake data.

From these data, estimates are made of f_w, f_1, f_2 and T_b for thyroid gland and are compared with ICRP and NCRP recommendations.

INTRODUCTION

THE ICRP[1] and NCRP[2] currently recommend a value of 2×10^{-6} $\mu c/cm^3$ for the $(MPC)_w$ (168-hr week) of I^{131} based on the thyroid as the critical organ and a maximum permissible dose rate of 0.6 rems/week to this organ. This $(MPC)_w$ value is estimated in the usual way, i.e. the dose to the organ is taken to be approximately proportional to the assumed uniform concentration in the organ, and the relationship between the concentration in the organ to the concentration in drinking water is assumed to obey first-order kinetics. ICRP states that T_b, the biological half-life for iodine in the thyroid gland, is 138 days and that f_w, the fraction absorbed from the gut and going to the thyroid, is 0.3. The value of T_b is stated to be estimated from their equation (48) which is

$$T_b = 0.693 \frac{mc}{If_w},$$

where: m (= 20 g) is the mass of the thyroid gland, c ($= 4 \times 10^{-4}$ g/g organ) is the concentration of stable iodine in the organ, I ($= 2 \times 10^{-4}$ g/day) is the daily intake of stable iodine in the body, and f_w is as defined above.†

ICRP has carefully pointed out that, in this method of estimating T_b, the assumption is made that the radionuclide has the same biological elimination time as the stable element. Although there is an abundance of data on iodine metabolism by both humans and small animals provided by the research of medical scientists and radiobiologists, this assumption does not appear to have been tested. This is

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

† There is evidently an inconsistency in the ICRP-calculated value of T_b, because when one inserts the above values into their equation it turns out that $T_b = 92$ days and not 138 days as stated. Even though this differs from the stated value by a factor of ~1.5, the effect on the $(MPC)_w$ value is negligible, because in calculating it, the effective half-life is used, and due to the shortness of the radiological half-life (8 days), there is only a slight change in the $(MPC)_w$. However, it does make a difference in the $(MPC)_w$ for a long-lived isotope of iodine such as I^{129} whose radiological half-life is 6.3×10^9 days. In this case the effective half-life is approximately equal to the biological half-life and the $(MPC)_w$ for this isotope will almost be doubled when the corrected, 92-day value is employed.

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understandable in view of the fact that radiobiologists focus on the important problem of effects of I^{131} on the gland, while medical scientists are interested in physiological tests of the gland. For the most part, neither group appears to have tested the assumptions in models for estimating biological parameter values applicable to internal dose estimation work.

The ICRP report uses a single-intake model and integrates the retention predicted by this model to obtain the retention from chronic exposure. It mentions that exploratory studies have indicated a fairly satisfactory extrapolation can be made. This has been found to be true in the case of Co^{60} ingestion by mice[3] and, also in the case of Cs^{137} ingestion by mice.[4] There does not seem to be any human data for the case of chronic ingestion of I^{131} with which to test this method. BUSTAD *et al.*[5] have thyroid-gland, I^{131}-uptake data on sheep fed chronically for periods as long as 4 years. However, in sheep there is a seasonal variation in uptake. In man it is not obvious that the uptake is affected by seasonal factors.[6]

Some exploratory experiments were carried out in this laboratory (ORNL) on the problem of estimating T_b from single-intake data, extrapolating to the case of continuous ingestion and comparing the extrapolated data with the measured amounts in the thyroid gland. In this experiment, five male volunteers ingested, daily, for periods ranging from 4 to 63 consecutive days, constant doses of I^{131} ranging from 150 to 1840 $\mu\mu c$ in resin-treated milk, and their thyroid glands were monitored utilizing a γ-ray scintillation counter to determine the uptake. One subject, ingesting 63 daily doses of 1840 $\mu\mu c$/day, collected 24-hr samples of urine for 63 days, and these were measured for their I^{131} content. After the intake stopped on the sixty-third day, the subject continued to collect 24-hour urine samples for a period of 4 days. Also, his thyroid gland was counted six times, using the γ-ray counter, in a period of 4 weeks. Thus, the decrease in activity could be followed.

Three of the above subjects also ingested daily doses of 150 $\mu\mu c$ for 11 consecutive days, and their thyroid uptake was measured. Two of these subjects also took a single dose of 92 nc and (at various times) their thyroid glands were counted. Also, they collected 24-hr urine samples for a period of 5 days after the intake. One subject ingested 1840 $\mu\mu c$/day for 11 days. His thyroid-gland burden of I^{131} was determined both during intake and after the intake was stopped.

From the data obtained on these five subjects, a partial test of the ICRP assumptions was made. It was found that the predicted uptake for chronic ingestion (of resin-treated milk containing protein-bound iodine) obtained from extrapolation of single-intake data gave a slight overestimate of the burden in a period of 11 days of intake. Extrapolating from decay-curve data of the subject who ingested sixty-three daily intakes also yielded a slight overestimate of the thyroid-gland burden, but the over-all agreement between the predicted and the observed burden was fairly satisfactory. The T_b for I^{131} in the thyroid glands of four subjects (the data on the fifth subject were inadequate to estimate his T_b) ranged from 37 to 153 days. The mean value of 74 ($\pm$70) days does not significantly differ from the 92-day value of ICRP. The average value of f_w was 0.16 ($\pm$0.08) (the range was 0.08–0.29). This mean value does not differ significantly from the 0.3 value at the 95 per cent confidence level. It is the purpose of this report to present these human data.

METHODS

Preparation of I^{131} *ingestion dose*

Cows' milk containing I^{131} and obtained from the UT-AEC Agricultural Research Laboratory was passed over an anionic exchange resin (Dowex 1 × 8—50–100 mesh in 3-cm i.d. column), recycled twice to remove the ionic iodine from the milk, and then pasteurized. Two cylindrical columns were connected in series. The milk flowed through the columns at the rate of 20 ml/min The column-effluent milk contained ~3.8 per cent of the original I^{131} concentration in the raw milk. The alkaline precipitation, $ZnSO_4$—NaOH method of ACLAND[7] used to separate protein-bound iodine from serum was applied to the column-effluent milk. Greater than 97 per cent of the total I^{131} activity was precipitated as compared with only ~4.7 per cent precipitated from raw untreated milk. No tests were made of the

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column-treated milk to establish definitively which proteins were binding the I^{131}. However it is believed that the resin-treated milk contained, mainly, protein-bound I^{131}.

The I^{131} bound to the protein constituents of the milk is apparently very firmly attached as evidenced by letting the resin-treated milk stand for a period of ~30 days and re-treating the milk. When the milk was recycled over the column again, only about 4 per cent of the I^{131} could be removed onto the exchange resin. There is an advantage in using resin-treated milk in a continual-intake study and this is connected with the stable-iodine intake into the body. It was desirable to maintain a constant intake of I^{131} by the human subjects participating in the chronic-ingestion experiment. In order to accomplish this, the volume of milk must be increased each day to compensate for the loss of I^{131} by radiological decay. When a significant concentration of stable iodine is present in the milk, the increased volume of milk ingested will result in an increased intake of stable iodine which will affect the uptake of I^{131}. In this study the raw milk contained an average of 0.03 μg stable iodine/ml. In the resin-treated milk this was reduced to ~0.001 μg/ml. Some of the subjects ingested as much as 500 ml of milk, and thus only 0.5 μg of stable iodine was taken into the stomach, which is negligible in comparison with the daily average intake of 200 μg of stable iodine.

Ingestion doses, ages, weights, and radiation doses to thyroid glands of subjects

Table 1 presents the age, weight, $\mu\mu$c of I^{131} ingested singly or daily, the estimated peak-dose rate to the thyroid gland, and the estimated total dose received by the gland. All subjects were found to be euthyroid as indicated by tests of protein-bound iodine in blood. All subjects ate regular meals consisting of their usual diets. The average age of the five subjects was 41 years (range, 36–53 years) and the average weight 191 lb (range, 152–225 lb). Subject A, who ingested 92,000 $\mu\mu$c in a single intake, experienced the highest estimated total dose (0.176 rems) to his thyroid, and the peak-dose rate was 110 mrems/week (according to ICRP, a thyroid burden of 0.14 μc delivers 0.6 rems/week to this organ). The total dose to the gland was obtained by integrating the rems/week delivered to this organ from 0 to ∞.

In the chronic ingestion studies, subjects A, B and E drank the resin-treated milk between 0900 a.m. and 1500 hours and after being counted on the thyroid counter (except on weekends). Subjects C and D drank their milk at ~1600 hours and were counted before the ingestion.

Excreta sample collection and analysis

Each individual void of urine was collected by subjects A and B for a period of about 5 days after the single ingestion of 92 nc of I^{131}. Four

Table 1. Data on human subjects participating in I^{131} experiment

Subject*	Age (yrs)	Wt. (lb)	Daily intake ($\mu\mu$c/d)	Duration of ingestion I^{131} (days)	Single intake ($\mu\mu$c)	Maximum dose rate to thyroid gland (rems/week)	Total dose to thyroid (rems)
A	36	220	150	11	92,000	0.110	0.176
B	36	187	150	11	92,000	0.055	0.076
C	37	225	1640	63	0	0.005	0.056
D	53	170	1840	8	0	0.005	0.010
E	42	152	150 1840	11 4	0 0	0.005	0.015
Average	41	191					

* All subjects were euthyroid as indicated by tests of protein-bound iodine in blood performed by the ORNL Health Division.

