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Human Subjects Project

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MAXIMUM PERMISSIBLE AMOUNTS OF NATURAL URANIUM IN THE BODY, AIR AND DRINKING WATER BASED ON HUMAN EXPERIMENTAL DATA

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Abstract—The distribution of uranium in the human body following intravenous injections of hexavalent and tetravelaent uranium has been studied in the case of eight terminal patients. At the dosage levels used the data indicate that the kidneys and the skeleton are the principal sites of deposition with approximately equal amounts in each. On this basis the kidneys become the critical organ and the toxic effect of the uranium rather than radiation damage becomes the limiting effect in determining the maximum permissible concentrations (m.p.c.) for occupational exposure. The influence of particle size on retention of inhaled material is considered in interpreting some of the available human data.

INTRODUCTION

A SPECIFIC shortcoming in the maximum permissible amounts in the body, q, in the air man breathes, $(\text{m.p.c.})_a$ or m.a.c., and in his drinking water, $(\text{m.p.c.})_w$, recommended by the National Committee on Radiation Protection[1] (NCRP), or the International Commission on Radiological Protection[2] (ICRP), or by AEC supported laboratories,[3] long recognized by these official bodies and also by workers in the field as well as others, is the inherent uncertainty in the values resulting from extrapolation of laboratory animal data to man. Extrapolation to man, using data obtained from controlled laboratory experiments with small research animals, a practice performed of necessity for many self-evident reasons, suffers primarily because of lack of knowledge as to how the extrapolation should be adequately performed. Because of this the values lack the desired certainty.

Some reduction in the uncertainty was achieved during investigation of the chemical toxicity of uranium on hospital patients by BASSETT *et al.*[4] Complete urinary uranium excretion studies, tests of renal function and blood studies were made and from these results the injected uranium dose which produces minimal damage to the kidney tubule of man was determined. However, autopsy data were not obtained since none of the subjects were terminal patients. Consequently, the uncertainty, in so far as the distribution of uranium was concerned, was not reduced or could not even be determined. However, late in 1953 an experiment to determine the distribution and excretion of uranium in man was initiated and the data obtained are believed to be an initial step, and a major one in overcoming the aforementioned difficulty.

Human biopsy and autopsy data on terminal patients have been made available in a careful experiment on the distribution and excretion of uranium in man,[5–7] in a co-operative study by the Health Physics Division, Oak Ridge National Laboratory and the Department of Neurosurgery, Massachusetts General Hospital. Uranium solutions, enriched with isotopes of U^{235} or U^{233}, were administered intravenously to patients who were in terminal stages of irreversible central nervous system disease but who were otherwise in generally good physical condition. From measurements of uranium

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found in biopsy and autopsy tissues the parameter values characterizing the distribution and excretion of uranium in man were determined. In addition, the burden of uranium in man to produce a definite nephrotoxic syndrome was determined from clinical tests on blood, from tests of renal function and from pathological examination of kidney tissues.

The purpose of this report is to present these terminal patient data together with the human parameter values derived from careful consideration of the data and the values for maximum permissible amounts, viz. q, $(\text{m.p.c.})_a$, and $(\text{m.p.c.})_w$ based on these findings. While the number of cases observed is small and the conclusions somewhat indeterminate because of the rather large variability found, still the general paucity of human data warrants the careful consideration of any results suggested by these data. It is concluded from considerations of the terminal patient data, patient data of BASSETT *et al.*,[4] and some data on industrial workers, that the primary hazard from chronic exposure to compounds of natural uranium regardless of their solubility, is due to chemical toxicity on the kidneys. These data would indicate that the safe burden in the kidney, dictated by considerations of chemical toxicity, is one-tenth the burden deemed permissible from radiological considerations. Also, at these dose levels, the human kidneys seem to deposit and retain as much uranium as does the skeleton. Therefore, the biological half-life in the kidneys seems to be the same as that in the skeleton. This finding was not evidenced in small research animals. If the biological half-life is increased, the $(\text{m.p.c.})_a$ and $(\text{m.p.c.})_w$ for soluble compounds is lower than that recommended by the ICRP and NCRP. For the case of insoluble compounds it is suggested that on the basis of dissolution and subsequent absorption of uranium from the lungs, the maximum permissible lung burden based on radiation exposure is too high; consequently, the $(\text{m.p.c.})_a$ for insoluble compounds of natural uranium is also too high. In order to determine the $(\text{m.p.c.})_a$ it was assumed, necessarily, that the retention and distribution of inhaled particulates appearing in Table C. III of the ICRP,[8] apply.

Specific data on the fate of inhaled uranium aerosols of different particle sizes are lacking for small animals, let alone human data, and consequently, the maximum permissible concentration values are not certain. It is believed that this inadequacy of information is due in part to the lack of an adequate hypothesis from which an experiment could be designed to obtain information for determining maximum permissible concentrations as a function of particle size distribution. A hypothesis, derived from considerations of a few small animal data obtained by LABELLE,[9] which takes particle size and its effect upon deposition and lung clearance into consideration, is advanced in this report. This concept has been applied to the animal inhalation data obtained by the University of Rochester and to some lung autopsy measurements of two industrial workers reported by EISENBUD and QUIGLEY.[10] The results of these applications are presented and discussed. Some specific suggestions and recommendations for experiments to obtain data pertinent to this problem are also presented.

SOLUBLE COMPOUNDS

Summary of terminal patient data

A summary of those results found in the experiment on the distribution and excretion of uranium in man pertinent to the problem of setting m.p.c.'s follows. The details of the experiment may be found elsewhere.[5–7]

Eight terminal brain tumor patients, six of which were comatose, whose average age was 45 years (they ranged from 26 to 63 years) were intravenously administered prepared solutions of uranium. Six patients were injected with hexavalent uranium while the other two were administered tetravalent uranium as uranium tetrachloride. The injections ranged from 4 to 50 mg of uranium.

Hexavalent uranium was found to clear rapidly from the blood into the urine. Sixty nine per cent of the injected dose was excreted in the first day (Table 1). Uranium excretion approaches the power function law (Figs. 1 and 2)[6] after about 10 hr post injection.

Autopsy measurements reveal that hexavalent uranium chiefly stores in bones and kidneys while tetravalent uranium prefers storage in

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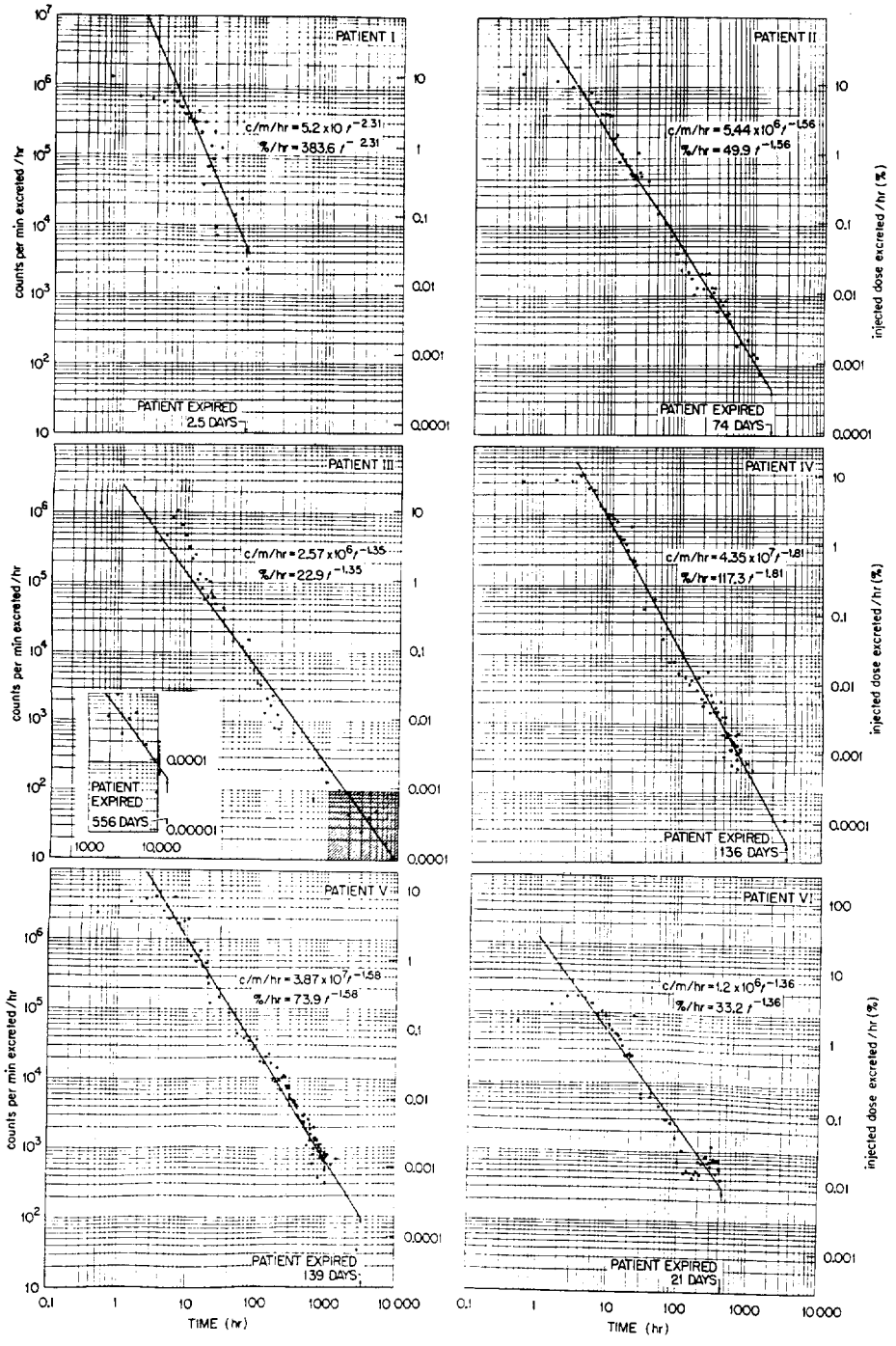

