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EVALUATION OF PLUTONIUM EXPOSURES IN MAN

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Abstract—This article is a review of the problem of evaluating the radiation hazard from plutonium in occupationally-exposed personnel. Although these people are exposed to plutonium most typically by inhalation, the only experimental kinetic studies conducted with human beings as the subjects involved the intravenous administration of plutonium. Kinetic data from animal studies indicate that when plutonium enters the body by inhalation it tends to be retained in the lungs for prolonged periods of time, being removed from the lungs with a half-time of the order of 300 days. The plutonium in the lungs thus acts as a continuous source of plutonium entering the circulation. It is suggested that the plutonium from the lungs introduces a significant error in those estimations of the plutonium body burden that are calculated from plutonium urinary excretion data using formulas derived from the injection experiments, and which at least tacitly assume that, after an initial period, the urinary plutonium reflects bone and liver plutonium concentrations. The animal studies suggest that it may be feasible to evaluate the lung burden more directly by external counting methods and through the use of plutonium fecal excretion data.

The animal plutonium-239 toxicity data are also reassessed in regard to the maximum permissible body burden of plutonium, and no change in the currently accepted value of 0.04 μc Pu^{239} is considered to be indicated on the basis of the available data.

1. INTRODUCTION

ALTHOUGH minute quantities of plutonium are found in nature, for all practical purposes this element is entirely reactor-produced. In particular, plutonium-239 is produced from uranium-238 by an (n, γ) reaction yielding U^{239} which decays by β^- emissions through Np^{239} to Pu^{239}.

Concern about plutonium as a health hazard arises principally in certain industrial situations involving its large scale processing. At present an appreciable number of people engaged in plutonium processing operations carry small but definite body burdens of Pu^{239}, as evidenced by traces of this isotope found in their urine specimens. These small body burdens are, in general, well below the maximum quantities regarded as being permissible, but it is essential that as high a degree of accuracy as possible be achieved in their estimations.

This report is a critical review of the methods used for estimating plutonium body burdens and for determining the maximum permissible body burden of plutonium.

As will be discussed, only a limited amount of data based on experience with plutonium exposures in human beings is available. To a large extent, therefore, our present concepts of the metabolic behaviour and the internal hazard of plutonium are necessarily derived from extrapolation of animal data and from comparisons with data on radium-226.

The present report is based on data taken directly from the literature. The references in the attached bibliography were selected on the basis of availability; the list does not purport to be exhaustive.

Following a brief review of the pertinent physical factors, animal data and experiences with plutonium in human beings, the methods of estimating the body burdens will be discussed and suggestions will be offered for future studies.

2. PHYSICAL FACTORS

The plutonium isotope of primary concern is Pu^{239} which decays to U^{235} by α-particle emission with a radioactive half-life of 24,360

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years.[1] The quantity of plutonium is often expressed in g, with the following relationship obtaining between weight and radioactivity:

$$1\ \mu c\ Pu^{239} = 15.9\ \mu g\ Pu^{239}$$

Pu^{239} decays principally by emission of α particles with energies ranging from 4.917 to 5.147 MeV. The lower energy α-particle emissions produce U^{235} in excited or metastable states which decay to the ground state by γ-ray emission.[1] The 100-keV gamma ray, with an abundance ratio of about 5.5×10^{-5} γ/decay, gives the highest peak in the γ-ray spectrum.[2] In some 4 per cent of the disintegrations a 17-keV X-ray is also produced.[2]

Pu^{238} is also of potential importance as a health hazard.[3] Pu^{238}, with a half-life of 86.4 years, decays to U^{234} by emission of 5.208–5.495 MeV α-particles.[1] The lower energy α-particle emissions are followed by γ-ray emission, with the most frequent γ-ray having an energy of 0.043 MeV.[1] Because the biological effects of Pu^{238} are not expected to be qualitatively different from those of Pu^{239}, the balance of this discussion will be chiefly in terms of Pu^{239}.

3. ESTABLISHED MAXIMUM PERMISSIBLE BODY BURDENS (q)

The maximum permissible body burdens (q) currently accepted by both the ICRP[4] and the NCRP[5] were adopted in 1950. For soluble forms of the element 0.04 μc Pu^{238}, Pu^{239} or Pu^{240} is given with bone as the critical tissue, and 0.4 μc Pu^{239} with the total body or with the liver as the critical tissue. Maximum permissible body burdens have not been established for plutonium in the lung.[4] The reasoning leading to the adoption of these figures has been discussed by LANGHAM.[6,7] Considerations of the differences in retention and toxicity between Pu^{239} and Ra^{226} in rats and mice and in the metabolism of radon between the rat and man led to the figures agreed upon.

Aside from such questions as the accuracy of the relative toxicity values, recurrent questions are: (1) whether the choice of bone as the critical organ under conditions of inhalation exposure is correct and (2) whether the q of radium itself should be revised.[3,6]

The basis of the plutonium q and some of the associated questions are further discussed by NORWOOD.[8] Of interest is the fact that in toxicity studies (cited in[8]) involving essentially equal radiation doses to the liver and to the bone, skeletal damage predominated. The choice of the critical organ is therefore not entirely a matter of gross Pu^{239} concentration but is also dependent upon other factors such as the distribution within the tissue, the radiosensitivity of the tissue and the recovery rate.

4. PLUTONIUM METABOLISM IN ANIMALS

Although in man the principal route of entry of plutonium into the body is via the respiratory tract, the only plutonium studies in man (excepting the studies of occupationally-exposed individuals) and most of the animal experiments reported have been concerned with the fate and effects of intravenously-injected plutonium. The animal studies will be reviewed first.

A. *Non-inhalation studies*

One of the earliest studies of plutonium metabolism in rats [9] indicated that following intramuscular and subcutaneous injections, the fraction absorbed was found to be valence-dependent, being least for the +4 plutonium, with 67 per cent remaining unabsorbed at the site of intramuscular injection after 256 days. With intraveneous injection, 73 per cent of the +4 plutonium and about half this fraction of the +3 and +6 plutonium was found in the liver after 4 days, a result attributed to the filtering out of colloidal plutonium by the reticuloendothelial system. The extra-hepatic plutonium distribution was similar in all cases and was independent of the valence state. The bulk of the absorbed and retained plutonium not in the liver was found in the skeleton. The principal route for excretion of plutonium in the rat was found to be via the feces. After 256 days 42 per cent of the absorbed plutonium had been excreted in the feces. The excretion rate following intravenous injection was higher than following intramuscular injection.