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fecal samples were submitted by subject A. Subject C collected 24-hr urine specimens for a period of 67 days and submitted two fecal samples on days 55 and 56 after his first intake of 1840 $\mu\mu c$ of I^{131}. The daily collection period for urine was from 1600 hours to 1559 hours, that is, from the time after ingesting a dose at 1600 hours to the time just before ingestion of the next daily dose.

Urine samples were analysed for I^{131} content by taking an aliquot of the specimen (100 or 200 ml depending on the volume of the specimen) and counting in a pickle-barrel counter containing a 4 × 2 in. NaI(Tl) crystal connected to a 200-channel analyzer. Figure 1 shows the counter and the analyzer. Fecal samples contained in plastic bags were also monitored in the pickle barrel counter.

Urine and fecal samples were corrected for radiological decay. For a single-ingestion dose, the counts/min in the urine (or fecal) sample voided at t units of time after intake and analyzed on day t_a ($t_a \geq t$) were corrected for radiological decay by multiplying by $e^{0.086(t_a)}$. For consecutive ingestions, the urine samples were collected in the interval ~1559 hours on day t to 1600 hours on day $t + 1$. The sample was analyzed on day t_a and the measured counts were multiplied by $e^{0.086(t_a - t)}$; that is, the measurements were corrected for decay from the time of ingestion on day t to the time of analysis, t_a. To illustrate, a sample voided on day 20 ($= t + 1$) and analyzed on day 23 ($= t_a$) was corrected by multiplying the counts by $e^{0.086 \times 4}$.

Counting methods and techniques

A 3 × 3 in. NaI(Tl) crystal having a ½ in.-thick lead side shield and connected to a 200-channel analyzer was used to measure the counts due to I^{131} in the thyroid gland. The subject lay on a cot, and the crystal was located immediately over his thyroid gland with the outer edge of the side shield indexed over the sternal notch (Fig. 2). Counting periods varied depending on the amount ingested by the subject, ranging from 5 min to as long as 40 min.

A typical spectrum of the γ-rays from I^{131} for the 3 × 3 in. crystal placed over the thyroid gland of a subject is shown in Fig. 3. The area

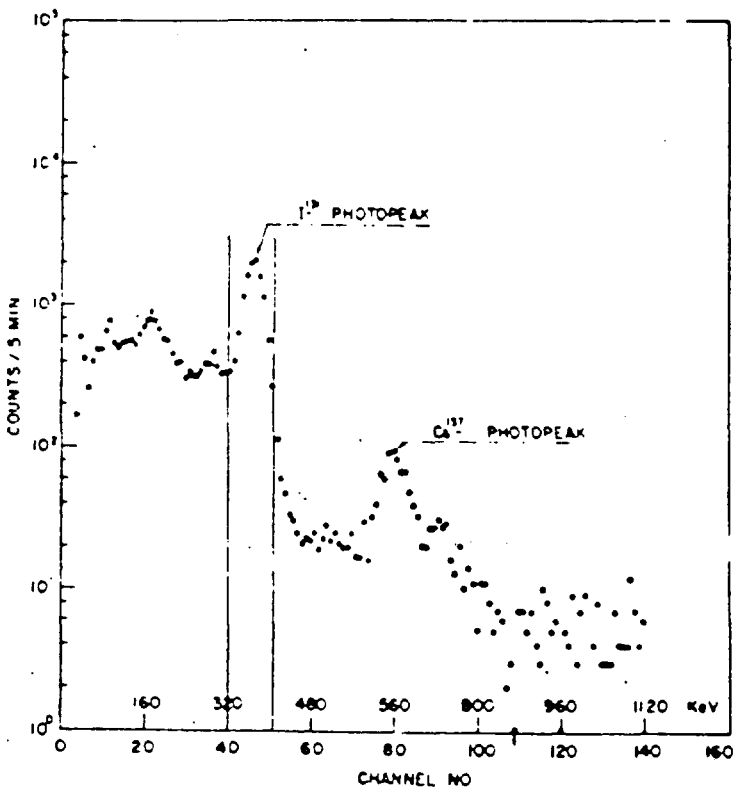

FIG. 3. Typical gross spectrum of γ-ray activity in thyroid gland for a few days after ingestion of 92 nc of I^{131}.

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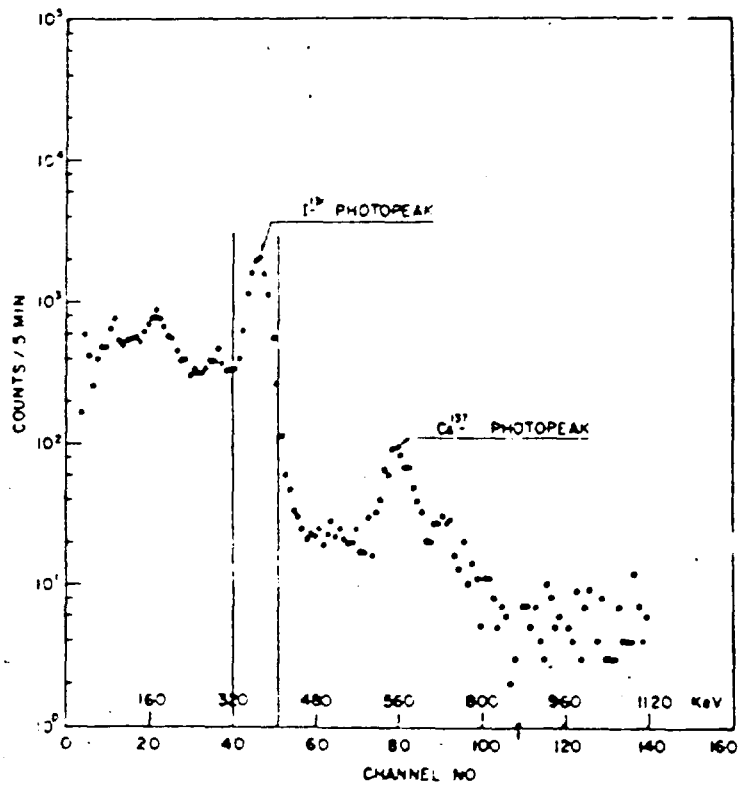

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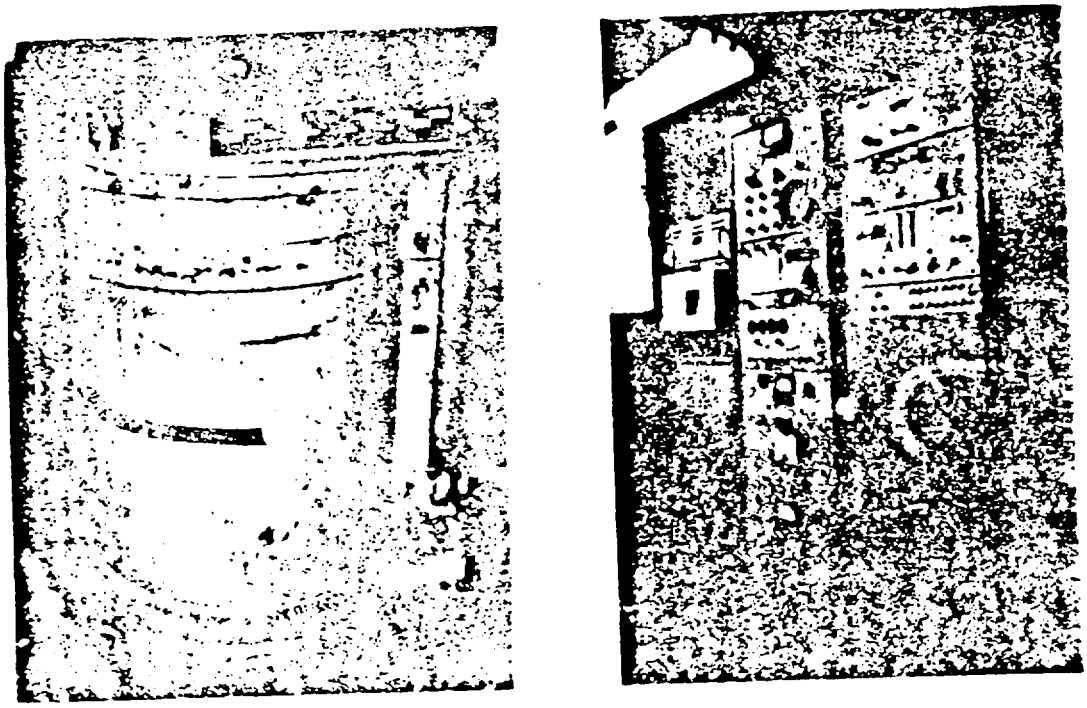
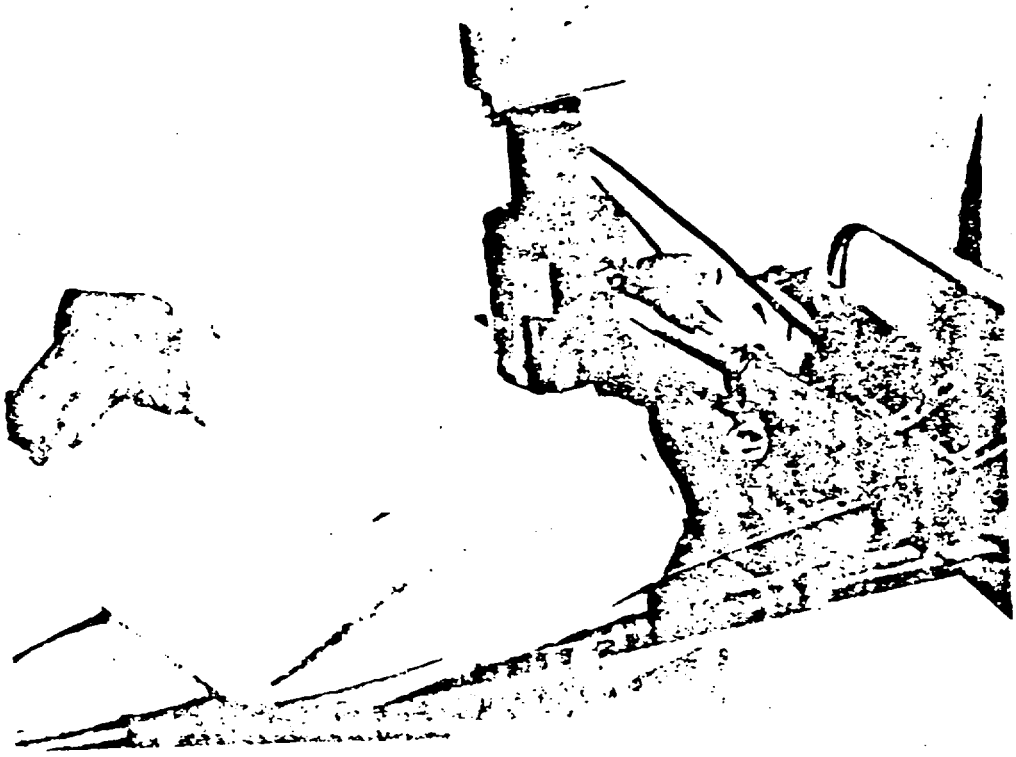