FIG. 1. Power function excretion equations.

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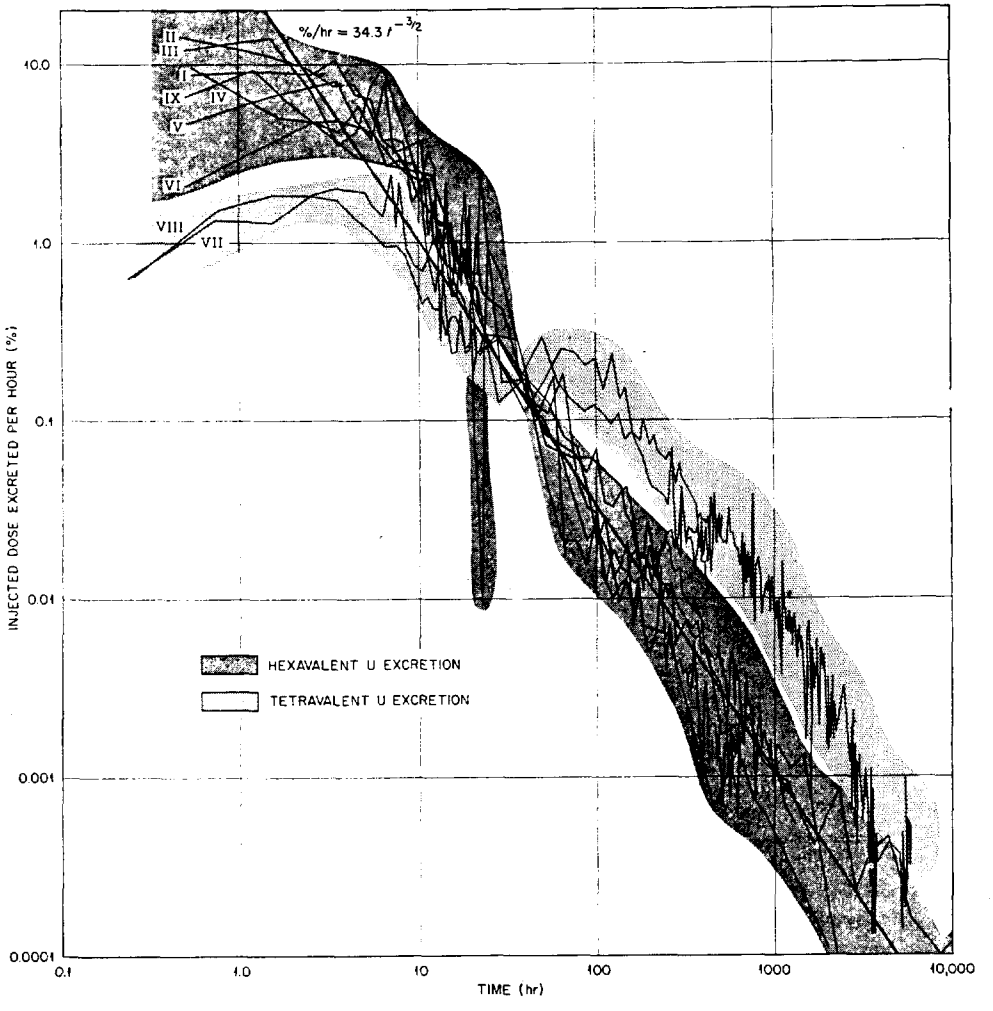

FIG. 2. Urinary rate of excretion for 8 terminal brain tumor patients following intravenous injection.

Table 1. *Percentage of injected dose excreted in first* 24 hr *collection of urine*

Patient*	I	II	III	IV	V	VI	VII	VIII
	59.4	78.0	83.8	77.2	66.5	49.1	20.0	16.9
Average			69.0				18.5	

* Patients I–VI injected with hexavalent uranium.

liver and bones (Table 2). Also, the uranium burdens in bone and kidneys for practical purposes are not essentially different from each other; they contain nearly identical amounts of uranium. This means the biological half-life for bones is the same as that for kidneys.

The biological half-life for bones is different for each patient (Fig. 3). It increases in proportion to $t^{4/5}$ where t is the time of expiration measured from the time of injection (Fig. 4). Fitting a single exponential term to the bone autopsy data by the usual least-squares procedure yields the equation $0.03 \exp(-0.693t/280)$ with t in units of days (Fig. 5, curve 1) which curve poorly fits the data and is inadequate because the biological half-life depends on the expiration time. A better fit of these bone

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Table 2. Percentage of injected dose per standard man organ or tissue for six terminal brain tumor patients

Organ of tissue	Sample amount (g)	Patient no. I	VI	II	V	III	VIII
		Expiration time (days)					
		2.5	18	74	139	566	21
Bone	7000	10.0	4.9	1.4	0.6	1.3	14.4
Kidney	300	16.6	7.2	0.7	1.2	0.4	1.1
Muscle	30,000	1.2	2.1	0.9	0.3	0.06	0.4
Skin and subcutaneous tissue	6100	1.8	1.0	0.1	0.06		
Fat	10,000	0.6	0.6			0.04	
Red marrow	1500			0.02	0.03	0.1	
Blood	5400	1.0	0.2	0.005	0.002	0.004	0.08
Stomach	250	0.08	0.02	0.003	0.001	0.001	
Small intestine	1100	0.2	0.2	0.03	0.01	0.006	0.1
Liver	1700	1.8	1.1	0.2	0.2	0.05	9.2
Brain	1500						
Lungs	1000	0.5	0.4	0.03	0.02	0.008	0.3
Heart	300	0.06	0.02	0.003	0.006	0.002	0.004
Spleen	300	0.6	0.2	0.1	0.02	0.006	5.6
Urinary bladder	150	0.03		0.002	0.001	0.0003	0.06
Pancreas	70	0.7	0.008	0.008	0.0006	0.0004	
Testes	40		0.01	0.008	0.002	0.002	0.008
Thyroid gland	20		0.003	0.0002	0.0001	0.0002	0.0009
Prostate gland	20		0.003	0.0004	0.0004	0.0001	0.003
Adrenal gland	20	0.02	0.01	0.003	0.001	0.0004	0.02
Miscellaneous tissues (blood vessels, cartilage, nerves, etc)	390	0.3	0.2	0.04	0.002	0.002	0.04
Total in tissues		35	18	4	3	2	
Total excreted in urine		69	63	92	85	98	

Patients I, VI, II, V and III injected with $UO_2(NO_3)_2 \cdot 6H_2O$; Patient VIII injected with UCl_4.

autopsy data is given by the equation 0.25 exp $(-1.19t^{1/5})$ (Fig. 5, curve 2). In order to determine a half-life with which to calculate m.p.c.'s the equation 0.25 exp $(-1.19t^{1/5})$ was integrated from $t = 0$ to $t = 70$ years and the area given by this integral is found to be identical to the integral of 0.11 exp $(-0.693t/300)$ (Fig. 5, curve 3) over the same time interval. Thus, from these considerations it is said that the biological half-life for uranium in bone is 300 days and it is the same in kidneys since kidneys contain the same burden as the bone.