Autoradiographic studies suggested that in bone, plutonium is selectively localized in the

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region of the osteoid matrix rather than in the mineral or crystalline structures of bone, in contrast to the behavior of calcium, strontium and radium. The half-time for retention of plutonium in the rat body was estimated as being greater than six months.[9]

The site of localization of plutonium in bone has more recently been studied by JEE *et al.*[10] and by FOREMAN,[11] who are in agreement that a calcified matrix is required for plutonium deposition. However, over 50 per cent of the *in vivo* deposited plutonium is not removable by decalcification.[10] The exact mechanism of plutonium fixation remains to be explained.

LANGHAM[12] reported another series of studies in which Pu^{239} was administered intravenously to rats. In agreement with the above[9] studies the principal route of excretion was via the feces, and the skeleton was a major site of deposition regardless of the valence state of the injected plutonium. Deposition in the liver at 4 days following injection ranged from 39.7 per cent of the injected dose for $Pu(NO_3)_4$ to 9.1 per cent for $PuO_2(NO_3)_2$. The corresponding figures for bone depostion were 29.3 per cent and 56.5 per cent, respectively. The distribution in other tissues was not greatly affected by the form in which the plutonium was administered. When plutonium was given orally however, it was found that 79 per cent of the plutonium absorbed from the gastrointestinal tract was deposited in the skeleton and 7.3 per cent in the liver.

While the rat studies mentioned above indicate what may be expected for the plutonium distribution in man, the most applicable long-term kinetic data have been obtained with larger animals.

Using adult beagle dogs, for example, STOVER *et al.*[13] injected tetravalent plutonium in doses of 0.0159–2.78 μc/kg. The resulting plasma Pu^{239} concentration curves after the first day were described by two power functions

$$P_1 = 0.0556t^{-1.63} \qquad (1 < t < 22 \text{ days}) \qquad (1)$$

$$P_2 = 0.000733t^{-0.293} \qquad (t > 22 \text{ days}), \qquad (2)$$

where P is the per cent of the injected dose per g of plasma and t is in days.

For the first 22 days the total excretion rate, X, and the urinary excretion rate, U, were described by the equations:

$$X = 0.0698t^{-1.59} \qquad (t < 22 \text{ days}) \qquad (3)$$

$$U = 0.0144t^{-1.52} \qquad (t < 22 \text{ days}), \qquad (4)$$

where X and U are expressed as fractions of the dose excreted per day and t is in days.

For the period from 22 days through 4 years, the corresponding Pu^{239} excretion equations were:

$$X = 0.00223t^{-0.485} \qquad (t > 22 \text{ days}) \qquad (5)$$

$$U = 0.000605t^{-0.409} \qquad (t > 22 \text{ days}) \qquad (6)$$

From the above equations the renal clearance of plutonium was calculated to be 33 g of plasma per day using the $t < 22$ days curves and 40 g/day using the $t > 22$ days curves, or about 7.5 to 9 per cent of the plasma volume per day. (The corresponding plasma clearance rate for Ra^{226} is cited[13] as being 1690 g of plasma per day.) Under these conditions it was found that in two dogs sacrificed at 29 and 44 days, 64 per cent of the injected plutonium was in the skeleton, 22 per cent in the liver, and 2–3 per cent in the other soft tissues. It was estimated that of the total of 16 per cent excreted during the 22-day to 4-year interval, 6 per cent came from the liver and 10 per cent from the skeleton. In the dog the ratio of fecal to urine plutonium excretion rates is lower than the ratio for the rat and in this respect the dog is the more like man.[12,13]

In a continuation of the above studies, STOVER *et al.*[14] present concentration and excretion data obtained 4–8 years after intravenous injection of Pu^{239} and Ra^{226} in young adult beagle dogs. At these times the observed Pu^{239} plasma levels were lower by factors of 0.94–0.04 than plasma levels calculated by extrapolation of equation (2). The observed urinary and total excretion rates, however, were in substantial agreement with rates calculated by equations (5) and (6). It was concluded that the previous equations result in satisfactory values for Pu^{239} retention up to 8 years, but it was also found that the liver-bone Pu^{239} ratio was dose-dependent, the retention in the liver being greatest at low dose levels.

B. *Inhalation studies*

The major occupational hazard from plutonium arises from its entrance into the body via

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the respiratory tract. Since there have been no plutonium inhalation experiments with human beings as the subjects, the animal studies in this field are especially pertinent to the problem of evaluation of exposures of human beings.

The extensive literature available on the retention and disposition of inhaled aerosols and particulate matter provides a substantial basis for predicting the fate of inhaled plutonium particles.[15,16] Many physical, chemical, anatomical and physiological variables are involved, including particle size, particle density, valence state, respiratory rate and tidal volume.

Particles are cleared from the lungs by several processes, depending largely on the particle size and solubility. In the bronchial and tracheal passages ciliary motion sweeps the mucus-entrapped particles up and out of the respiratory tracts, after which the particles are swallowed and are either absorbed from the gastro-intestinal tact or are excreted in the feces. Although the fraction absorbed from the gastro-intestinal tract is relatively low, this route may, nevertheless, be an important mode of entry in the occupational situation. The gastro-intestinal absorption factor in rats was found to be only 0.0028 per cent of the amount of plutonium fed as the nitrate, with about 90 per cent of the absorbed Pu^{239} being deposited in the skeleton.[17] Similarly, LANGHAM[12] reported that the gastro-intestinal plutonium absorption factor in rats was 0.01 per cent, and SCOTT *et al.*[9] obtained a figure of 0.007 per cent.

Particles not cleared from the lung by ciliary action may be engulfed by phagocytes which migrate from the alveolar ducts, and are acted upon by the ciliated epithelium, or they may enter the lymphatic system and be deposited first in a pulmonary lymph node, and later be transported to a bronchial or mediastinal node.[15]

Among the earliest efforts to study the fate of plutonium deposited in the plumonary system were the studies reported by SCOTT *et al.*[9] In these studies plutonium solutions were introduced directly into the lungs of rats through tracheal canulae. After 128 days 74 per cent of the retained $Pu(NO_3)_4$ was in the lungs and about 20 per cent was in the skeleton.

In more recent experiments the intratracheal method was used in Hormel miniature swine.[18] Within 4 days after intratracheal administration, 85–98 per cent of the administered dose was detected in the feces. The distributions presented in Table 1 were obtained in nine animals that lived 480–695 days.[18]

The Pu^{239} concentrations in the liver and skeleton following intratracheal administration are higher than those following intragastric administration, a fact which may be due in part to direct absorption into the blood or into the lymphatic systems in the lungs.