[illegible] Pulse-height counter and 200-channel analyzer.



Position for counting ^{125}I in thyroid gland with NaI(Tl) crystal.

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beneath the curve in the energy band 3[illegible]–408 keV was used to estimate the burden of I^{131} in the gland. The efficiency of the counter was determined by counting the thyroid gland of a plastic phantom which contained a known amount of a solution of KI^{131} in the thyroid gland. This factor was used to convert the counts determined on the gland of all the subjects to μc. There is probably some systematic error in the estimated burden because the depth and position of thyroid glands are known to differ for different subjects. Thus, the geometry and absorption layers will be different. Also, there was an opportunity for some additional random error in the estimated burdens due to lack of reproducibility of the placement of the crystal over the gland. Attempts were made to keep this at a minimum by locating the subject's neck as close to the counter as possible and by reference to the midline position of the body.

A few whole-body counts were also taken with an 8 × 4 in. NaI(Tl) crystal located over the subject when he reclined on a curved bed having a radius of 1 M (the 1-M arc position). In this measurement a 512-channel analyzer was used to record the γ-ray spectrum. The efficiency for this count was estimated from measurements made on a plastic phantom whose organs contained a known amount of I^{131} approximating that found in standard man. Only a few counts were made on each of the subjects in the 1-M arc position. Some error of relatively small, but unknown, magnitude is to be expected in this measurement because of variations in distribution of I^{131} in the organs. Further studies need to be carried out to determine the magnitude of this error.

Interpretation and least-squares treatment of the data

In interpreting the data, the approach and terminology employed by ICRP is used. Let q denote the total μc in the body, f_2 the ratio of the μc in the critical organ to that in the body, P the rate of intake into the critical organ, and λ the effective decay constant. Then, for the rate of change in the critical organ,

$$\frac{d(qf_2)}{dt} = P - \lambda qf_2 \qquad (1)$$

Also, let (MPC)$_w$ be the concentration in water (or milk), 2200 ml the daily intake of water (or milk) into the body, and f_w the fraction absorbed from the gut to the critical organ, i.e.

$$P = 2200 f_w (\mathrm{MPC})_w \qquad (2)$$

In equation (2) let 2200 (MPC)$_w$ be denoted by I, the daily intake into the gut.

In the interval 0 to t, let I units/day be ingested. Then

$$qf_2 = f_w \frac{I}{\lambda}(1 - e^{-\lambda t}) \qquad (3)$$

is the amount present in the organ at any time t during continuous ingestion of I units/day for t days. Let t_1 be the time at which $I = 0$. Then in equation (1) $P = 0$ and the amount present at time $t (t \geq t_1)$ is

$$q(t_1)f_2 = q(t_1)f(t_1)_2 e^{-\lambda(t-t_1)}, \; t \geq t_1. \qquad (4)$$

From equations (3) and (4),

$$q(t)f_2 = f_w \frac{I}{\lambda}(1 - e^{-\lambda t_1})e^{-\lambda(t-t_1)}, \; t \geq t_1 \qquad (5)$$

is the burden of the critical organ at time t following continuous ingestion for a period of t_1 units of time, $t \geq t_1$. This equation is applicable to the data obtained in the experiments in which the intake was stopped after t_1 units of time.

For single ingestion, t_1 in equation (5) is small, $e^{-\lambda t_1}$ can be expanded in Taylor series, and we find

$$q(t)f_2 = f_w I_0 e^{-\lambda(t-t_1)} \qquad (6)$$

where $I_0 = It_1$, the amount ingested in the single intake. Actually, in our experiments a discrete intake of I_0 units/day rather than a continuous intake constituted the exposure regimen. To interpret these data, the equation for the amount present on day t after i discrete intakes is, from equation (6) (for t_1 is negligible compared to t)

$$q(t)f_2 = f_w I_0 \sum_{i=0}^{t} e^{-\lambda(t-i)}, \; t = 0, 1, 2, \ldots \qquad (7)$$

This can be summed to t terms to obtain

$$q(t)f_2 = f_w I_0 \frac{e^{\lambda}}{(e^{\lambda} - 1)} \frac{e^{-\lambda t}}{}, \; t = 0, 1, 2, \ldots \qquad (8)$$

When λ is small enough, we have equation (3) again, and the data can be interpreted in terms of a continuous intake. Otherwise, some correction has to be made to take care of the differences in the denominator of equations (3) and (8) when the data are interpreted with the continuous-intake model.

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We shall also interpret the whole-body-retention data and excretion data in terms of a linear combination of exponentials. Let $R_s'(t)$ denote the fractional biological retention in the body for the case of a single ingestion. Let λ_j' denote the biological decay constant for the jth exponential term. Assume

$$R_s(t) = \sum_{j=1}^{n} a_j e^{-\lambda_j' t} \tag{9}$$

represents the biological retention in the body. The excretion is denoted by $E_s'(t)$, where

$$E_s'(t) = 1 - R_s'(t),$$

while the rate of excretion is

$$\dot{E}_s'(t) = \frac{dE_s'(t)}{dt} = \frac{-dR_s'(t)}{dt} = \sum_{j=1}^{n} \lambda_j' a_j e^{-\lambda_j' t} \tag{10}$$

To take into account the decay by radiological processes, equations (9) and (10) must be multiplied by $e^{-\lambda_r t}$. This yields

$$R_s(t) = R'(t) e^{-\lambda_r t} = \sum_j a_j e^{-\lambda_j t} \tag{11}$$

and

$$\dot{E}_s(t) = E_s' e^{-\lambda_r t} = \sum_j \lambda'_j a_j e^{-\lambda_j t} \tag{12}$$

where

$$\lambda_j = \lambda_r - \lambda_j'.$$

Now we can convert equations (11) and (12) such that they will apply to the case of continuous intake of I units per day. Let $R_c(t)$ denote the retention and $E_c(t)$ the rate of excretion at time t for the case of continuous intake of a constant I units per day for t days.

If at time $\tau (t > \tau)$, $Id\tau$ units are taken into the body, then the retention at time t is $R_s(t - \tau) Id\tau$. Summing over all τ, we find

$$R_c(t) = I \int_0^t R_s(t - \tau)\, d\tau = I \sum_j \frac{a_j}{\lambda_j} (1 - e^{-\lambda_j t}). \tag{13}$$

For the rate of excretion, we obtain

$$\dot{E}_c(t) = I \int_0^t \dot{E}_s(t - \tau)\, d\tau = I \sum_j a_j \frac{\lambda_j'}{\lambda_j} (1 - e^{-\lambda_j t}). \tag{14}$$

In the case of discrete daily intakes of I_0 units each day, then a discrete sum has to be taken. Let t be an integral number of days, t' a fractional part of a day, and $T = t + t'$ the time from the first intake of I_0 units. Then we find

$$R_c(t) = I_0 \sum_j a_j \left(\frac{e^{a_j} - e^{-a_j t}}{e^{a_j} - 1} \right) e^{-a_j t} \tag{15}$$

while for daily excretion, denoted by ε, we have

$$\varepsilon(t + 1) = I_0 \sum_j a_j \left(\frac{1 - e^{-\lambda_j'}}{1 - e^{-\lambda_j}} \right) \left(1 - e^{-\lambda_j (t+1)} \right). \tag{16}$$

The thyroid-gland, decay-curve data obtained on the subjects were treated by the method of least squares. Here, let ϕ denote the residual sum of squares, Y_i the calculated i^{th} value of the ordinate, Y_{0i} the observed value, and W_i' a weight factor. Now, the sum of squares of weighted residuals is

$$\phi = \sum_{i=0}^{n} W_i' (Y_i - Y_{0i})^2$$

with $Y_i = \ln A + Bt_i$, ϕ is minimized with respect to A and B, and Y_0 being the logarithm of the ordinate.