In the study of chemical toxicity of uranium, LUESSENHOP *et al.* found that a body burden of 0.1 mg/kg of body weight produces a definite nephrotoxic effect.

Power function equations were fitted to the body burden measurements (Fig. 6) and to the urinary excretion measurements (Fig. 2). Excretion measurements made in the first 10 hr were omitted from the calculations. The

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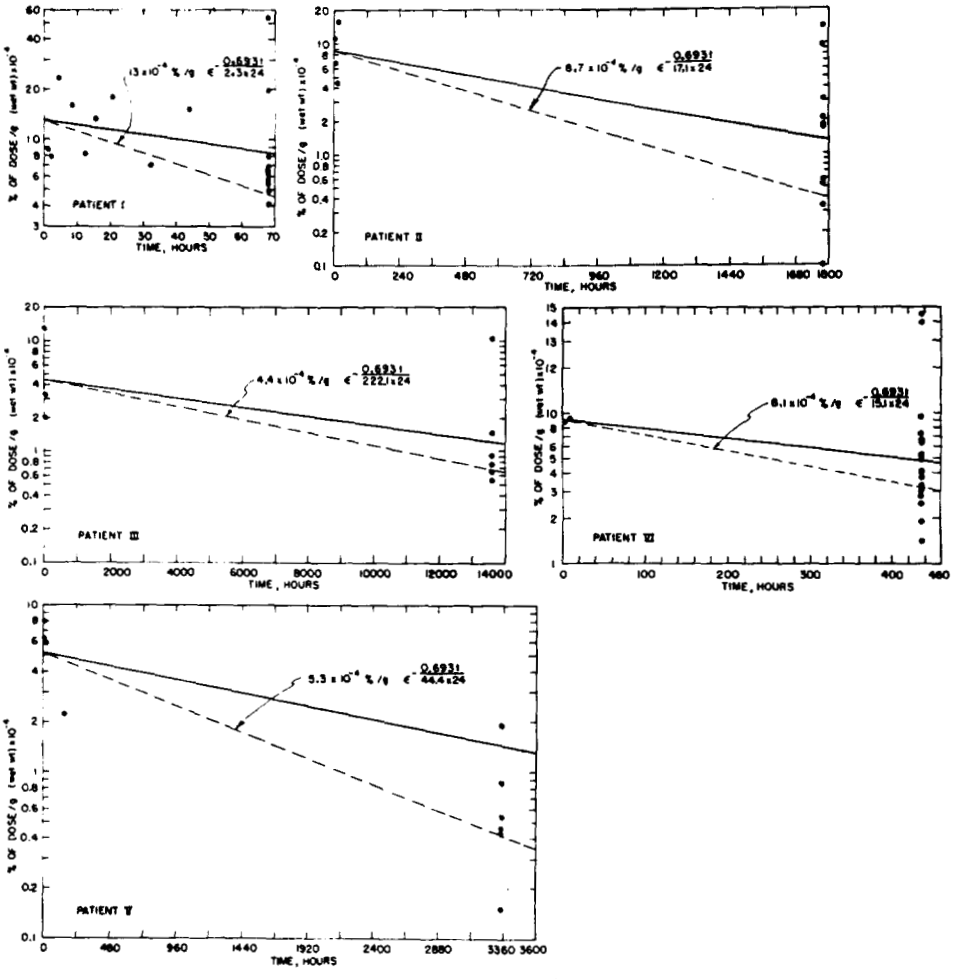

FIG. 3. Best fitting exponential curves for U VI bone biopsy and autopsy samples. The broken curve is that for compact bone samples. The solid curve is for all bone samples.

best fitting equation for body burden is $0.6t^{-1/2}$. The equation for organ burden in bone (or in kidney) is $0.20t^{-1/2}$. Hence, f_2, the fraction in the critical organ relative to that in the total body is $\frac{1}{3}$. The best fitting power function excretion equation is 34.3 per cent/hr $t^{-3/2}$, where t is in hours.

Comparison of terminal patient data with other data

The results of this study with the terminal patients are not in accord with those results obtained from small animals.[2,3] In small animals the principal organ for hexavalent uranium storage is bone; 85 per cent of the uranium in the body resides in bone. The data presented here suggest that in humans there are two principal storage organs, bones and kidneys; 33.3 per cent of the uranium residing in each organ. The biological half-life in kidneys of small animals is 30 days and f_2', the fraction going from blood to kidneys is 0.33. In humans the biological half-life is 300 days and f_2' is 0.11.

In general, there was very little, if any, difference exhibited in the urinary excretion of hexavalent uranium by patients of BASSETT *et al.* (Rochester patients). This is surprising in view of the fact that their clinical states were different. None of the Rochester patients had

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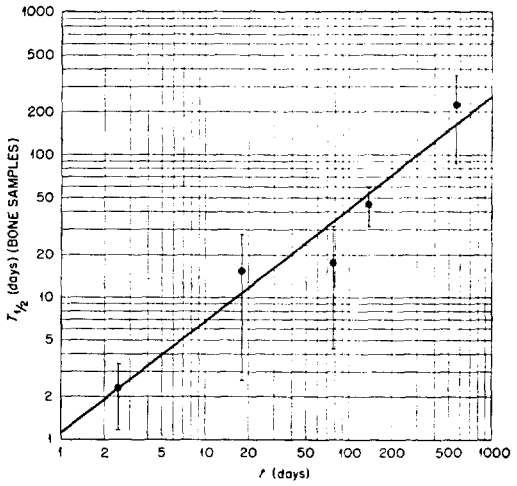

FIG. 4. Biological half-life of uranium in bone plotted vs. expiration time.

maladies comparable in severity to the terminal patients (Boston patients). There was a slight difference in experimental technique with respect to: (a) sample collection (Rochester patients voided at natural times whereas Boston patients were catheterized); and (b) level of injection dose (Rochester patients were

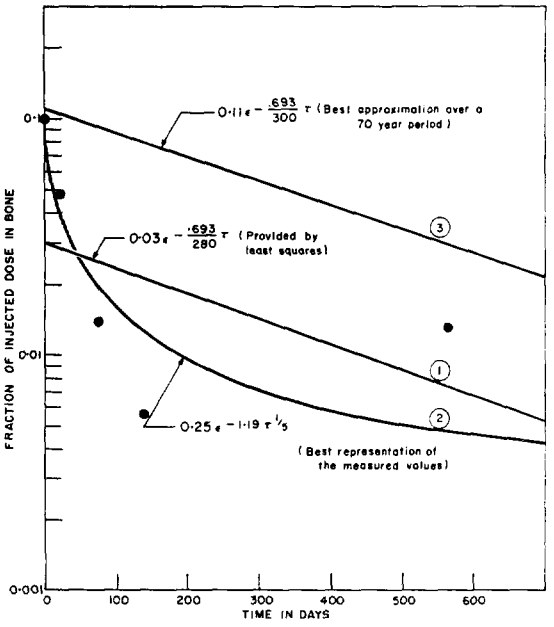

FIG. 5. Biological half-life of uranium in bone.

administered smaller (0.4–4 mg) doses of uranyl nitrate hexahydrate). The urinary excretion findings were similar in these respects: (a) the best fitting power function excretion equation, 57.2 per cent/hr $t^{-1.8}$ (Fig. 7) differed slightly from that of Boston patients, viz. $34.3t^{-1.5}$; and (b) the amount of uranium excreted in the first day was essentially the same, 76 per cent as compared with 69 per cent.