The role of particle size on the retention and distribution of inhaled $Pu^{239}O_2$ particles in beagle dogs have been studied by BAIR and MCCLANAHAN,[19] BAIR and WILLARD[15] and BAIR, TOMBROPOULOS and PARK.[20] In the first of these studies[19] four dogs were exposed by inhalation to a $Pu^{239}O_2$ aerosol having particle sizes ranging from 0.05 μ to 4 μ diameter. Two of the dogs were killed immediately after exposure and the other two were studied for 39 weeks after exposure. The body retention of Pu^{239} was described by 3 exponential terms, with half-times of 6, 25 and 1400 days in one dog and 3, 15 and 1800 days in the other. The slow component accounted for 49 per cent of the retained activity in the first dog and 67 per cent in the second. This component is accounted for chiefly by the fractions remaining in the lungs and lymph nodes (43 per cent in one, 60 per cent in the other). After 39 weeks only 0.060 and 0.029 per cent of the Pu^{239} originally retained was found in bone and 0.043 and 0.13 per cent in the liver. Most of the activity not found in the lungs and lymph nodes was

Table 1. *Per cent of administered dose of* Pu^{239} (+4) *Nitrate per organ in swine,* 480–695 *days after various modes of injection*[18]

Route	Intravenous			Intratracheal			Intragastric		
Organ									
Liver	19	33	44	0.0007	0.0002	0.0004	0.0003	0.0001	0.0002
Skeleton	31	44	27	0.004	0.001	0.001	0.0003	0.0002	0.0003

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excreted in the feces (55 and 38 per cent), and only 1.6 and 1.3 per cent was excreted in the urine. In the next study[15] plutonium oxide particles with three mass median diameters (MMD), 0.65 μ, 3.3 μ and 4.3 μ were used, and in a third[20] six sizes, 0.23 μ, 2.3 μ, 3.3 μ, 4.3 μ. 6.1 μ and 7.6 μ MMD particles, were used. Except for the 4.3 μ group in the first series, in which the particles were administered as a dust, all of the experiments involved inhalation of aerosols. In addition, in the last (third) study, one group was exposed to an aerosol of 0.88 μ MMD $Pu(NO_3)_4$ particles and an other was injected intravenously with $Pu(NO_3)_4$. The amounts of plutonium deposited in the respiratory passages and in the alveoli and the subsequent retention in the lungs were found to vary with the particle size and chemical form. Table 2 summarizes the distribution of the body burden of plutonium found after 30 days in the last study.

Table 2. Distribution of plutonium in beagles as per cent of body burden 30 days after inhalation[20]

Particle size (MMD)	Nitrate	Oxide	
	0.88 μ	0.23 μ	2.3–7.6 μ
Lung	67	71	96–98
Bronchial lymph nodes	0.5	3	0.3–1.5
Liver	12	0.9	0.05–2
Muscle	2	4	0.01–0.8
Skeleton	16	1	0.03–1
Remaining tissues	3	20	1

The urinary and fecal Pu^{239} excretion rates, expressed as the per cent of the body burden of plutonium remaining at the beginning of each day, fell steadily during the 30-day study. Table 3 summarizes the excretion rate data for days 1 and 30, as read from graphs in the original report.[20]

In extended studies of the 4.3 μ particle PuO_2 group, the extended half-time for Pu^{239} disappearance from the lungs was estimated to be about 300 days. During this period the activity in the bronchial lymph nodes rose asymptotically toward 10 per cent of the alveolar-deposited Pu^{239}. The skeleton and liver Pu^{239} concentrations ranged between 0.005 and 0.2 per cent of the total Pu^{239} throughout the study.

In longer term inhalation studies,[21] $Pu^{239}O_2$ doses large enough to produce mortality in dogs were used. The mean whole-body clearance from 2 weeks to 150 days postexposure was described by the equation

$$p = Ae^{-0.0009t} \tag{7}$$

where p is the whole-body burden at time, t, in days and A is the amount deposited at $t = 0$. The half-time for plutonium in the body was estimated to be 820 days with 95 per cent of the plutonium recovered at autopsy in the lungs, 4 per cent in the bronchial and mediastinal lymph nodes, and only 1 or 2 per cent in all other tissues. The times of death ranged from 55 to 412 days postexposure.

Table 4 presents a comparison[22] of the distribution of Pu^{239} in dogs following inhalation with that following intravenous injection 30 days after administration. It may be noted that the $Pu(NO_3)_4$ administered intravenously in this study was not complexed with citrate, and this may affect the distribution, as compared with the results in other studies in which citrate is used.

Much higher fecal excretion rates were observed in the inhalation studies than were observed in the injection studies, as is shown in Table 5.[22]

Table 3. Dependence of Pu^{239} *excretion rates on chemical form*[20]

Form and particle size	0.23 μ PuO_2		2.3–7.6 μ PuO_2 or 0.88 μ $Pu(NO_3)_4$		$Pu(NO_3)_4$	
Route	Inhaled		Inhaled		Intravenous	
Day	1	30	1	30	1	30
Urine %/day (U)	0.2	0.07	0.08	0.006	0.06	0.006
Feces %/day (F)	10.	0.6	20.	0.1	0.2	0.005
Ratio F/U	50	12	250	17	3	1

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Table 4. Effect of mode of administration on Pu^{239} *distribution in dogs*[22]

	Per cent of body burden 30 days after Pu^{239} administration				
	Lung	Liver	Spleen	Muscle	Bone
Intravenous	0.3	80	6	3	6
Inhalation	70	10	0.2	2	20

It seems clear that in Pu^{239} inhalation studies a wide variety of results can be obtained, depending upon the values of the many factors involved in the experimental situation. It is equally clear that significant differences exist between the distributions and excretion rates when Pu^{239} is administered intravenously and when it is administered by inhalation.

Table 5. Effect of mode of administration on Pu^{239} *excretion rates in dogs*[22]

	Approximate per cent of Pu^{239} body burden excreted per day		
	At: 7 days	14 days	30 days
Intravenous			
Urine (U)	0.01	0.009	0.005
Feces (F)	0.03	0.007	0.004
Ratio F/U	3	1	1
Inhalation			
Urine (U)	0.04	0.02	0.006
Feces (F)	0.6	0.4	0.2
Ratio F/U	15	20	33

5. PLUTONIUM TOXICITY STUDIES

It is beyond the scope of this report to review the voluminous literature on all phases of the toxicity of plutonium. Instead, only two of the most recent references containing material most pertinent to the maximum permissible body burden question will be discussed. Additional references to other aspects of the toxicity problem are listed at the end of this article.