This procedure was programmed* for the IBM-7090 computer, and the values of A and B together with the variances in A and B were calculated. Two sets of weight factors W_i' were employed. Calculations were made for the case where all $W_i' = 1$, i.e. unit weights, and also for the case where $W_i'^{-1} = \text{Var } Y_i$. It was assumed that all of the variance in the ordinate value was due to counting. Thus, the variance was estimated from the counts. The effect of weighting the residuals on the parameters is to take out the bias of the smallest ordinate value (those containing the largest error) on the best-fitting curve. In the section on results, the best-fitting curves for the case where unit weights and where $W_i'^{-1} = \text{Var } Y_i$ were employed are shown plotted together with the data.

RESULTS

Single-intake studies

Figure 4 presents the thyroid-gland data on the two subjects ingesting the single intake of 92 nc. The data are noted to show an initial increase in the first day followed by a leveling

* We are indebted to George Atta, Mathematics Division, for the use of his program.

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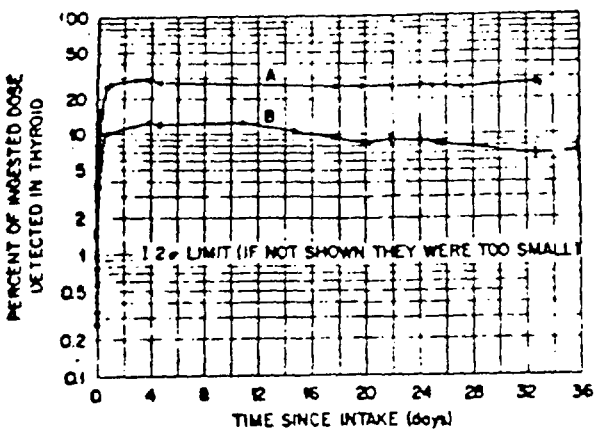

FIG. 4. I^{131} in human thyroid of two subjects following single ingestion of protein-bound iodine in milk (corrected for radiological decay).

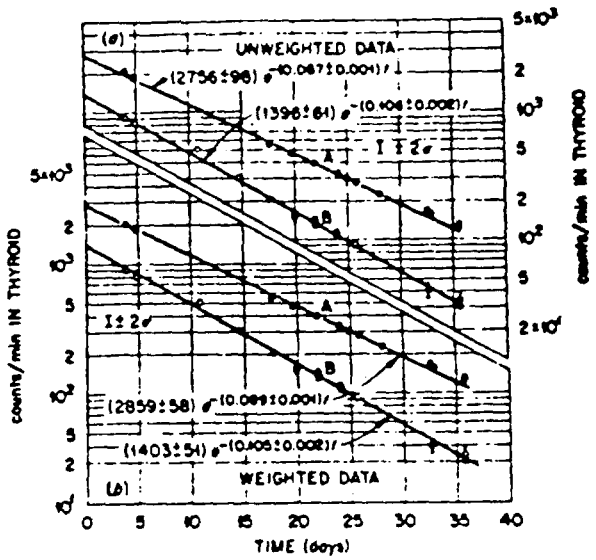

FIG. 5. Least-squares treatment of thyroid-decay curves.

off at ~2 days, and then they begin to decrease along a single-exponential path. The uptake of I^{131} by the thyroids of these two subjects is noted to differ, and the biological half-lives differ.

In processing these data by least squares, the r[illegible]rements made in the first 24 hr were o[illegible]d from the calculations. Figure 5 presents the graphs of the data (uncorrected for radiological decay) obtained on these two subjects. Figure 5(a) shows the data, together with the plot of the best-fitting curve, for the case of $W_i = 1$, i.e. unweighted data, and the equations for the curves. The errors on the parameters are two standard errors.

Figure 5(b) presents the plot of the data, together with the best fitting curves, obtained when $W_i^{-1} = \mathrm{Var}\, Y_i$. The abscissa is the time in days following the single ingestion. Table 2 presents the rounded-off values of f_w and T_b for these two subjects. Both subjects ingested 92 nc. The estimate of f_w is obtained by taking the intercept of the best fitting curves and dividing by the ingested dose. To estimate the biological half-life, the equation is

$$T_b = 0.693/(\lambda - \lambda_r)$$

where λ is the effective decay constant and $\lambda_r (= 0.693/8d^{-1} = 0.08662d^{-1})$ is the radiological decay constant.

It can be seen in Table 2 that f_w differs only a little regardless of whether weighted or unweighted data are employed. T_b, on the other hand, is quite different for subject A when the data are weighted as compared with the calculation based on unweighted data. This is due to the fact that λ approaches λ_r in the denominator of the equation for T_b, and T_b is quite sensitive to small changes occurring in the denominator. The last three measurements made on subject A markedly affect the value of λ and, hence, the calculated value of T_b. These last three points have larger variance than any of the other

Table 2. Biological parameter values estimated from best-fitting parameters obtained by least-squares treatment of thyroid-decay curve data

Subject	Ingested dose (nc)	f_w			T_b (days)		
		weighted	unweighted	weighted*	weighted	unweighted	weighted*
A	92	0.28	0.27	0.29	291	1823	153
B	92	0.14	0.14	—	37	36	—

* Last three measurements of subject A's curve omitted from least-squares calculation (see text).

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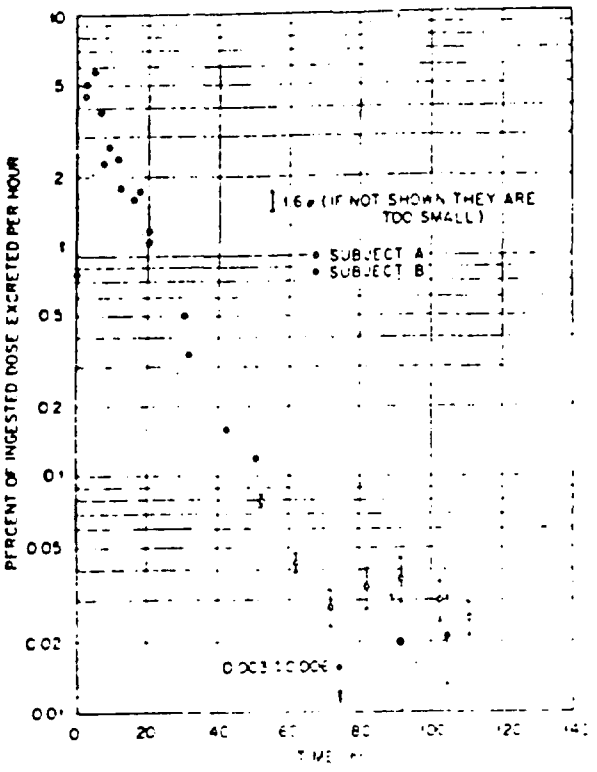

FIG. 6. Urinary excretion of I^{131} following single ingestion of 92 nc in resin-treated milk.

points. It was felt these points might also be biased because of his intake of milk containing I^{131} from fallout. The regular milk in his community was, at the time of these measurements, increasing in its content of I^{131}. Because of this, the last three points were omitted from the least-squares calculation. Subject A's indicated biological half-life then became 153 days.

The urinary-excretion measurements for these subjects are shown in Fig. 6. A rapid decline in the rate from ~7 per cent/hr, extrapolated to time zero, to 0.7 per cent at 24 hr was noted. Subject A showed an increase in rate in the first 8 hr. Subject B's rate starts at ~5 per cent/hr in the first few hr and then declined. There was only a slight difference between A's and B's rates after about 8 hr.

Figure 7 shows the cumulative urinary excretion of these same two subjects. Subject B's curve increases more rapidly than does A's curve. This is in keeping with the thyroid-uptake curve. A had a greater uptake than B and excreted less than B in the same period of time.

Four fecal samples were collected by A, representing total fecal excretion for the first 4 days after ingestion. They contained a total of 1.9 per cent of the dose. Subject B did not collect any fecal samples. Subject A also collected two saliva samples and a sample of perspiration. At 3 hr there was secreted in saliva ~1.0 per cent/hr, and at 6.7 hr the rate was 0.2 per cent/hr. At 8 hr all the perspiration collected from feet and ankles in plastic boots worn by the subject contained <0.03 per cent of the ingested dose. The amount of this perspiration is not known.

From the cumulative urinary excretion and

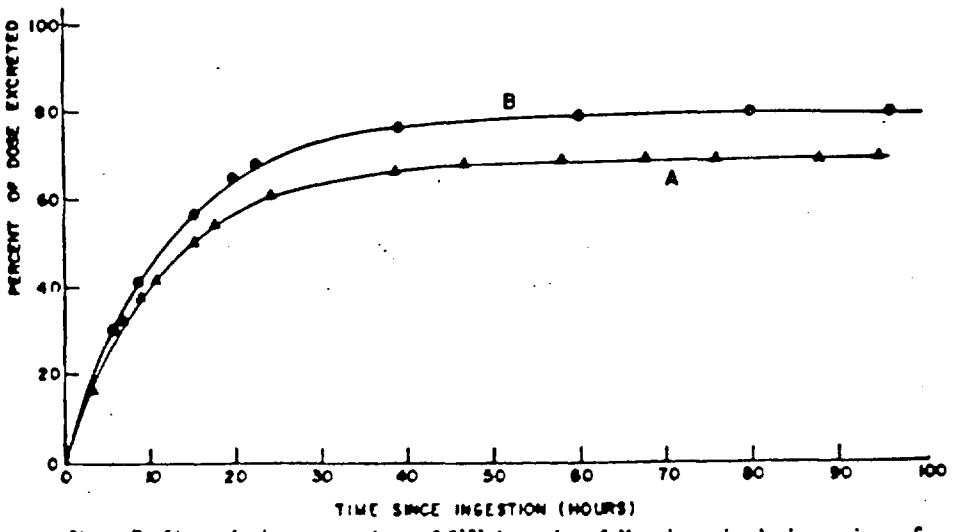

FIG. 7. Cumulative excretion of I^{131} in urine following single ingestion of protein-bound I^{131} in milk (corrected for radiological decay).