Maximum permissible body burden, q

Based on chemical toxicity. NEUMAN[12] recommended a safe kidney burden of 2–3 μg/g of kidney for chronic exposure. Since NEUMAN'S

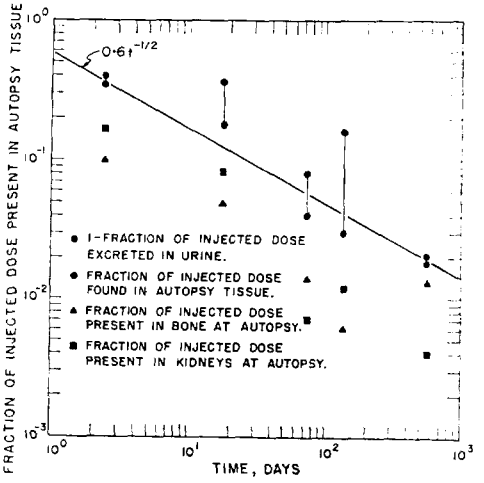

FIG. 6. Uranium burden in organs and body.

recommendation (1948) additional human data have been made available upon which to base a safe burden in kidney.

In the experiments with the terminal patients, the value of LUESSENHOP *et al.*, 0.1 mg/kg body weight, assuming a 70 kg man and 300 g of kidney and one-third of the dose in kidney, corresponds to 6 μg/g of kidney.

EISENBUD and QUIGLEY[10] have urinary excretion data from five individuals who received a short massive exposure to uranium hexafluoride. Abnormal urinary findings were said to have persisted for a few days but in all cases they returned to normal, indicating only minimal effects on the kidneys despite the relatively high exposures encountered. The

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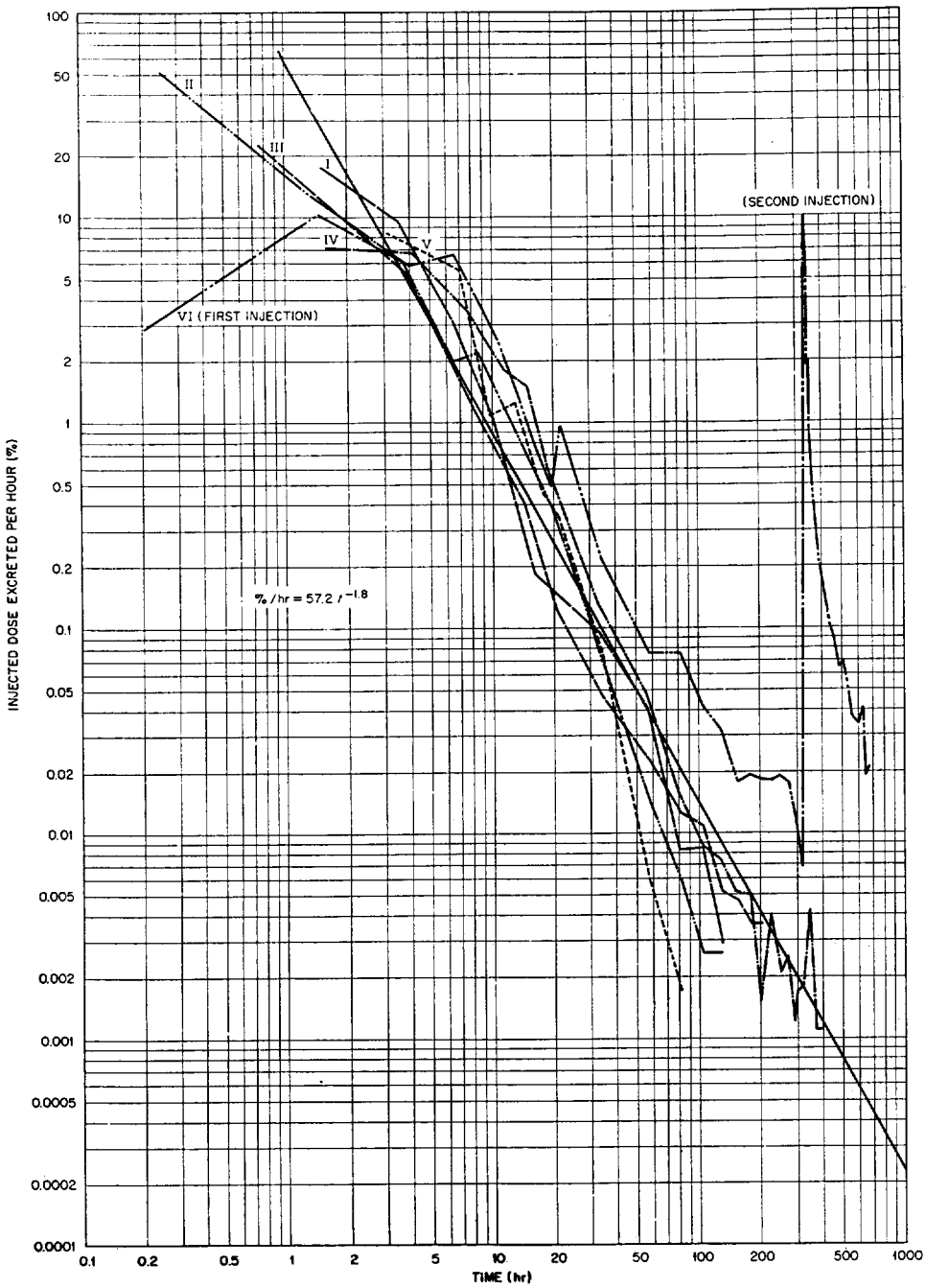

FIG. 7. Urinary rate of excretion for 6 patients at the University of Rochester, following intravenous injection.

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average concentration of uranium in the first days urine of these individuals was 1.28 mg/l. of urine. Assuming 1 l. of urine excreted per day, 69 per cent of the uranium introduced into the blood-stream excreted in the first day, one-third of this amount is in the circulating blood and 300 g of kidney, then this excretion level is found to correspond to 2 μg/g of kidney.

The sixth Rochester patient, studied by BASSETT *et al.*, was administered two intravenous injections of uranyl nitrate hexahydrate, the first of which contained 3.1 mg and the second, injected 17 days after the first, contained 3.1 mg. BASSETT *et al.* concluded tolerance had been reached after the second injection because they noted a slight rise in urinary catalase and protein. These injections correspond to a kidney burden of 4 μg of uranium per g of kidney assuming one-third of the second injection deposited in kidney and that the amount present in the kidney from the first injection is given by the equation $0.20It^{-1/2}$, which equation fits the kidney data of the terminal patients. (In the equation I is the injection dose. The time t is in units of days.)

The average of these three values, 2, 4 and 6 μg/g of kidney is 4 μg/g of kidney. This is slightly different from NEUMAN's recommendation of 2–3 μg/g of kidney as a safe burden for chronic exposure and assuming 300 g of kidney and one-third stored in the body resides in kidney, then the safe burden is 2700 μg of U_{nat}. In terms of radioactivity this is equivalent to 0.0009 μc* of U_{nat}. Thus, from the standpoint of chemical toxicity, the permissible body burden is 0.0009 μc U_{nat}.

Based on radiological considerations and the human data. When the human parameter values are used to calculate qf_2, the burden to give 0.3 rem/week to the kidney, it is found that

$$qf_2 = 8.4 \times 10^{-4} m/\Sigma E(r.b.e.)N = 0.0026\ \mu\text{c U}_{\text{nat}},$$

where $m = 300$ g and $\Sigma E(r.b.e.)N = 94$ MeV.[2] Setting $f_2 = \frac{1}{3}$ and solving for q yields $q = 0.008\ \mu$c U_{nat}. Thus, on the basis of radiation exposure, when the body contains 0.008 μc U_{nat}, the kidney, the critical organ receives 0.3 rem/week. However, 0.008 μc of U_{nat} is nine times that deemed permissible from chemical toxicity considerations. Because of this large factor, it is necessary to accept the value, 0.0009 μc U_{nat}, based on chemical toxicity considerations.