In a summary of data accumulated over several years on the toxicity of plutonium in mice, FINKEL and BISKIS[23] reported finding no tumors among mice that had been injected with 0.04 or 0.08 μc Pu^{239}/kg. In these two groups 195 animals remained alive 200 days after injection. With injected doses ranging from 0.16 μc Pu^{239}/kg to 6.1 μc Pu^{239}/kg, the incidence of malignant bone tumors increased as a function of dose in a manner described by a power function, approximately as follows:

$$I = 0.5D^{1.15} \tag{8}$$

where I = tumor expectancy/mouse and
D = amount of Pu^{239} injected in μc/kg.

(Equation (8) was derived from Fig. 13 of Ref. [23], but is not given in the original article.) Using equation (8) as a basis for extrapolation, an incidence of only 0.012 tumors/mouse attributable to Pu^{239} would be expected at the 0.04 μc/kg injected dose level. Since the control incidence was 0.02 tumors/mouse, it is obvious that statistically significant evidence of increased tumor incidence would require the use of many hundreds of animals at the lower dose levels.

Using groups of 8–12 beagle dogs, JEE *et al.*[24,25] found that intravenously-injected Pu^{239} doses of 0.096 μc/kg and greater produced high incidence rates of osteogenic sarcoma (7 tumors/8 dogs for 0.096 μc/kg and 12/12 for 0.3 μc/kg). One tumor occurred in a dog injected with 0.048 μc/kg and one in another injected with 0.016 μc/kg. Further studies of the toxicity of Pu^{239} at the lower dose levels are planned.[24]

6. PLUTONIUM EXPERIENCE IN MAN

A. *Body burdens*

LANGHAM[26] has reviewed the problem of occupational exposure to Pu^{239} at Los Alamos, Hanford, Chalk River, and in England. Altogether, several thousand employees have been studied by means of urinalysis for plutonium. Basic data of use in relating known body burdens to excretion rates are available from three principal sources of data on the behavior of plutonium in man: (1) Patients given tracer doses of plutonium intravenously, (2) employees occupationally exposed to plutonium and (3) autopsy data on a few formerly occupationally-exposed employees.

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The patient data originally reported by LANGHAM, BASSETT, HARRIS and CARTER[27] have been supplemented and re-examined in subsequent reports.[3,6,7,28,29,30] In 1945, twelve patients were injected intravenously with 4.6–6.5 μg Pu^{239} prepared by dissolving Pu metal in nitric acid and then diluting with 0.41 per cent sodium citrate.[27] Three patients were injected with PuO_2^{2+} in doses of 6.5–95 μg Pu^{239},[27] and one was given a mixture of 5 μg Pu^{239} and 0.3 μg Pu^{238} (regarded as a total of 120 μg Pu^{239} equivalent) as PuO_2^{2+}.[30]

Autopsy material was obtained from seven patients who died in the first few months after Pu administration, and the tissue Pu^{239} distributions, regarded as representing the situation 5 months after injection, were in substantial agreement with the comparable distribution in beagles, as indicated in Table 6. In no case was any radiation injury attributable to plutonium found.

Table 6. Pu^{239} *Distributions five months after intravenous injection*[6]

	Per cent of injected dose per tissue	
	Beagle	Man
Skeleton	60	66
Liver	21	23
Spleen	0.2	0.4
Kidneys	0.2	0.4

In the kinetic studies, sixty-four blood samples were obtained from among eleven patients during the first 23 days following injection, and six samples from among five patients during the 29- to 46-day period (Table 5 in Ref. [27]). Although the individual values of blood Pu levels varied widely, the means fell on a fairly smooth curve from 35.7 per cent of the injected plutonium in the blood volume at 4 hours after injection to 15.7 per cent at one day, 1.2 per cent at 10 days, and 0.3 per cent at 30 days.

The urinary excretion of plutonium was followed in fifteen of the patients; one for 16 days, two for 22 days, one for each 23, 25, 27, 30, 34, 36, 37, 58 and 65 days, and three for 138 days.

The urinary Pu^{239} excretion data were fitted by a smoothed curve described by the power function;[27]

$$Y_u = 0.0023t^{-0.77} \tag{9}$$

where Y_u is the fraction of the injected dose excreted per day, and t is in days after injection. The standard error of the estimate was ± 32 per cent.

Similarly, the total excretion rate (urine plus feces) was described by:

$$Y_{u+f} = 0{\cdot}0079t^{-0.94} \tag{10}$$

with the standard error of the estimate being 17 per cent.

Urinary samples obtained from one of the patients on the 523rd to 526th days after injection, and another group of urinary samples beginning on the 1610th day after injection had 0.002 per cent of the injected dose per day and 0.0011 per cent per day, respectively. Four daily samples from another patient beginning at 1645 days had an average of 0.0008 per cent per day.

The Pu urinary excretion data were further extended with data obtained from three employees who had accumulated body burdens of plutonium prior to being removed from further exposure to plutonium. Although their body burdens had been achieved through chronic exposure by inhalation, their dose was expressed in terms of an "effective" single dose as if it had been given at some "effective time" between the limits of exposure. The dose and time were calculated by fitting equation[10] to two values for the excretion rates taken an appreciable time apart. With this procedure, effective doses of 1.3 μg, 1.2 μg, and 1.0 μg at 37, 53 and 42 days prior to the first urine assay used in the calculation were assumed. With these data the urinary plutonium excretion curve was extended to 1750 days and the final adjusted fit was:

$$Y_{ua} = 0.0020t^{-0.74} \tag{11}$$

where Y_{ua} is the adjusted urinary excretion rate. The standard error of the estimate for the adjusted expression was 42 per cent.

Equations (9) and (11) are important because they have been used as the basis for estimating body burdens from urinary plutonium excretion rates in man in almost all subsequent calculations.[28,31,32,33,34]

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Unfortunately no fecal data are given for the period after 138 days in these studies[27] because it was considered that the feces would include plutonium removed from the lungs by ciliary action and ingested, which would complicate the analysis.

For a total excretion rate after 138 days, an equation is given which sums the 138-day fecal rate and the adjusted urinary rate:

$$Y_{ua+f} = 0.0020t^{-0.74} + 0.0063t^{-1.09} \quad (12)$$

Integration of this expression and evaluation at 5 years indicates that a total of only 8.7 per cent of a single injected dose of Pu^{239} would be excreted in this period.