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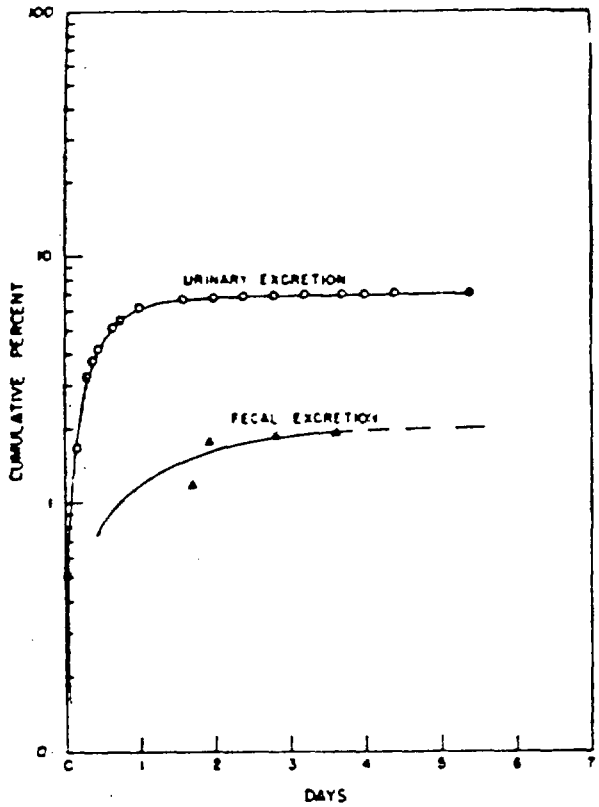

FIG. 8. Cumulative excretion curves. Subject A. Ingested single dose of 92 nc I^{131} in resin-treated milk (corrected for radiological decay).

fecal excretion of these two subjects, an estimate was made of the per cent of dose present in the body; and from these data and the thyroid-gland uptake, the fraction of the total body burden present in the thyroid gland was estimated. At 4 days Subject A excreted 69 per cent in urine and 1.9 per cent in feces. The body burden was then ~29 per cent. The thyroid gland at 4 days contained ~28 per cent (Fig. 4). Thus, the fraction present in the thyroid of this subject was ~0.97. In the case of subject B, 80.5 per cent of the ingested dose was excreted in urine at four days. It was estimated that feces would cumulate ~3.8 per cent. Thus, his body would contain ~16 per cent. Since there was ~12 per cent present in his thyroid on day 4, then the fractional thyroid burden would be about 0.75.

If one took these fractions to be estimators of f_g, how would they compare to the value observed when the subject chronically ingested I^{131}? To gain insight into this, use was made of subject A's cumulative urinary- and fecal-excretion data and his thyroid-gland data to construct a body-burden curve. Figure 8 shows the cumulative fecal and urinary excretion plotted vs. time. The smooth curves are free-hand curves visually fitted to the data. Adding these curves and subtracting the sum from 100 per cent, we obtained an estimate of the body burden. Figure 9 shows a graph of this difference plotted vs. time. At 5 days, 72.5 per cent was excreted. From the thyroid-gland data, an estimate can be made of the long-term component of this body-burden curve by assuming the long-term component of the thyroid-gland data equals, essentially, the body-burden curve at 5 days. The parameters of the short-term component were estimated from a plot of the difference between the data and the long-term component—the standard "peel-off" procedure. For this subject we find

$$R_e(t) = I(0.71e^{-1.47t} + 0.29e^{-0.0001t}).$$

Extrapolating this to continuous exposure, we obtain

$$q(t) = R_c(t) = I[0.48(1 - e^{-1.47t}) + 3.22\,(1 - e^{-0.0001t})].$$

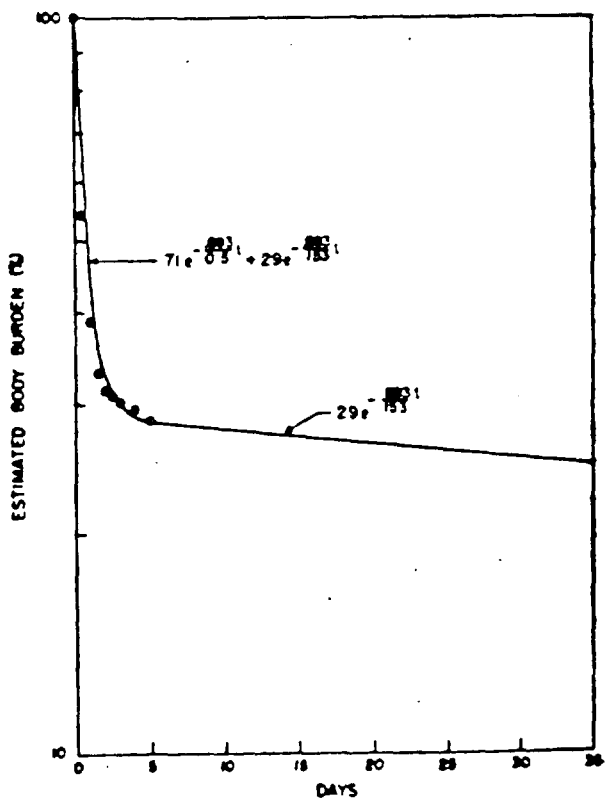

FIG. 9. Body burden curve. Subject A. Estimated from cumulative excretion data and thyroid gland data

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At infinity the body would contain 3.7 daily intakes. Extrapolating the single-intake equations of the thyroid-gland curve to the case of continuous ingestion, we obtain

$$qf_2 = 3.22I(1 - e^{0.0901t}).$$

At infinity the thyroid gland would contain 3.22 daily intakes. From these two pieces of information, we find

$$f_2 = \frac{3.22}{3.7} = 0.87.$$

The per cent of the ingested dose voided in the first 24-hr urinary excretion of subjects A, B, and C is shown in Table 3. Also shown are the I^{131} ingestion dose and the ml of milk ingested. The average per cent of ingested dose excreted by all three subjects in the first 24 hr was 67 ± 5 per cent.

Table 3. Per cent of ingested dose excreted in urine one day after ingestion

Subject	Dose ($\mu\mu c$)	Volume milk ml	Per cent ingested dose excreted in 24 hr*
A	92,000	500	61
B	92,000	500	69
C	1840	10	71
D	1840	10	--
E	1840	10	--

* Average ± standard deviation = 67 ± 5.

Daily intake studies

Subjects A, B, and E also ingested daily for 11 days 150 $\mu\mu c$ I^{131} in resin-treated milk, and their thyroid glands were counted. From Table 2 the parameter values (weighted data) can be inserted into equation (8) together with the value of I_0 (= 150 $\mu\mu c$), and the burden of the thyroid gland can be predicted and compared with the measured burden. Figures 10, 11 and 12 show the measured thyroid burdens of these subjects and the burden predicted by extrapolation of the single-intake data. Also shown for purposes of comparison is the predicted burden using ICRP parameter values. For all three subjects the ICRP-predicted burden overestimates the measured burden. In the case of subjects A and B the extrapolated burden

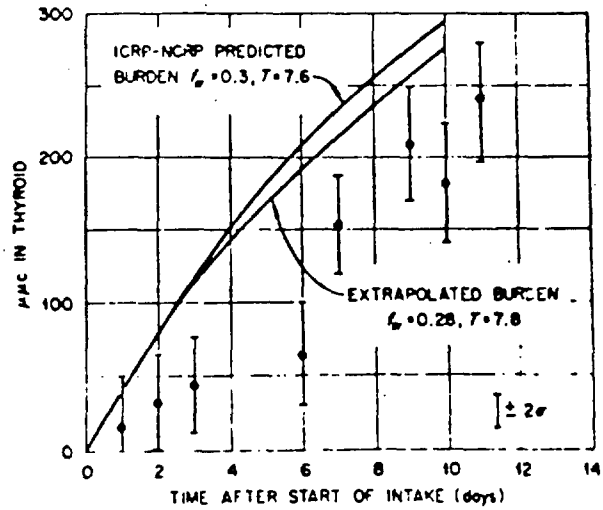

FIG. 10. Thyroid gland burden of I^{131}, subject A ingesting 150 $\mu\mu c$ daily for 11 days, resin-treated milk.

agrees more closely with actual measurements, but, nevertheless, it is an overestimate also.

Figure 13 presents the thyroid data for subject C, who ingested sixty-three daily intakes, and for subject D, who ingested eight daily intakes. Figure 13(a) shows the graph of the data and the best-fitting curves together with the parameters of the best-fitting equations estimated from least-squares treatment of the unweighted data. The same data are shown in Fig. 13(b), but here the best-fitting curves and parameters were estimated from least-squares treatment of

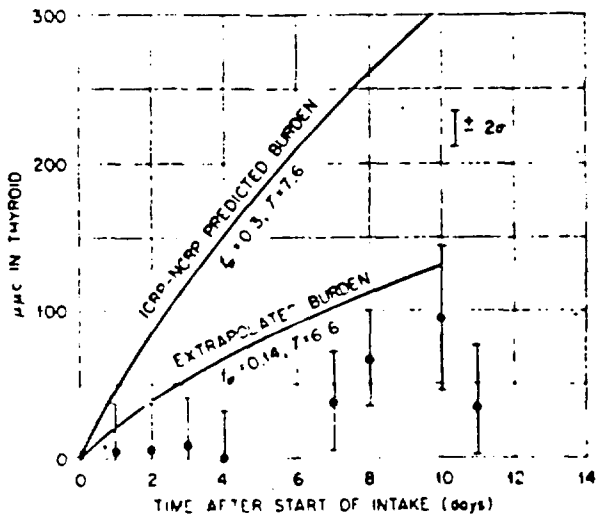

FIG. 11. Thyroid gland burden of I^{131}, subject B ingesting 150 $\mu\mu c$ daily for 11 days, resin-treated milk.