Maximum permissible concentration in air, $(m.p.c.)_a$, based on chemical toxicity and human data

When the $(\text{m.p.c.})_a$ is calculated with either the exponential law or the power function law retention it is found that they give essentially the same values, viz. $1 \times 10^{-12}\ \mu$c U_{nat}/cm^3 of air.

$$(\text{m.p.c.})_a = \begin{cases} \dfrac{3.5 \times 10^{-8}\, qf_2}{Tf_a(1 - \exp(-0.693t/T))} \\ \qquad = 1.3 \times 10^{-12}\ \mu\text{c U}_{\text{nat}}/\text{cm}^3 \\ \dfrac{5 \times 10^{-8}\, q}{f_a' \int_0^t 0.6(t-\tau)^{-\frac{1}{2}} d\tau} \\ \qquad = 1.1 \times 10^{-12}\ \mu\text{cU}_{\text{nat}}/\text{cm}^3. \end{cases}$$

where $q = 0.0009\ \mu$c, $f_2 = \frac{1}{3}$, $f_2' = 0.11$, $T = 300$ days, $f_a' = (0.25 + f_1)f_2'$, $f_1 = 10^{-4}$, $t = 1.825 \times 10^4$ days (50 years) and $f_a' = f_a/f_2'$. In the equations it is to be noted that human parameter values are used in all cases except for the values of f_1 and f_a' (fraction of inhaled particulates absorbed into the bloodstream) which values were obtained from ICRP.[13] There are no human experimental measurements of these latter values and this adds to the uncertainty of $(\text{m.p.c.})_a$.

Maximum permissible concentration in water $(m.p.c.)_w$, based on chemical toxicity and human data

When the $(\text{m.p.c.})_w$ is calculated with either the exponential law or the power function law for retention it is found that they yield nearly identical values, $5.8 \times 10^{-6}\ \mu$c/cm^3, and $5.1 \times 10^{-6}\ \mu$c/cm^3, respectively. The equations

* $1\ \mu\text{c U}_{\text{nat}} = 1\ \mu\text{c U}^{238} + 1\ \mu\text{c U}^{234} + \frac{9}{370}\ \text{c}\mu\ \text{U}^{235}$

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for computing these values are:

$$(\text{m.p.c.})_w = \begin{cases} \dfrac{3.15 \times 10^{-4}\, q f_2}{T f_w (1 - \exp(-0.693t/T))} \\ \qquad = 5.8 \times 10^{-6}\ \mu\text{c/cm}^3 \\ \dfrac{4.54 \times 10^{-4} q}{f_1 \int_0^t 0.6(t-\tau)^{-\frac{1}{2}}\, d\tau} \\ \qquad = 5.1 \times 10^{-6}\ \mu\text{c/cm}^3 \end{cases}$$

where $q = 0.0009\ \mu$c, $f_2 = \frac{1}{3}$, $f_w = f_1 f_2' = 5.5 \times 10^{-5}$, $f_1 = 5 \times 10^{-4}$, $f_2' = 0.11$ and $t = 1.825 \times 10^4$ days (50 years) and $T = 300$ days. For practical purposes the value $6 \times 10^{-6}\ \mu$c of U_{nat} per cm^3 of water is selected as the $(\text{m.p.c.})_w$. It is to be noted that the human parameter values are used in the calculations except in the case of f_1, which value was obtained from ICRP,[13] also. Because of the many uncertainties involved the $(\text{m.p.c.})_w$ cannot be considered as determined.

Comparison with other recommendations

The values for q and the m.p.c.'s prescribed from considerations of the human data and chemical toxicity have been found to be substantially lower than those recommended by ICRP or NCRP or the University of Rochester. However, the values recommended by these three bodies have been found to be substantially different from each other, viz. the current ICRP recommendation for occupational exposure (40 hr/week) to soluble compounds of U_{nat} is 270 μg/m^3[14] while NCRP recommendation corresponds to 76 μg/m^3[15] and the University of Rochester recommends 50 μg/m^3[16] (the period of exposure is not cited but it is generally assumed that this concentration is for 40 hr/week). The $(\text{m.p.c.})_a$ based on chemical toxicity and the human data, for occupational exposure, is 9 μg/m^3 which value is a factor of 30 lower than ICRP' recommendation and a factor of 5 lower than the University of Rochester's recommendation.

The basis for the 270 μg/m^3 (this value was suggested by the Harriman, New York, Conference, April 1953) is not indicated by ICRP.[17] Consequently, the reasons for the difference between ICRP value and the NCRP value are not known. Regardless of the reasons, it can be shown that the kidney burden resulting from exposure to 270 μg/m^3, 40 hr/week, assuming the exponential law for retention and employing small animal parameter values, would be 21 μg/g of kidney tissue, seven times higher than the safe burden of 3 μg/g of kidney. Therefore, the ICRP recommendation is believed to be in error.

The basis for the NCRP recommendation is the small animal data obtained by investigators at the University of Rochester. The small factor of difference (1.5) between the NCRP' value, 76 μg/m^3, and the Rochester value, 50 μg/m^3, is due to the assumption, by NCRP, that Rochester's recommendation was for an 8 hr day, 7 days/week, exposure period.[18] A careful examination of the record of the exposure periods for small animals exposed to dusts consisting of soluble compounds of U_{nat} reveals that the animals were exposed for an average of 28 hr/week.* Hence, the 50 μg/m^3 level corresponds to an exposure period of 28 hr/week. If it can be said that animals, continuously (168 hr/week) exposed, would store six times more uranium than that observed and that the toxicological response from continuous exposure would be six times more pronounced, then the $(\text{m.p.c.})_a$ would have to be 9 μg/m^3.

On the basis of these considerations of the small animal findings, the 9 μg/m^3, which is equivalent to $3 \times 10^{-12}\ \mu$c/cm^3, is only a factor of 3 greater than the value recommended on the basis of human data and chemical toxicity.

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* For example, dogs and rats received 1600 hr of exposure in a period of 12 months to four different levels, 0.04, 0.25, 0.40 and 2.0 mg/m^3[19] of $UO_2(NO_3)_2$, while rats and guinea pigs were exposed for 900 hr.[19] These exposure periods represent 31 and 26 hr/week, respectively. Also, dogs and rats were exposed for 1680 hr while rabbits and guinea pigs were exposed for 1200 hr to UF_6 at two different levels, 0.05 and 0.20 mg/m^3.[20] These exposure periods correspond to 33 and 23 hr/week. In addition, dogs and rats were exposed for 1700 hr,[21] rabbits and guinea pigs for 1000 hr,[21] to UCl_4, at two different levels, 0.05 and 0.20 mg/m^3,[21] for 1 year. These exposure periods correspond to 33 and 19 hr/week.

The average of all the above exposure periods is 28 hr/week.

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INSOLUBLE COMPOUNDS

Preliminary considerations of the values of q and $(m.p.c.)_a$ recommended by ICRP and/or NCRP

There are no human data from controlled experiments with which to evaluate the m.p.c.'s for insoluble compounds of U_{nat}. Nevertheless, some elementary considerations of the dissolution of lung stored uranium and its absorption into the bloodstream, lead to the conclusion that the current recommendations are a factor of 10 too high.

Currently, the ICRP recommends $q = 0.01\ \mu c$[14] for insoluble compounds, based on lungs as the critical organ. Consider, the amount entering the bloodstream per day, $\lambda q f_2$, due to dissolution of uranium in lung and its absorption in blood:

$$\lambda q f_2 = 6 \times 10^{-5}\ \mu c/\text{day}$$

where λ, the effective biological decay constant for lungs is $0.693/120\ \text{days}^{-1}$, while $q = 0.01\ \mu c$ and $f_2 = 1$. This amount, $6 \times 10^{-5}\ \mu c/\text{day}$, is ten times higher than the amount entering the bloodstream from daily inhalation of the $(m.p.c.)_a$ of soluble compounds of U_{nat} which is $2 \times 10^7\ (m.p.c.)_a\ f_a' = 5 \times 10^{-6}\ \mu c/\text{day}$, where $(m.p.c.)_a = 1 \times 10^{-12}\ \mu c/cm^3$ and $f_a' = 0.25 = f_a/f_2'$. Thus, the value of q based on radiological considerations, is a factor of 10 too high. Therefore q, on the basis of these chemical toxicity considerations, should be $0.001\ \mu c$.

Because of the above considerations, it is believed that the current $(m.p.c.)_a$, $3 \times 10^{-11}\ \mu c/cm^3$, prescribed by ICRP, for insoluble compounds of U_{nat}, is also high by a factor of ten. Therefore, it is recommended that the $(m.p.c.)_a$ for insoluble compounds, should be $3 \times 10^{-12}\ \mu c/cm^3$.

Comparison with other recommendations

In experiments with the small animals, University of Rochester investigators found that an exposure period of 33 hr/week[22] to an insoluble compound, UO_2, at a dust level of $50\ \mu g/m^3$, resulted in a lung deposition and retention of $12\ \mu g/g$ of lung, after 1 year of exposure. From these data, and on the basis that $25\ \mu g/g$ of lung[23] corresponds to 0.3 rem/week (α-particle r.b.e. = 10), they recommended levels of $50–100\ \mu g/m^3$[23] for application in the field. Again they did not indicate the period of exposure but it may be presumed that it is for 40 hr/week.