A "biological half-time" was calculated[26] by assuming that after 1750 days the excretion rate would remain constant at 0.001 per cent of the injected dose per day. On this basis, to increase the total amount excreted from 8.7 per cent at 5 years to 50 per cent would take another 113 years, for a total of 118 years. (If an exponential excretion rate were assumed, the fraction of the amount remaining would be constant and the biological half-time would be even longer: 0.69315/0.00001 = 69315 days = 190 years. For practical purposes, the conclusion is the same: plutonium remaining in the body after 5 years is, effectively, there permanently.)

The complexity of the problem of estimating the Pu^{239} lung burdens in employees has been discussed by LANGHAM.[28,29] An attempt was made, however, to use the urinary to fecal ratios as a measure of lung burden. Table 7 is abstracted from data obtained in studies of twenty-five non-exposed Los Alamos employees and sixteen employees with various degrees of exposure to plutonium.[28]

Data on the five exposed subjects included in Table 7 were used to estimate the lung burdens, using kinetic data obtained in rats by ABRAMS *et al.* cited in Refs.[28,29] For the eleven exposed subjects for whom data are given in the original publication but which are not included in Table 7, the urinary or the fecal excretion rate, or both, was/were too low to be useful. The estimated Pu^{239} lung burdens given by two methods were about ten times the systemic burden. A model for evaluating the lung burden hazard was proposed, based largely on rat data and assuming an elimination half-time of about six months for the insoluble particles deposited on alveolar surfaces.

The lung burden problem has also been considered by HEALY.[32] In his words, "Relatively insoluble quantities of plutonium in the lung may be regarded as a pool of material isolated from the normal metabolism of the body but continually injecting plutonium into the blood stream at a rate dependent upon the character of the deposited material and relevant physiological processes." In deriving equations to relate the lung burden to the urinary excretion rate, HEALY assumes a constant fractional removal per unit time for the lung burden, so that the quantity, Q, remaining in the lung at a time, t, following acute fixation of a quantity, Qo, is given by: $Q = Qoe^{-\lambda t}$. The exponential constant, λ, in this equation includes the rate of loss due both by solubilization and by ciliary action, so the rate of transfer to the circulation is some fraction, λ_s, of Q. It was then assumed

Table 7. Comparison of fecal and urinary excretion of plutonium by Los Alamos workers in relation to mode of exposure[28]

Type of exposure	Approximate time after exposure (months)	Feces (c/m.24 hr)	Urine (c/m.24 hr)*
Average of 25 with no exposure		0.9 ± 0.4	0.7 ± 0.4
Burning Pu metal	½	1190	1.3
Spray of $PuO_2(NO_3)_2$	1	3400	5.0
Spray of $Pu(NO_3)_4$	9	196	2.6
Spray of $Pu(NO_3)_4$	10	130	7.3
Spray of $Pu(NO_3)_4$	11	237	4.3

* Counts of less than 1 have no statistical significance.

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that LANGHAM's equations were applicable for obtaining the urinary and fecal excretion rates of the systemic plutonium, and the combined functions were integrated to predict urine and feces excretion rates of plutonium deposited in the lungs. In an application to an exposure case, the rate of fall of the excretion rate was not sufficient to provide an accurate estimate of λ, although samples were obtained for 1600 days.

B. *Computer programs*

The major computer programs or "codes" which have been developed for relating the body burdens of occupationally-exposed personnel to their Pu^{239} urinary excretion rates are all based on LANGHAM's equations described above. In particular, LAWRENCE's program,[31] PUQFUA, estimates a series of single exposures which would produce the observed concentrations in urine by assuming that the body burden due to each individual exposure can be described by LANGHAM's power functions for intravenous injections. From these estimates the body burden is calculated both in microcuries and as a fraction of the MPD. When no known accidental exposure has occurred between urine samples, it is assumed that the exposure occurred half-way between the samples. The program includes a "validation" routine in which the observed excretion rate is compared with the excretion rate calculated from the preceding sample. If the calculated value is equal to or less than the observed value, the preceding sample is considered valid; otherwise it is rejected for calculation purposes.

SNYDER[33,34] avoids the problem of rejection of data in a program which treats intake into the blood as a continuous function of time, this function being obtained by integration of the single injection equation. SNYDER[34] compares the estimates obtained by PUQFUA and by several of his own programs. In some cases the estimates differed by factors of 3 or 4, but it is not clear which method is to be preferred nor what the major sources of error are.

Although an error of a factor of two could well be expected with any of the computer programs, it should be mentioned that in one case in which autopsy material became available following a criticality accident, the estimated body burden based on tissue samples was 0.018 μc of Pu^{239}, and that predicted by the PUQFUA program was 0.019 μc, based on urine assays several years before the accident (31).

7. DISCUSSION OF THE LOS ALAMOS DATA

The data of LANGHAM *et al.*[27] were reanalyzed using the BNL Merlin computer to give both exponential and power function least squares fits for:

(a) the mean patient Pu^{239} urinary excretion data from day 1 through 138 days (from Table 7 in Ref. [27]).
(b) the adjusted urinary excretion data on Los Alamos personnel for 140 through 1750 (from Fig. 5 in Ref. [27], and
(c) the combination of (a) and (b).

So that the power function fits would be plotted as straight lines, log-by-log graph paper was used. The results are shown in Fig. 1. The Los Alamos personnel data for days 1–138 (ten open points) are included in Fig. 1 but were not used in the present calculations. The following equations describe the power function fits obtained:

$$\text{(a)} \quad Y_u = 0.00241t^{-0.794} \quad (\text{slope } 0.794 \pm 0.027) \quad (13)$$

$$\text{(b)} \quad Y_u = 0.00956t^{-0.947} \quad (\text{slope } 0.947 \pm 0.072) \quad (14)$$

$$\text{(c)} \quad Y_u = 0.00193t^{-0.721} \quad (\text{slope } 0.721 \pm 0.015) \quad (15)$$

The power functions (a) and (c) are in substantial agreement with the equations given by LANGHAM *et al.*[27] It is to be noted, however, that the slope obtained for (b), fitted to the Los Alamos personnel data, is appreciably steeper than for either (a) or (c). Inspection of Fig. 1 shows that the reason the slope for (c) is less than either that of (a) or (b) (instead of being intermediate) is attributable to the inflection in the mean data curve (not shown, but apparent from the data points) between days 140 and 300, corresponding to the transition from the patient data to the Los Alamos personnel data. The tendency for the power function slope to become steeper for the day 140–1750 period than for the early period is interesting because it suggests several possibilities. Before discussing