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weighted data. As can be seen in Fig. 13, the influence of the smallest ordinate value (the last point) is reduced when the weighted sum of squares is treated. From these best-fitting equations and equation (8), the parameter values f_w and T_b can be obtained for these two subjects and the burdens in the thyroid glands during the period of chronic intake can be predicted and compared with the measured burdens.

Table 4 presents the values of the parameters f_w and T_b obtained from the numerical data appearing in Fig. 13 and equation (8). For subject C the f_w and T_b values are quite different, depending on whether the weights were set equal to unity or to Var Y_i. The parameters obtained from the weighted least-squares treatment are employed to predict the thyroid uptake during daily ingestion.

Figures 14 and 15 show the thyroid-burden measurements on these two subjects both during their period of daily intake and in the following period when the intake stopped. Plotted on the ordinate is the $\mu\mu c$ in the thyroid, while plotted

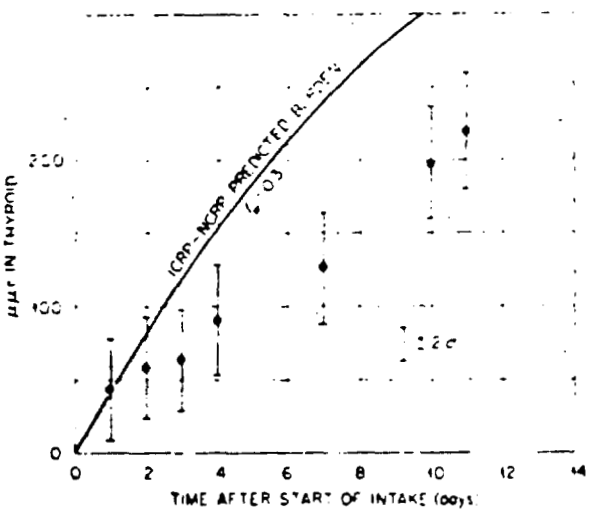

FIG. 12. Thyroid gland burden of I^{131}, subject E ingesting 150 $\mu\mu c$ daily for 11 days, resin-treated milk

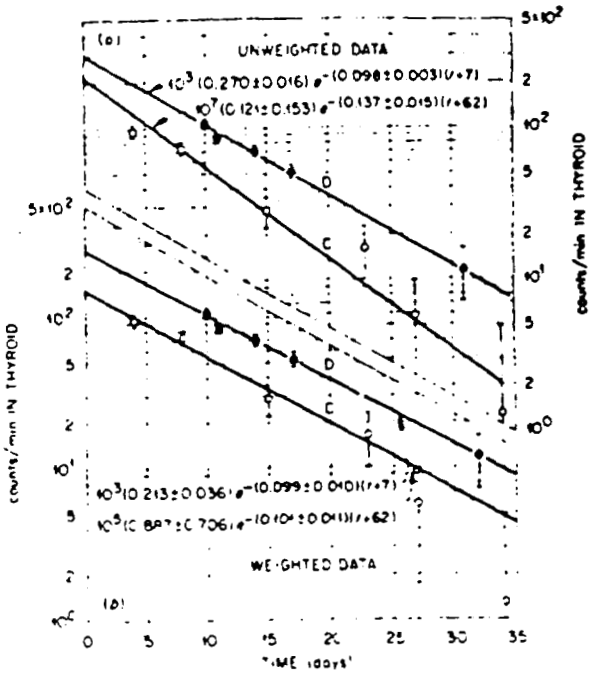

FIG. 13. Least-squares treatment of thyroid decay curves.

on the abscissa is the time in days from the first intake. Also shown in these figures are the predicted thyroid burdens employing ICRP data and the predicted thyroid burdens based on equation (8) into which the f_w and T_b values appearing in Table 4 were inserted. For both subjects, the ICRP-predicted burdens overestimated the observed burdens. Also, in the case of subject C, the extrapolated burden slightly overestimated the observed level in thyroid.

Figure 16 presents the thyroid-gland data on subject E, who ingested 1840 $\mu\mu c$ daily for 4 days. There were only three measurements made on this subject. The data are not adequate to estimate T_b and f_w. Also plotted (Fig. 16) is the ICRP-predicted burden. Note that it passes slightly above all meaured burdens.

Subject C's urinary excretion of I^{131} is shown

Table 4. Biological parameter values estimated from best-fitting parameters obtained by least-squares treatment on thyroid-decay-curve data

Subject	Dose ($\mu\mu c$)	f_w		T_b (days)	
		Weighted	Unweighted	Weighted	Unweighted
C	1840	0.08	0.17	47	14
D	1840	0.14	0.14	57	61

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in Fig. 17. As can be seen in the first 10 days, the measured excretion rate rises from [illegible] per cent/day to a level of about 90–95 per cent/day and from then on fluctuates around 95 per cent/day. Note the point at 60 days is ~15 per cent/day. On this day the subject had influenza accompanied by diarrhea and vomiting. His urinary volume on this and the succeeding 2 days was quite low since he was on a negative water balance. It can be noted that the rate of I^{131} excretion on these days was also lower than usual. After I^{131} intake was stopped, the rate of excretion decreased precipitously. On the sixty-sixth day the level in urine was less than the limit of sensitivity for detecting I^{131} in urine.

Fecal samples obtained from this subject on day 55 and day 56 contained 3.8 and 3.9 per cent of the daily intake, respectively.

The cumulative intake of I^{131}, the cumulative urinary excretion, and the estimated cumulative

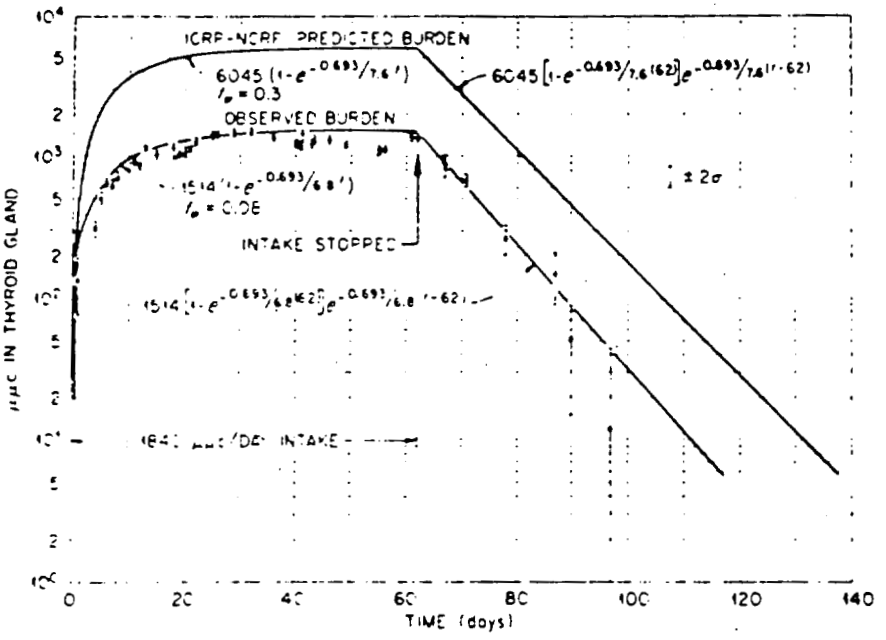

FIG. 14. Thyroid gland burden of I^{131}, subject C ingesting 1840 $\mu\mu c$ daily for 63 days.

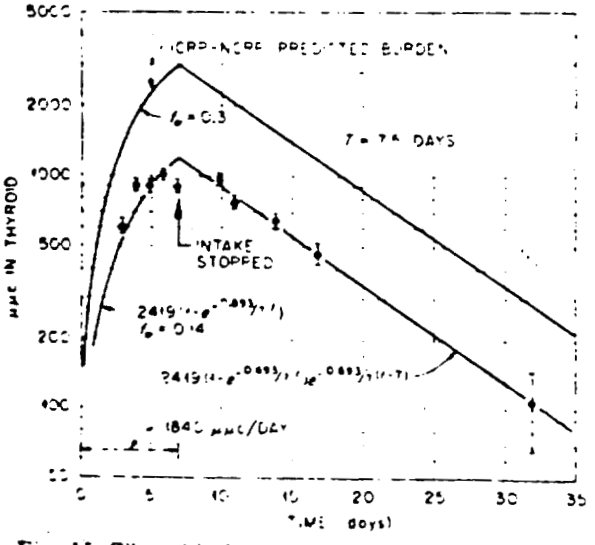

FIG. 15. Thyroid gland burden of I^{131}, subject D ingesting 1840 $\mu\mu c$ daily for 8 days.