Taking into consideration that continuous exposure of these animals could be expected to lead to a lung burden five times greater than that observed, then the level of exposure, $50\ \mu g/m^3$, could be expected to result in a burden of $60\ \mu g/g$ of lung for the case of continuous exposure, 24 hr/day, 7 days/week. Expressing these μg values in terms of μc yields $1 \times 10^{-12}\ \mu c/cm^3$ which is equivalent to a lung burden of $1 \times 10^{-6}\ \mu c/g$ of lung. Assuming 1000 g of lung, the $(m.p.c.)_a$ for insoluble compounds of U_{nat} therefore, would be $1 \times 10^{-12}\ \mu c/cm^3$.

EISENBUD and QUIGLEY[10] have autopsy data on two industrial workers who died from non-occupational causes and were exposed to high concentrations of UF_4 and UO_2 for periods of 1 or 2 years. One worker was exposed for 2 years to an average concentration of 17,000 $\mu g/m^3$ and 10 months later he died and the lung burden measured $0.35\ \mu g/g$. Another worker died 15 months after exposure for a year to $5{,}000\ \mu g/m^3$ and his lungs measured $0.23\ \mu g/g$. There were no measurements listed for kidneys or bones or lymph glands from these workers.

EISENBUD predicted, from the small animal data, that the worker exposed for 2 years would have $600\ \mu g/g$ while the worker exposed for 1 year would have $56\ \mu g/g$. Because of the large difference between the predicted burden and the measured burden, he questioned the application of animal results directly to man without knowledge as to comparative relation of deposition and clearance rates in the two species. He concludes that the safety factor in the $(m.p.c.)_a$ for insoluble compounds is unnecessarily conservative but that more data are needed before an upward revision in the $(m.p.c.)_a$ could be permitted.

It is agreed, more human lung autopsy measurements are needed, but in addition to the measured lung burdens there is need for measurements of the particle sizes inhaled by the workers. It is believed that the large discrepancies can be explained in terms of the

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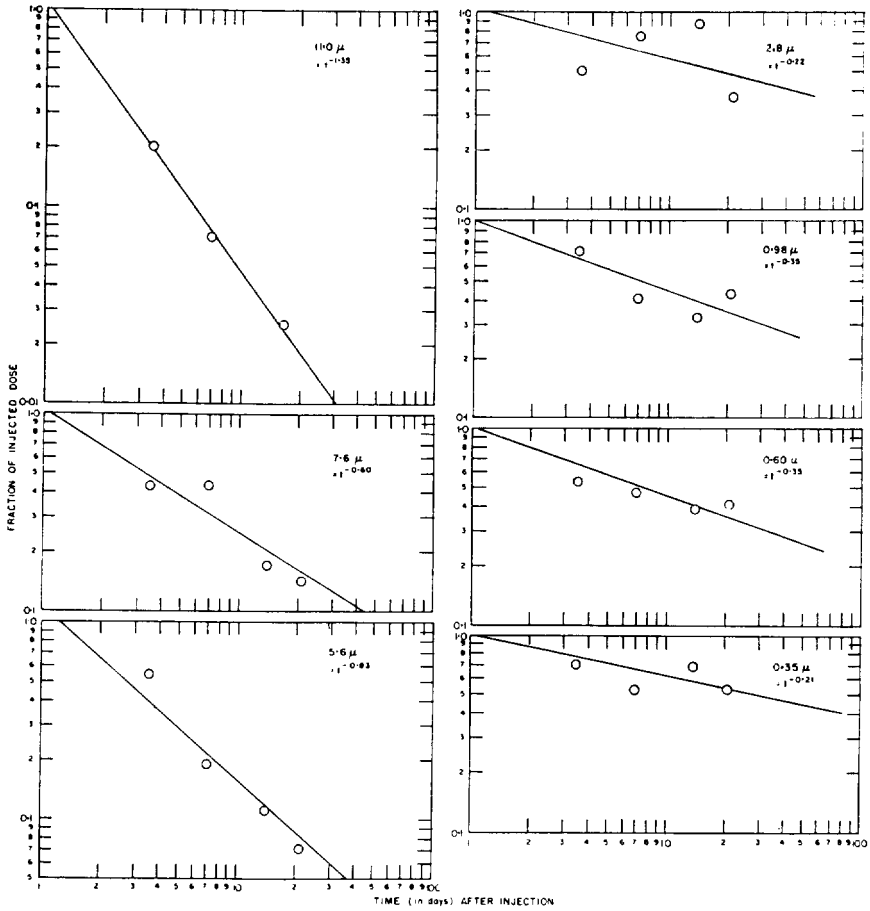

FIG. 8. Time retention of U in lungs of rats after intratracheal injection of various sizes of UO_2 dust particles.

particle size as the following considerations show.

Particles size effect on lung retention and clearance

LABELLE,[9] in an effort to understand the effect of particle size on the toxicological response shown by animals, provided some data which go a long way in understanding the effect of particle size on the retention and clearance of uranium from the respiratory tree. In his experiment, LABELLE intra-tracheally injected slurries of UO_2, composed of different sized particles into rats. He killed these rats at 3, 7, 14 and 21 days after injection and measured the burden in lungs, kidneys and femur. LABELLE graded the oxide particles by an elutriation technique, that of CUMMINGS,[25] and obtained seven different sizes of particles, ranging from 11 to 0.35 μ in diameter. He then injected each rat with a dose of 30 mg/kg of body weight of the seven graded sizes and placed the rats in cages where they stayed until the time of sacrifice.

Log x log graphs of the fraction of the injected uranium plotted versus the time of sacrifice reveals smaller particles are eliminated more slowly from the lungs than larger size particles (Fig. 8). Furthermore, the retention data can be approximately represented with the power function, At^{-n}, while A, the intercept at $t = 1$

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day, is unity and n, the exponent is a function of particle diameter, x. An approximate relationship between the exponent of the power function and the particle diameter is $n(x) = 0.26x^{-0.56}$(Fig. 9).

From the above considerations, a quantitive relationship between retention in lungs at any time t after deposition of a unit amount of uranium is:

$$R(t, x) = t^{-n(x)} \tag{1}$$

where, $R(t, x)$ is the amount present at time t after injection of particles of diameter x, and where:

$$n(x) = 0.26x^{-0.56} \tag{2}$$

In equations (1) and (2) t is in units of days and x is in units of μ.

A concept for determining $(m.p.c.)_a$ as a function of particle size

If the concentration in the air is denoted by $(\text{m.p.c.})_a$, then the amount deposited in the lungs during a time interval $d\tau$ at time τ is $2 \times 10^7(\text{m.p.c.})_a D(x)\, d\tau$ where $D(x)$ is the fraction of the inhaled aerosol deposited in alveolar passageways. The burden in the lung at a later time t, is then:

$$q(x, t) = 2 \times 10^7(\text{m.p.c.})_a \int_0^t D(x)(t - \tau)^{-n(x)}\, d\tau \tag{3}$$

Performing the indicated integration in equation (3) yields:

$$q(x, t) = 2 \times 10^7(\text{m.p.c.})_a D(x) t^{1-n(x)}/(1 - n(x)) \tag{4}$$

Equation (4) was solved for the $(\text{m.p.c.})_a$ to give unit lung burden after 10^{-1}, $\frac{1}{2}$, 1, 2, 3 and 50 years of continuous exposure, assuming $D(x) = 1.22\{\exp(-0.9x) - \exp(-2.3x)\}$, which equation approximately represents the alveolar retention data of HATCH and HEMEON.[26] A graph of the $(\text{m.p.c.})_a$ to give unit lung burden as a function of particle size shows that large concentrations of large particles are required to maintain unit lung burden (Fig. 10).