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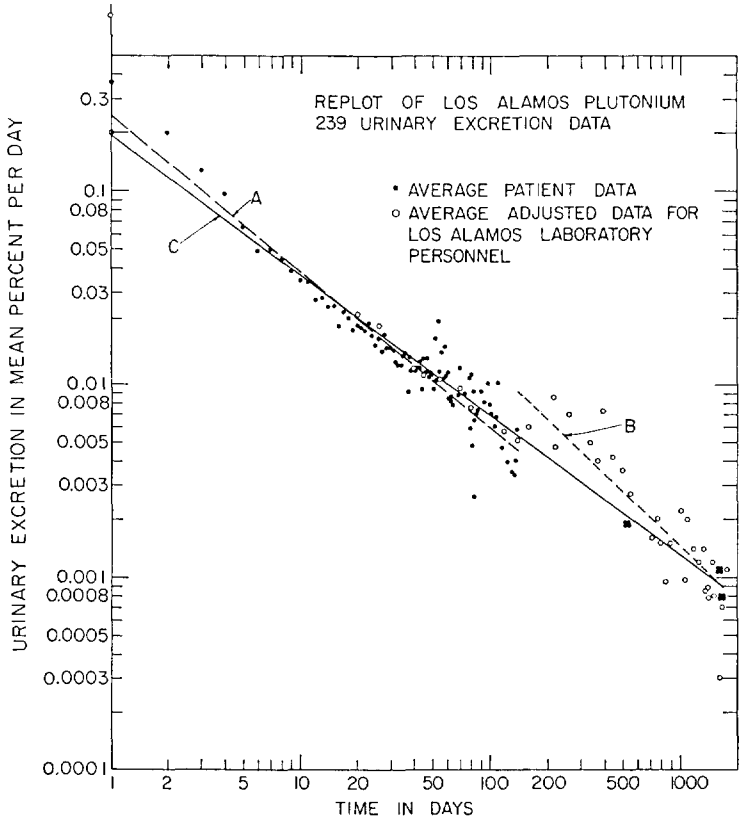

FIG. 1. Replot of Los Alamos plutonium-239 urinary excretion data abstracted from Ref. [27]. Curves A, B and C are power function fits for various portions of the data, as is explained in the text.

these, we shall consider the meanings and implications of power function fits with respect to the problem of using urinary excretion rates to estimate body burdens of plutonium.

The estimation of the body burden from the urinary excretion rate would be straightforward if a function relating the two variables were known. The connecting function, however, is difficult to obtain because the body burden cannot be measured directly. If the plutonium in the body could be regarded as being in a single compartment, it would be expected that a constant fraction of the amount present would be excreted daily and that both retention and excretion would be described by single exponential equations. Instead, the fraction excreted becomes progressively smaller. This phenomenon may be interpreted as indicating that the excreted plutonium originates in "deeper and deeper" compartments, i.e. those with progressively slower turnover rates. A rational approach in this situation predicts that the excretion curve may be described as a series of exponential terms.[35,36] In practice, however, calculations involving multiple exponential terms become cumbersome, and it often happens that a series of exponential terms can more conveniently be represented by a single power function. For example, a power function is often used to describe the decay of mixed fission products.

Extrapolation of a single power function beyond the time of an empirical fit of the data implies the assumption that the fractional rate of loss will continue to decrease. In the absence of data to the contrary, however, it would seem at least equally reasonable to assume that eventually the compartment having the slowest turnover rate would become the rate-limiting source of plutonium, and that from then on the excretion rate would be a constant fraction of the amount present in that compartment, resulting in final exponential curves for both the excretion and retention values. If this is the case, extrapolation of the power function will give an overestimate of the excretion rate

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at late times, and hence its integration will give an corresponding underestimate of the retained body burden. In the estimation of the retention from a single injection, this discrepancy is not serious. Integration of LANGHAM's[6,27] total excretion rate function, $Y_{u+f} = 0.0079t^{-0.94}$, over the time interval of 1 day to 50 years indicates that a total of only 10 per cent of the injected dose is excreted during this interval:

$$\int_1^{18262} 0.0079t^{-0.94}\,dt = 0.104 \qquad (16)$$

Half of the Pu excreted (5 per cent of the initial burden) is excreted in the 1-day to 230-day interval. If 10 per cent is an overestimate of the total plutonium excreted in 50 years, the amount retained at any intermediate time of interest is seen to be not greatly different from the amount present at the end of the first day. Thus, insofar as evaluation of the hazard involved in the retention of a dose of Pu^{239} is concerned, there is little to be gained by use of a more precise function; LANGHAM *et al.*'s equations are adequate and any error made by extrapolation beyond the 1750 days of the empirical fit can, at most, underestimate the plutonium retained by 10 per cent of the initial quantity.

On the other hand, the observation that the slope from day 140 to day 1750 on a log-by-log plot is steeper than the slope from day 1 to day 138 may provide a clue to the physiology of the situation. Such a change in slope is consistent with a reduction from a multiple to a single exponential process. Figure 2 shows the extraponential equation:

$$U = 0.000176e^{-0.00124t} \qquad (17)$$

where U is the fraction of the initial Pu burden excreted in the urine per day and t is time in days, fitted to the Los Alamos personnel data (reproduction of Fig. 5 from Ref.[26]). The exponential and power function fits are about equally good for this portion of the curve with correlation coefficients of 0.90 and 0.88, respectively. This "final" (if such it is) exponential term could represent the rate-limiting plutonium compartment. In this case, integration of equation 17

$$\int_0^t 0.000176e^{-0.00124t}\,dt = \frac{0.000176}{0.00124}\left(1 - e^{-0.00124t}\right) \qquad (18)$$

shows that at most this rate-limiting compartment accounts for only about 14 per cent of the injected plutonium. Since about 90 per cent of the injected plutonium remains in the body after 1750 days, this result implies that the bulk (75 per cent) of the systemic plutonium is so firmly bound that it does not have a perceptible degree of participation in the processes causing turnover of body constituents.

It is not possible to tell whether the "slowest" component observed represents a systemic location or whether it could represent plutonium entering the system for the lungs. The half-time of 557 days (0.69315/0.00124 = 557) is compatible with the half-time obtained for the disappearance of plutonium from the lungs of dogs, but comparable lung Pu^{239} disappearance data for human beings are not available. The dog data[15,19,20] strongly suggest that when Pu^{239} enters the body by inhalation, the plutonium remaining in the lungs becomes, relative to the amounts in the skeleton and liver, a tremendous reservoir of activity. If the urine Pu^{239} excretion rates include material originating in the lungs, interpretation in terms of skeletal retention will tend to give an overestimate of the body burden.