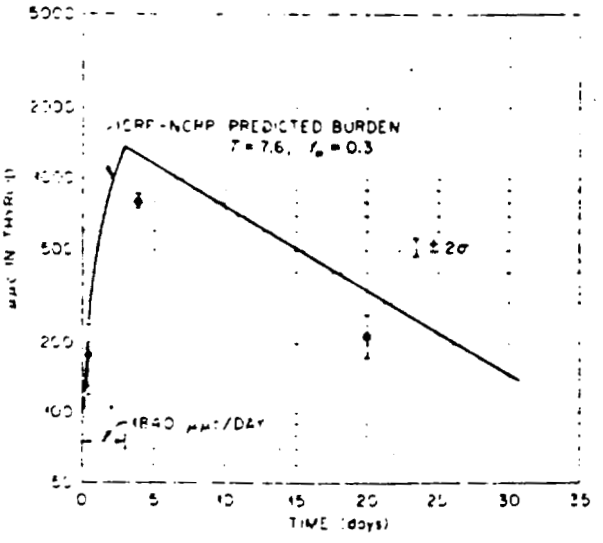

FIG. 16. Thyroid gland burden of I^{131}, subject E ingesting 1840 $\mu\mu c$ daily for 4 days.

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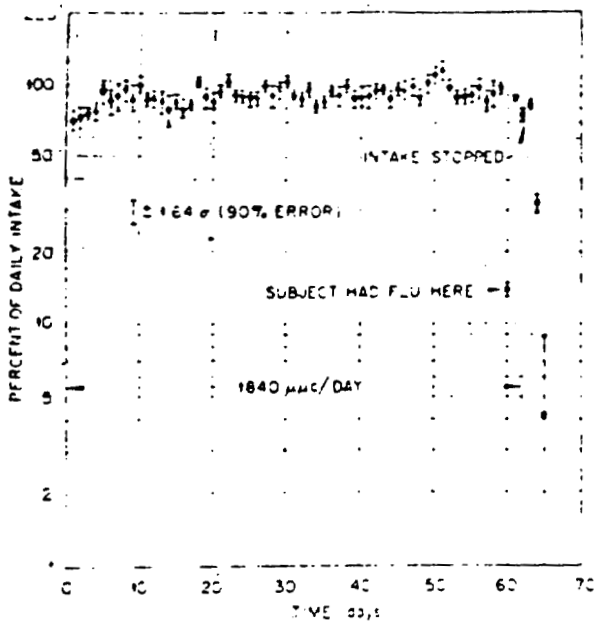

FIG. 17. Daily urinary excretion of I^{131}, subject C ingesting 1840 $\mu\mu c$ I^{131} daily in resin-treated milk for 63 days.

fecal excretion for this subject are shown in Fig.

The cumulative intake plots as a step function because of the discrete intakes. The cumulative fecal excretion was estimated from the two fecal excretion measurements, i.e. it was assumed that 4 per cent of the ingested dose was excreted per day. From these measurements

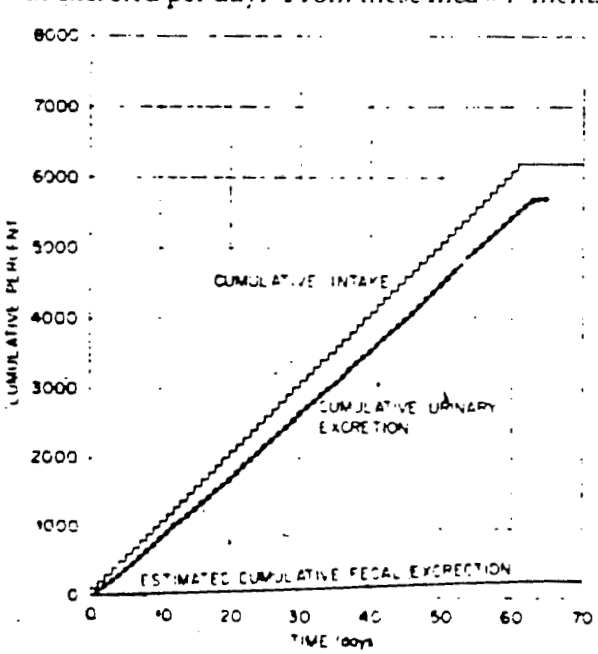

FIG. 18. Cumulative intake and excretion for subject C ingesting 1840 $\mu\mu c$ I^{131} daily for 63 days.

of intake and excretion, an estimate of body burden can be made. However, this is more than likely an upper-bound estimate of the body burden, because the data cannot be corrected for the fraction undergoing radiological decay in the body.

Figure 19 presents the graph of the estimated body burden. The body burden is noted to be a discontinuous function of time. This is due to the discrete intake of daily amounts and the rapid urinary excretion of a large fraction of the intake. Also plotted for purposes of comparison is the ICRP/NCRP-predicted body burden. Note that it passes above the estimated body burden. To bring these curves together, f_1 was

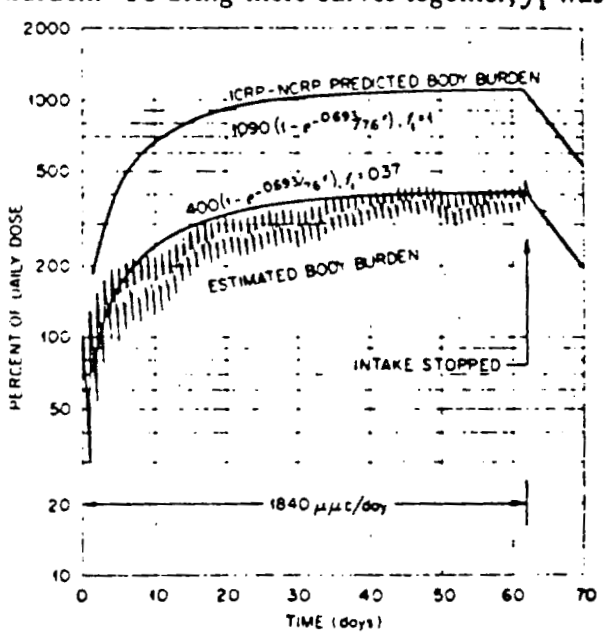

FIG. 19. Estimated body burden of subject C ingesting 1840 $\mu\mu c$ I^{131} daily for 63 days.

arbitrarily set equal to ~0.37 instead of 1, and then the predicted-body-burden curve would agree more closely with the estimated-body-burden data.

From these data and the thyroid-gland data, an estimate of f_2 can be obtained. Since the asymptotic body-burden level is ~400 per cent of daily intake and the daily intake was 1840 $\mu\mu c$/day, then $4 \times 1840\ \mu\mu c = 7360\ \mu\mu c$ are present in the body. As shown in Fig. 14, 1514 $\mu\mu c$ are present in the thyroid at equilibrium. Thus, $f_2 = 1514/7360 = 0.21$.

Two whole-body measurements were also made on subject C from which an estimate of f_2 can be computed. The two measurements were

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~1.5 nc (±2 nc) and 4.2 nc (±3 nc); the average is ~3 nc. This is less than the above 7.4 nc estimate, probably due to the fact that the 7.4 nc estimate was obtained by subtracting the cumulative excretion values from the cumulative intake values. This can be shown to be an overestimate of body burden.

The average f_2 value estimated from counts on the whole body and thyroid gland is 0.4.

DISCUSSION

Comparison of parameters T_b, f_w, and f_2 estimated in this study with values estimated by others

Gathering together the values of T_b estimated from the data appearing in Tables 2 and 4, we find that the average is 74 days ± 70 days (one standard deviation). The range is from 37 to 153 days. This mean value does not differ significantly from the corrected value of 92 days implicit in the reports of ICRP and NCRP. Also, it does not differ from the 92.4-day value for the longest-term component of Lushbaugh's whole-body-retention equation[8,9]

$$R(t) = 0.815e^{-\frac{0.693t}{0.33}} - 0.185e^{-\frac{0.693t}{92.4}}, \ t \text{ in days.}$$

In LUSHBAUGH's study[9] the subjects took orally 8 μc of I^{131} as NaI.

The average f_w computed from data in Tables 2 and 4 is 0.16 ± 0.08. The range is 0.08 to 0.28. The above value is not significantly different from ICRP's value of 0.3 at the 95 per cent confidence level.

It is clear that one of the reasons why the mean T_b and f_w values do not differ significantly from the ICRP values is connected with the large variance associated with the mean values. More data are needed on many different subjects to decrease the standard error of the mean values. It appears from this study that the ICRP values can be considered to be conservative values.

Validity of estimated f_2 value

One may use the multiple-exponential model to check on the validity of the f_2 value estimated from the body burden obtained by differencing the intake and excretion of subject C and show that this difference is an overestimate of body burden. To prove this in a somewhat rigorous fashion, consider equation (14). When integrated to t units of time, it reads

$$\int_0^t E_e\,dt = I\sum_j \frac{a_j\lambda_j'}{\lambda_j^2}\left[\lambda_j t - (1 - e^{-\lambda_j t})\right] \quad (17)$$

This is the cumulative excretion to be expected in the case of a continuous intake of a constant amount of material, I, each day. We subtract this from the cumulative intake It to obtain the difference d or

$$d = I\left[t\left(1 - \sum a_j\frac{\lambda_j'}{\lambda_j}\right) + \sum a_j\frac{\lambda_j'}{\lambda_j^2}(1 - e^{-\lambda_j t})\right]. \quad (18)$$

Now when $\lambda_j' = \lambda_j$, i.e. we are dealing with a long-lived emitter present in the body, and because $\Sigma a_j = 1$, we have $d = R(t)$, as can be seen from equations (14) and (18). For I^{131} $\lambda_j' \neq \lambda_j$ and the quantity

$$\sum a_j\frac{\lambda_j'}{\lambda_j} < 1$$

and thus d is not a valid estimate of the body burden R and is in fact an overestimate.