Equation (4) is not adequate for application to the case of a distribution of particle sizes. However, it can be made adequate by multiplying by $\frac{4}{3}\pi\rho x^3 P(x)$, where ρ is the density of the particle, assumed to be spherical, $P(x)$ is the probability distribution of sizes whose mean size is $\bar{x}$ and whose standard deviation is s, and integrating the resultant expression over all

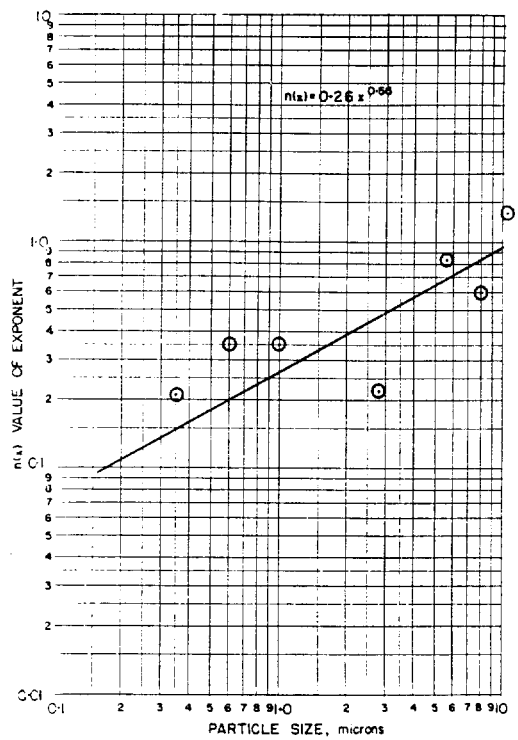

FIG. 9. Value of exponent in the power function for different particle sizes of UO_2.

sizes, and dividing by a normalization factor, the integral over all sizes of $\frac{4}{3}\pi\rho x^3 P(x)\, dx$. In equation form this is:

$$q(\bar{x}, s, t) = \frac{\int_0^\infty x^3 P(x) q(x, t)\, dx}{\int_0^\infty x^3 P(x)\, dx} \tag{5}$$

where $q(\bar{x}, s, t)$ is the lung burden after continuous exposure to an aerosol composed of a distribution of particle sizes. The denominator of equation (5) is said to be the third moment of the distribution, its value depending upon the choice of distribution. In many practical situations the particles in an aerosol can be characterized by the log-normal distribution. The

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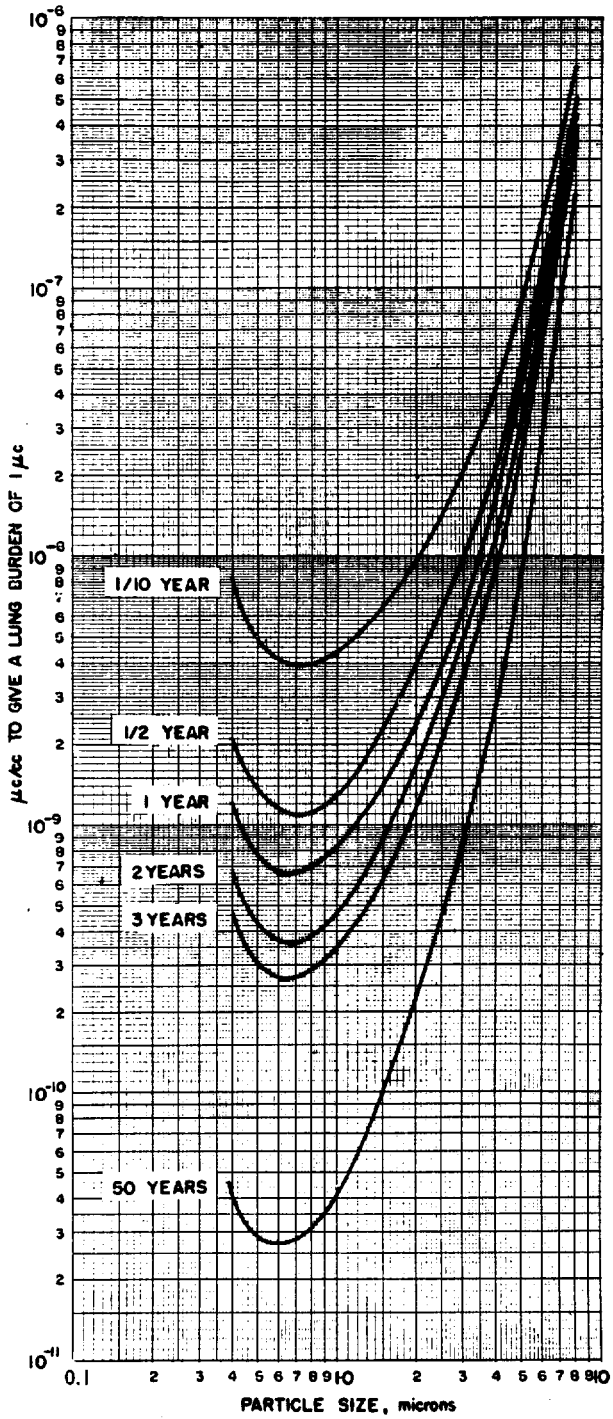

FIG. 10. Concentration of aerosols of different particle size to give a lung burden of 1 μc for periods of continuous exposure specified.

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parameters for a log-normal distribution are x_g, the geometric mean and s_g, the geometric standard deviation. The equation for the log-normal distribution is:

$$P(x) = \frac{1}{\log s_g \sqrt{(2\pi)}} \times \exp\left\{-\frac{1}{2}\frac{(\log x - \log x_g)^2}{\log s_g}\right\} \quad (6)$$

and the third moment of this distribution is: $x_g^3 \exp(4.5 \log^2 s_g)$.[27] Thus, the lung burden resulting from inhalation of an aerosol whose particle sizes are log-normally distributed is given by:

$$q(x_g, s_g, t) = \bar{x}_g^3 \exp(-4.5 \log^2 s_g) \int_0^\infty x^3 P(x) q(x, t)\, dx \quad (7)$$

Application of concept to animal inhalation data and human autopsy data

When equation (7) was applied to the lung burden measurements obtained in the inhalation experiments with small animals performed by the University of Rochester a considerable overestimate of the burden was evidenced. In part this overestimate is due to an incorrect assumption, namely, the alveolar retention data of HATCH and HEMEON apply to uranium dusts. In experiments with uranium oxide of 2.6 μ and 0.45 μ, WILSON *et al.*[28] found 0.9 per cent and 8.3 per cent of the inhaled dose, respectively, retained or more precisely, deposited in the alveolar passageways. In recent experiments performed in this laboratory, it was found that 10 per cent of inhaled enriched uranium fumes, whose mean particle size is 0.36 μ, is deposited in lower respiratory passages of dogs. Thus, more of the finer material was deposited, and a smaller amount of the uranium dusts are retained. Because of this, the equation for $D(x)$, which is for the HATCH and HEMEON data, was divided by a factor of 10.

In the inhalation experiments performed on dogs and rats by the University of Rochester, 1 and 10 mg/m^3 levels of uranium dioxide dust whose geometric mean particle size was 1.3 μ,[29] and geometric standard deviation was 2.3μ,[29] furnished the exposure. Both species were exposed for 1 year. The lung burden was predicted with equation (7) for this distribution of particles and these levels of dust, assuming that dogs breathe 2.5 m^3/day and 100 g of dog lung, and taking into consideration the fact that they received one-fifth of a continuous exposure. For rats, 0.1 m^3 daily air intake and 1 g of lung was assumed. The predicted lung burden was slightly less than that observed for dogs and about a factor of 10 greater than that measured in rats (Fig. 11a and 11b).

In the experiments with UF_4 dust, at 3.0 and 0.5 mg/m^3, $x_g = 1.84$[30] and $s_g = 2.43$,[30] the predicted lung burdens computed with equation (7) were greater, but by not more than a factor of 10, than the measured lung burdens for rats and dogs (Fig. 12a and 12b).

For application to EISENBUD and QUIGLEY's autopsy data, the average air concentration was assumed to be for occupational exposure and the geometric mean particle size = 2.4 and geometric standard deviation = 2.4 was also assumed. In addition it was necessary to take into consideration the fact that these workers' exposures ceased before they died, thereby allowing for elimination of uranium from lungs during conditions of non-exposure. (For discussion of the manipulation of the power function for application to the case of continuous exposure followed by a non-exposure period, the reader may consult the paper by HEALY.[31]) Under these conditions the predicted lung burdens were 800 and 100 μg/g of lung, little different from the extrapolated values determined by EISENBUD and QUIGLEY, viz. 600 and 56 μg/g, but extremely different from the measured burdens, 0.35 and 0.23 μg/g. On the other hand, had these workers been exposed to particles whose mean diameter, $x_g = 6\ \mu$ and whose standard deviation = 2.0 μ, then the predicted lung burdens would be 9.0 and 0.3 μg/g of lung.