8. IMPLICATIONS OF TOXICITY DATA FOR THE MAXIMUM PERMISSIBLE BODY BURDENS

Although a few individuals have or have had Pu^{239} body burdens equal to or slightly greater than the established maximum permissible body burden (q), 0.04 μc, no injury attributable to Pu^{239} has been reported in this group. The small number of people involved and the relatively short period of observation, however, do not provide sufficient evidence to prove the complete safety of the established q value. It is, therefore, necessary to use the animal data as parts of the basis for judging whether or not the established q value should be changed.

This, of course, immediately raises the perennial question of how radiation effects

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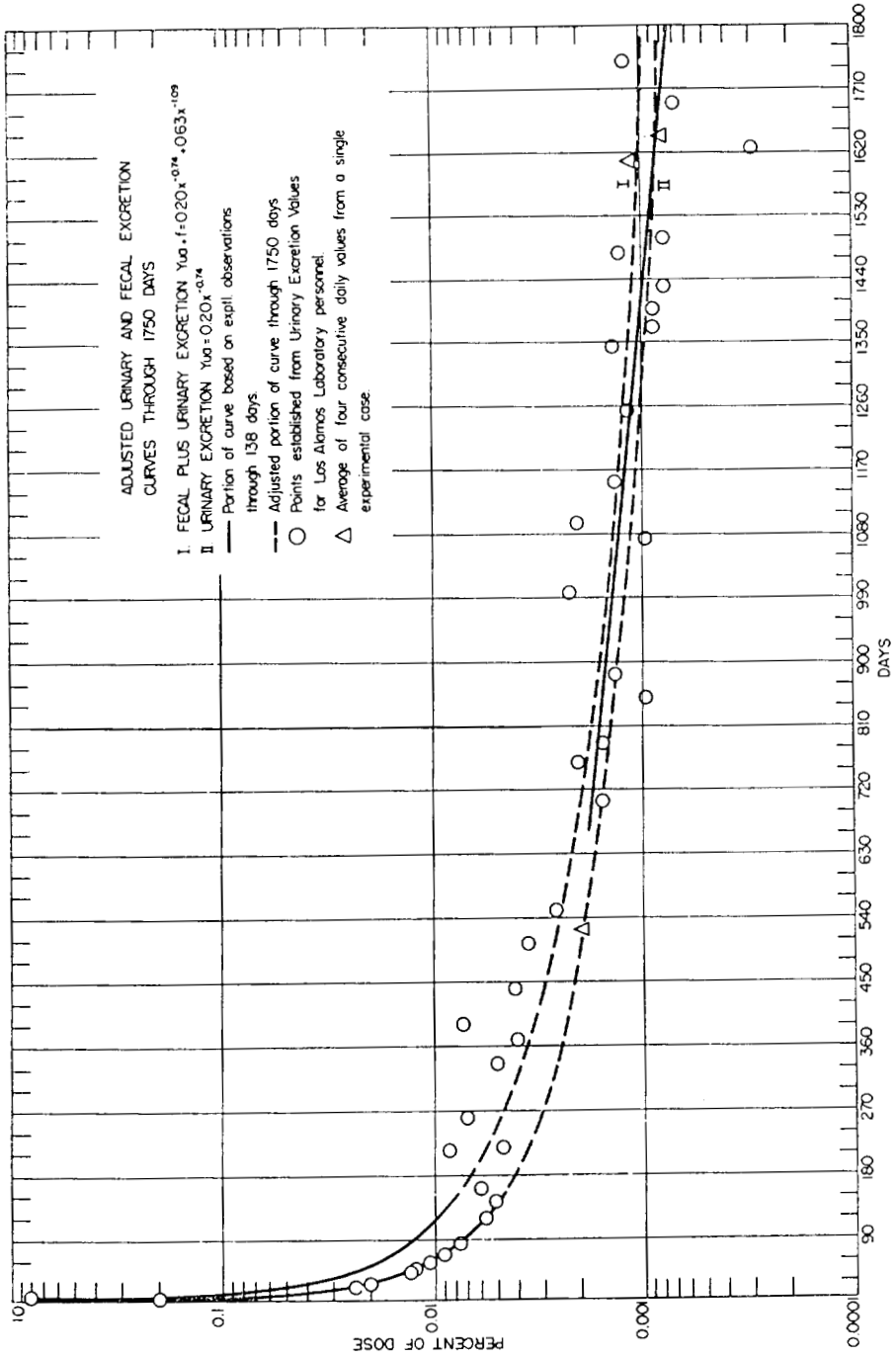

FIG. 2. Fitting of a terminal exponential function to the Los Alamos personnel urinary excretion data subsequent to day 630. (Data from Ref. [27].) The equation for the fit (the solid line after day 630) is given in the text.

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in animals can be extrapolated to man. Many factors such as weight, metabolic rate and life span are involved, and often differences seem to be explainable only as being properties of the species concerned. With some reservations on this point, however, certain comparisons may be made.

A method that has often been used for extrapolating animal radiation data to man is by comparison with radium-226.[37] With Ra^{226}, the lowest injected dose that increased the incidence of osteogenic sarcomas in mice was 1.2 μc/kg.[37] This dose produced an incidence of 0.06 tumor/mouse, a figure coincidentally equal to the tumor incidence rate reported for injected doses of 0.16 μc Pu^{239}/kg in mice.[23] Thus the Pu^{239}/Ra^{226} injected dose ratio for equal effectiveness in terms of tumor induction in mice is 0.16 μc/kg/1.2 μc/kg = 0.133. If it is assumed that this ratio is also applicable to the q values, the figure comparable to the Ra^{226} q value of 0.1 μc (Ref.[4] p. 77) is thus 0.013 μc Pu^{239}. By this criterion, the Pu^{239} q value of 0.04 μc is too high, by a factor of 3. It must be noted, however, that this result is based on a comparison of injected doses, and since other data indicate that the retention of Ra^{226} is lower than that of Pu^{239} by the same factor, 3,[7] use of the ratio of retained doses instead of injected doses would lead to agreement with the listed Pu^{239} q value. The retention data for the animals used in this comparsion, however, are not available.[23]

With beagle dogs, the lowest Pu^{239} dose which has been observed to produce skeletal tumors is 0.016 μc/kg.[23] Injected Pu^{239} doses of 0.096 μc/kg and 0.3 μc/kg produced osteogenic sarcomas in 7/8 and 12/12 dogs, respectively.[24] It is apparent that when the Pu^{239} dose is expressed in μc/kg, the dog is much more sensitive to Pu^{239} than is the mouse. Man in turn, being larger, may be expected to be more sensitive than the dog. The sensitivity ratio is much less than would be predicted however, if only the relative weights were to be considered. Thus a dog/mouse weight ratio of about 300 is associated with a dog/mouse sensitivity ratio of only 10. It may be noted that $(300)^{0.4} \simeq 10$ If a similar relationship between weight and sensitivity applies in extrapolating from dog to man, the value $(7)^{0.4} = 2.2$ is obtained. Since the Pu^{239} retention in dogs is about 70 per cent the 0.016 μc/kg injected dose in dogs thus may be translated into the value $(0.016)(.7)/2.2 = 0.0051$ μc/kg, as the value for man corresponding to the lowest retained dose that has produced a tumor in a dog. For the standard 70-kg man, this would be a body burden of 0.36 μc Pu^{239}. The currently accepted Pu^{239} q value of 0.04 μc therefore has on this basis the usual safety factor of 10.