What then is a good estimate of body burden? Also, since we have a crude measurement of body burden for subject C, how good is it? To gain some insight we need to calculate a theoretical excretion curve and whole-body-retention curve. To do this we employ equations (15) and (16) and some estimates of the parameters λ_j and a_j. We assume two exponential components and that the longer-term component has the same parameter values as the equation for the thyroid-gland data, i.e. we let $\lambda_2 = 0.101$ day^{-1} and $a_2 = 0.08$. Since $a_1 + a_2 = 1$, then $a_1 = 0.92$. For λ_1 we assume it to be the same as subject A's (Fig. 9), i.e. $\lambda_1 = 1.47$ day^{-1}. Thus, the equation for retention is

$$R(t + t') = I_0\left[0.92\left(\frac{e^{1.47} - e^{-1.47t}}{e^{1.47} - 1}\right)e^{-1.47t'} + 0.08\left(\frac{e^{0.101} - e^{-0.101t}}{e^{0.101} - 1}\right)e^{-0.101t'}\right], \quad (19)$$

while that for excretion is

$$\varepsilon(t + 1) = \left[I_0\left(0.91\,\frac{1 - e^{-1.88}}{1 - e^{-1.47}}\right)(1 - e^{-1.47(t+1)}) + 0.09\left(\frac{1 - e^{-0.016}}{1 - e^{-0.101}}\right)(1 - e^{-0.101(t+1)})\right]. \quad (20)$$

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In equation (19) let $t' = 0$ and $t' = 1$, i.e. calculate the retention at the time of intake ($t' = 0$) and just before the next intake ($t' = 1$). Then we have the following two equations:

$$R(t + 0) = I_0[2.16 - 0.27e^{-1.47t} - 0.85e^{-0.101t}]$$

and

$$R(t + 1) = I_0[1.16 - 0.06e^{-1.47t} - 0.77e^{-0.101t}]. \quad (21)$$

The excretion-curve equation will be

$$\varepsilon(t + 1) = I_0[0.90 - 0.89e^{-1.47(t+1)} - 0.014e^{-0.101(t+1)}]. \quad (22)$$

Now note from equations (21) and (22) that when $t \to \infty$

$$\left.\begin{array}{l} R(\infty) \to 2.16\ I_0 \text{ just after an intake,} \\ R(\infty) \to 1.16\ I_0 \text{ just before the next intake,} \\ \varepsilon(\infty) \to 0.90\ I_0 \text{ for all integral times} \end{array}\right\} \quad (23)$$

i.e. the asymptotic body-burden curve fluctuates between 2.2 I_0 to 1.2 I_0 and the excretion curve only rises to 0.90 I_0. A material balance is not to be expected because of radiological decay of the I^{131} in its passage through the body. In fact ~10 per cent of the daily intake undergoes decay in the body (equation (23)). This is to be compared with the measured excretion rates for subject C. In Fig. 17, when equilibrium was reached he excreted an average of ~95 per cent per day in urine and ~4 per cent per day in feces, giving a total of ~99 per cent per day and not 90 per cent per day. Why? This might be due to the fact that the excreta samples were corrected for radiological decay by multiplication by $e^{0.086(t_a - t)}$ where t_a is the time of analysis measured from t and $t + 1$ is the time of voiding. If we correct the measured amounts back to the time $t + 1$ of voiding, then we would have $0.99e^{-0.086}$ ~0.90 per day.

Since I_0 for subject C is 1840 $\mu\mu c$/day, then the body burden at equilibrium fluctuates between 4.0 and 2.2 nc. This is in agreement with the values of 1.51 and 4.2 nc as estimated from the whole-body counter. Thus, it would appear from these admittedly crude and elementary considerations that f_2 should range between ~0.36 and ~1.0. The average value, 0.68, is somewhat different from the value 0.20 employed by ICRP. However, this cannot be said to be an adequate estimate of or check on f_2. More human data for the case of chronic exposure are needed.

Extrapolations from single intake to continuous intake

We have found in limited studies of two individuals that the parameters reflected in the thyroid-gland uptake after ingestion of a single intake of I^{131} appear to be applicable for extrapolation to the case of continuous intake (Figs. 10 and 11). However, the extrapolated thyroid-gland burdens are noted to be somewhat in excess of the measured burdens. Why? One reason for the occurrence of the overestimate is that there is a lag period in thyroid-gland uptake (Fig. 4), and the continuous-intake model does not contain a correction for this lag time. Better agreement should be obtained by extrapolating a two-component retention equation for the thyroid-gland-uptake data. Another reason for the overestimate is that the intake of I^{131} in dietary milk was decreased during the ingestion of resin-treated milk. Thus the background level in the thyroid gland is probably not constant, whereas a constant background level was subtracted from the measurements. More experimental data are needed here too. More attention needs to be paid to the fluctuation of the background levels before ingestion of the milk containing a known quantity of I^{131} and to the decrease in the background level of the thyroid when the subject terminates his ingestion of dietary milk.

Thyroid-gland uptake during or after ingestion of resin-treated milk containing I^{131}

We do not have sufficient data to determine whether or not the metabolism of the protein-bound I^{131} is different from ionic I^{131} in milk. It can be speculated that when the milk arrives in the stomach, the HCl in gastric juice or enzymes will set the bound I^{131} free and the metabolism of protein-bound iodine will not be materially different from metabolism of ionic iodine. However, more data are needed here to more adequately establish if there is a difference in thyroid uptake when resin-treated and untreated milk are ingested.

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$(MPC)_w$ Based on these data

Even though the biological parameters do not significantly differ from ICRP's values, we can compute an $(MPC)_w$. We find that it is 4×10^{-5} $\mu c/cm^3$ (168-hr week) instead of 2×10^{-5} $\mu c/cm^3$ (ICRP's value) or only different by a factor of 2. Actually, if the 92-day value of T_b were employed in ICRP's calculation of $(MPC)_w$ rather than the 138-day value, then $(MPC)_w = 3 \times 10^{-5}$ $\mu c/cm^3$ and not 2×10^{-5} $\mu c/cm^3$. Thus, the $(MPC)_w$ calculated from the data obtained in our studies only differs by a factor of 1.3.

SUMMARY AND CONCLUSIONS

In order to obtain some data on the thyroid-gland uptake of I^{131} during and after ingestion of resin-treated milk and to test assumptions made by ICRP and NCRP regarding extrapolations of data from single intake to the case of continuous intake, some exploratory studies were conducted in which five male volunteers ingested resin-treated milk containing I^{131}. The five volunteers ingested daily, for periods ranging from 4 to 63 consecutive days, constant doses of I^{131} of either 150 or 1840 $\mu\mu c$. Thyroid uptake was measured with a γ-ray scintillation counter. Two of the subjects at a later time ingested a single high dose of 92,000 $\mu\mu c$. From these single-intake data, f_w (the fraction passing from the gut to the thyroid) and T_b (the biological half-life) were estimated. With these parameter values and the ICRP-NCRP single-exponential model for estimating thyroid burden as a function of time during a continuous and constant intake, predictions of the thyroid burden could be made and compared with the measured burden. The predicted burdens were slightly in excess of the measured burdens, probably because there were a lag time and a decreasing background in the thyroid-gland uptake.

Two subjects ingested the resin-treated milk, one for 8 and one for 63 consecutive days, and the thyroid uptake was measured with a scintillation counter. After the intake was stopped, the thyroid gland was counted, and the biological half-life and f_w were estimated from these measurements. Then, predictions were made of the burden during intake. These predictions agreed favorably with the measured burdens, but for the subject ingesting for 63 days there was also a slight overestimate. Since the fifth subject ingested milk containing I^{131} for only 4 consecutive days, the data were not adequate to estimate T_b and f_w.

From these studies the mean T_b was 74 ($\pm$70) days and ranged from 37 to 153 days. The mean f_w was 0.16 ($\pm$0.08) and ranged from 0.08 to 0.28. These values are not significantly different from the corrected ICRP values of $T_b = 92$ days and $f_w = 0.3$.

Urinary-excretion data and fecal-excretion data were obtained in this study. An average of 64 ($\pm$5) per cent of the ingested dose was excreted in urine during the first day after a single intake. In a period of 5 days after intake of a single dose, $\sim$1.9 per cent of the dose was excreted in feces. An average of about 4 per cent of the daily intake, as estimated from two samples, was excreted per day in feces on the fifty-fifth and fifty-sixth day of continuous intake of 1840 $\mu\mu c$ per day. The daily urinary excretion averaged about 95 per cent per day when equilibrium was apparently reached. (These averages correspond to excretion corrected back to the preceding day's intake.) Actually, at equilibrium 10 per cent of the daily intake undergoes radiological decay in the body.

An estimate of the body burden for the subject ingesting sixty-three daily doses was made by differencing the cumulative-intake and cumulative-excretion data. An estimate of f_2 from this body burden and thyroid-gland burden was found to be $\sim$0.21. However, mathematical studies showed that this method of estimating body burden leads to an overestimate, and thus 0.21 is a lower-bound estimate. From only two measurements of body burden and thyroid-gland burden, it is indicated that f_2 is about 0.4. From mathematical analysis it is indicated that f_2 fluctuated between $\sim$0.36 and $\sim$1, the average being $\sim$0.68. More data are needed to establish adequately the value of f_2.

The present study suggests that the single-intake data can be extrapolated to the case of continual intake when the parameters are estimated for each individual. It is also suggested that the single-exponential-compartment model of ICRP is a fairly adequate representation of the data on I^{131} uptake by human thyroid glands. The foregoing statements are only suggestions, however, and they rest on

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relatively few cases observed over periods of time that are short compared with a 50-year-exposure period. It is indicated from these few human studies that the ICRP-NCRP recommendations of $(MPC)_w$ are conservative and differ by only a factor of ~ 2.

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