DISCUSSION

Conservativeness of $(m.p.c.)_a$, $(m.p.c.)_w$ and q

The values for q, $(\text{m.p.c.})_a$ and $(\text{m.p.c.})_w$ based on the human data and chemical toxicity are lower than those recommended by others and therefore they may be said to be conservative. These m.p.c. values are lower for two

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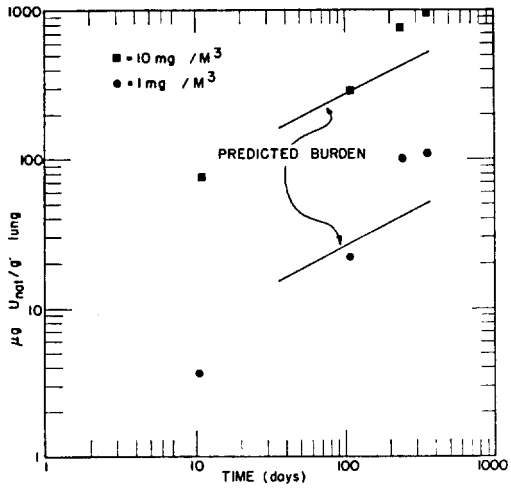

FIG. 11(a). Comparison between predicted and measured lung burdens of dogs exposed to UO_2 dust at levels of 1 and 10 mg U/m³

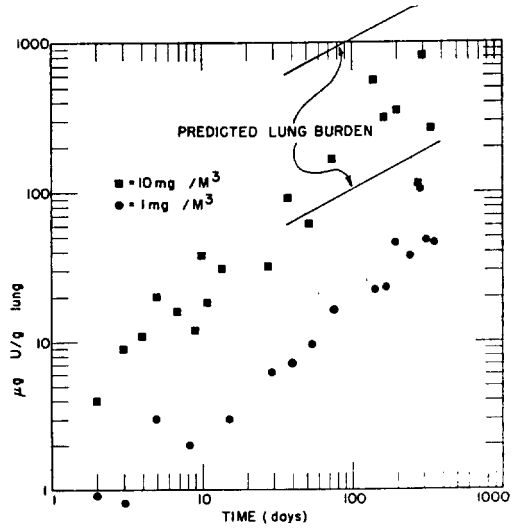

FIG. 11(b). Comparison between predicted and measured lung burdens of rats exposed to UO_2 dusts at levels of 1 and 10 mg U/m³.

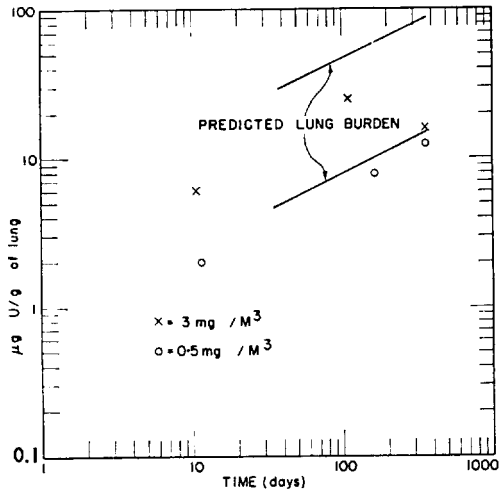

FIG. 12(a). Comparison between predicted and measured lung burdens of dogs exposed to UF_4 dust at levels of 0.5 and 3.0 mg U/m³.

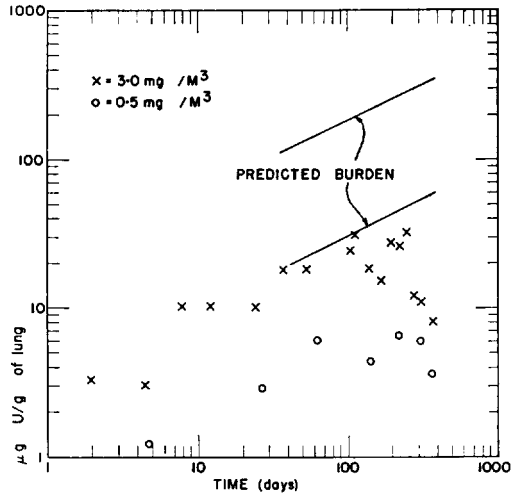

FIG. 12(b). Comparison between predicted and measured lung burdens of rats exposed to UF_4 dusts at levels of 0.5 and 3.0 mg U/m³.

reasons; (a) human kidneys are considered to retain more uranium and to store it for longer periods of time and (b) these m.p.c. values are for continuous and chronic exposure. These points require elaboration.

There is some element of doubt as regards the application of the data obtained from terminal brain tumor patients to normal subjects. If it were known that normal subjects' kidneys did not concentrate uranium to the extent indicated somewhat higher m.p.c. values would be in order. Some indirect evidence, the agreement between excretion patterns demonstrated by the Rochester patients and the terminal patients, leads to the belief that the tissue distribution is the same. Admittedly however,

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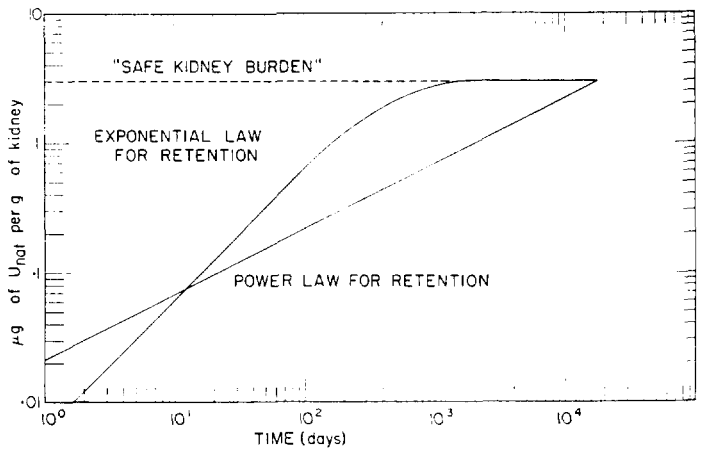

FIG. 13. Natural uranium kidney burden resulting from continuous inhalation of 1×10^{-12} μ/cc of U_{nat}.

this evidence is inadequate and data from normal subjects is required before ultimate confidence can be placed in the terminal patients findings. Moreover there is evidence from animal experiments of a dose effect, and that at lower levels the relative size of the kidney burden may be smaller.

The m.p.c. values, applicable to the case of chronic exposure, have been designed such that the kidney burden at the end of 50 years of continuous exposure will not exceed the safe level (Fig. 13) after termination of exposure. The power law predicts that after 50 years of exposure the kidney burden will be maintained at an essentially constant level—the decrease will be less than a factor of 2—even though the exposure has been terminated for 20 years. In this light the m.p.c.'s do not appear to be conservative.

Inadequacy of data for determination of $(m.p.c.)_a$ as a function of particle size

The data obtained by LABELLE on lung retention of various size particles are inadequate for determining $(m.p.c.)_a$ for various distributions of particle sizes. This was evidenced in the application to the inhalation data. The agreement between the predicted and measured lung burdens is fortuitous, perhaps, since LABELLE injected slurries of oxide particles and saline into the rats lungs. The effect upon the clearance mechanisms by the saline vehicle is not known. Hence, these data cannot be said to be representative of the clearance of particulates from the respiratory tree which were deposited upon inhalation. However, a modified procedure would yield useful data.

Suggested experiment to obtain data for determination of $(m.p.c.)_a$ as a function of particle size

An experiment which would yield the necessary data would consist of the following:

(1) Prepare slurries of oxide particles of different sizes by LABELLE's elutriation technique.

(2) Disperse these slurries in a chamber similar to the chamber of WILSON *et al.*

(3) Allow experimental subjects to inhale the homogeneous size particulate matter from the chamber through a mask and a special valve to direct the air flow.

(4) After the inhalation exposure collect excreta samples in addition to samples of lung, bone and kidney and measure these for uranium.

(5) Plot the data and determine the parameters of distribution and excretion of inhaled uranium as a function of the particle size comprising the aerosol inhaled.

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