The question of the Pu^{239} q value has been the subject of much previous discussion.[7] The above calculations indicate that the most recently available data may be used to support retention of the 0.04 μc Pu^{239} q figure. At the same time it must be pointed out that doing so still involves invoking numerous questionable assumptions, such as the relationship of Pu^{239} toxicity to Ra^{226} toxicity, which may be valid, but which also deserve further study.

9. SUMMARY AND CRITIQUE ON THE PRESENT STATUS OF THE PLUTONIUM PROBLEM IN MAN

The chief reason for concern over the toxicity of plutonium for man arises from the fact that a substantial number of people are employed in the processing of plutonium, and that, despite the use of protective equipment, some of these people excrete detectable quantities of plutonium in their urines, indicating the presence of internally-distributed plutonium in their bodies. From the nature of their work and in the absence of any evidence to the contrary, it is assumed that the plutonium in the body has entered via the respiratory route. Plutonium can enter the blood more or less directly from the lungs or may be cleared from the lungs by ciliary action, swallowed, and absorbed from the gastro-intestinal tract. It is, of course, also possible for plutonium to enter the body through cuts and puncture wounds, but these are usually treated promptly, and the evidence available indicates a very high retention at the site of entry.[6] The local injury that may be produced by such retention is important, but does not seem to be germane to the present discussion.

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Data from animal studies and the available human data are in agreement in indicating that plutonium which reaches the circulation becomes deposited chiefly in the skeleton and in the liver. The skeleton is regarded as the critical organ because the animal data indicate that skeletal lesions, particularly osteogenic sarcomas, are the principal causes of death attributable to plutonium in the body when plutonium is injected intravenously.

However, although the principal route of entry of plutonium into the body is by inhalation the methods currently in use for evaluating the body burdens tend to ignore the presence of plutonium in the lungs. The lung deposition had earlier been thought to be unimportant because it was assumed that plutonium was rapidly cleared from the lungs. More recent data, however, in dogs indicate that, depending upon the particle size, the lung retention half-time may be a year or so, and that 70–90 per cent of the retained Pu^{239} may be in the lungs or associated structures. Plutonium in the lungs therefore acts as a constant source of plutonium entering the circulation, and may result in erroneous estimates of the non-lung body burden in those programs that estimate the body burdens from Pu^{239} urinary excretion rates. It is also clear that the urine values provide no reliable information about the lung burdens.

The animal lung data also raise a question as to the validity of extrapolating from data based on injection of Pu^{239} intraveneously by adjusting excretion data obtained from employees exposed to Pu^{239} by inhalation to a virtual injection date. In the latter subjects, if Pu^{239} is still being translocated from the lungs to the circulation, the Pu^{239} urine excretion rates will be maintained at a higher level than would be the case if the plutonium were coming from systemically-deposited (i.e. liver and skeleton) activity only.

Determination of the amount of plutonium in the lungs of the occupationally-exposed personnel therefore emerges as one of the most important of the unsolved problems in the evaluation of plutonium toxicity in man. Even if it is conceded that the presence of plutonium in the lung is not as serious a problem as is its presence in the skeleton, the data are needed for evaluation of the systemic body burdens.

A major difficulty in the assessment of the Pu^{239} lung burden is the lack of information available, at least in the published literature, on the nature of the plutonium-containing material to which the employees are exposed, particularly the chemical state and the particle size of the inhaled material. The animal studies which have been conducted involve a wide range of particle sizes. A dependency of retention on particle size has been noted, but it is not clear which, if any, of these particle sizes have real significance for the human occupational situation. Presumably the necessary data could be obtained, although the practical difficulties of meaningful air sampling and particle size evaluations are recognized. Alternatively, it may be worthwhile to expose dogs to plutonium by inhalation under field conditions, i.e. in the same environment occupied by the employees, or in an analogous laboratory situation. It seems possible that in such an experiment, more meaningful figures for the relationship of the plutonium retained at a time zero to that retained at later times, relative distributions, and excretion rates could be obtained than are now available. Without these data the extrapolation of animal Pu^{239} inhalation data to man does not have a satisfactory basis.

Another approach which is reportedly being explored further is the whole-body counting method.[2] However, because of the theoretical limitations imposed by the low energy, and hence low penetrability, of the Pu^{239} X- and γ-rays, external counting methods probably cannot be used to obtain total body Pu^{239} burdens in man. For the same reasons it may not be possible to use an external counting method to obtain absolute values for Pu^{239} lung burdens. It may, however, be practical to use the whole-body counting method to determine the retention half-time in the lungs. To achieve this it is necessary only that the material being counted remain in a fixed location in the body so that the counting efficiency remains constant. This information coupled with fecal excretion data could give absolute values for the lung Pu^{239} burden, if it can be established that the disappearance rate of the plutonium seen by the whole-body counting method is representative of that of the plutonium throughout the lung.

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If, as postulated by HEALY,[32] the disappearance of plutonium from the lung may be represented by a single exponential, the data obtained with an external counter over the lungs would probably be more precise than the fecal data and would yield a value for the fractional rate of loss, λ. Although previous studies indicate that the fecal data are too variable for use in calculating λ, the averaged fecal data would provide a sufficiently accurate estimate for the rate of plutonium excretion from the lungs, λQ, and division by the λ obtained by lung counting would provide an estimate of Q, the amount of plutonium in the lung.

There is the possibility that with improvements in the form of remote handling and protective equipment, the problem of exposure of personnel to Pu^{239} can be further reduced.[38] It should not be expected, however, that the problem will cease to exist. The newer methods of instrumentation make it possible to assess the minute quantities of plutonium involved more accurately, and as better data become available additional re-evaluations of the plutonium inhalation hazard will be necessary.

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