

## ● Biological Factors in Modeling: Species Comparisons

### ESTIMATION OF HUMAN GONADAL Pu AND Ce CONCENTRATIONS FROM ANIMAL DATA\*

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**Abstract**—Data were obtained from the literature for gonad and body weights and for the Pu or Ce content of the gonads and body at death for several laboratory animal species, five human Pu injection cases, and 731 human adults exposed environmentally to Pu in fallout. Data for Pu concentration in gonads, liver, and bone samples of 59 male and five female occupational Pu cases (including four completely analyzed whole bodies) were obtained from the U. S. Transuranium Registry. A logarithmic function was used to relate fractional Pu or Ce concentration in testes and ovaries to body weight of the animals and to predict fractional Pu or Ce concentrations in human gonads,  $[Pu]_G \cdot Pu_B^{-1} = aBW^b$ , where  $[Pu]_G$  or  $[Ce]_G$  is the nuclide concentration in gonads ( $Bq\ g^{-1}$  of wet weight),  $Pu_B$  or  $Ce_B$  is the nuclide content of the body at death, and BW is body weight (kg). The fractional Pu and Ce concentrations in both the testes and ovaries are inverse and nearly linear functions of body weight. The regression lines of fractional Pu or Ce concentration in testes and ovaries have similar slopes ( $b = -1.07 \pm 0.14$ ); however, the nuclide concentrations (coefficient a) in ovaries are six times greater than in testes. Extrapolation of the animal data yielded fractional Pu concentrations in human testes and ovaries that agree with those calculated for the occupational cases and those recommended by the International Commission on Radiological Protection. The good agreement between the fractional concentrations of Pu and Ce in the testes and in the ovaries suggests that these data can be substituted in metabolic models of chemically similar elements for which gonadal data are scarce.

#### INTRODUCTION

MUTATIONS of chromosomes in ova and sperm that can result in defective offspring are an important biological effect of ionizing radiation (NAS 1956). Accordingly, the International Commission on Radiological Protection (ICRP) limited radiation doses to gonads from external sources and from radionuclides that distribute uniformly in the body or concentrate in gonads (ICRP 1958, 1959). The earlier radiation protection philosophy of the ICRP

implicitly limited genetic damage from radionuclides that are not uniformly distributed in the body. It was assumed that if radiation doses to the most intensely irradiated tissues were limited, less-irradiated tissues such as the gonads would be adequately protected.

The radiation protection philosophy recently adopted by the ICRP requires that the risk of radiation damage to gonads be explicitly taken into account (ICRP 1977). Gonadal data for many radiologically important elements are scarce for experimental animals and almost nonexistent for human ovaries and testes, and default values have been adopted for the concentrations of these radionuclides in gonads (ICRP 1979). The actinide elements, particularly Pu, were an exception because the go-

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gonadal content of Pu and Am had been reported for a number of laboratory animals, and the Pu content of the gonads of three human males and one female had been measured (Langham et al. 1950; ICRP 1972; Richmond and Thomas 1975). Those data were used to estimate a "best value" for the fractional Pu concentration in human gonads,  $1 \times 10^{-6}$  of body Pu per gram of ovaries or testes, and that value was applied to all the actinides (ICRP 1979).

Gonadal Pu content and concentration vary widely among experimental animals. Gonad fraction of body weight also varies, ranging for testes from  $2.1 \times 10^{-3}$  (dog) to  $6.2 \times 10^{-2}$  (Chinese hamster) and for ovaries from  $8.3 \times 10^{-5}$  (macaque monkey) to  $4.7 \times 10^{-4}$  (mouse). However, gonadal Pu concentrations of experimental animals consistently decrease with increasing gonad and body weight. Stather and Rodwell (1977) defined the relationship, relative testes Pu uptake, which normalized the Pu fraction in testes for both body and testes weight, as

$$\text{relative Pu uptake in testes} = \text{Pu}_T \text{Pu}_B^{-1} W_B W_T^{-1} \quad (1)$$

where  $\text{Pu}_T$  and  $\text{Pu}_B$  are the Pu contents of the testes and the whole body, respectively, and  $W_T$  and  $W_B$  are the respective weights of testes (g) and whole body (kg).

New data were compiled on the deposition of Pu in gonads of injected animals and in gonads of human beings exposed to Pu in nuclear weapons testing fallout and on the microdistribution of Pu in gonadal tissues (Thomas et al. 1985; ICRP 1986). The implications for the genetic risk of internally deposited Pu were evaluated (NCRP 1987). Equation (1) was rearranged, generalized to include ovaries, and designated as relative Pu concentration in gonads (ICRP 1986).

Relative Pu concentration in gonads

$$= \text{Pu}_G W_G^{-1} \text{Pu}_B^{-1} W_B \quad (2)$$

The median relative Pu concentration in testes was 0.09 (range 0.05 to 0.70) for three human male Pu injection cases and 15 animal experiments with soluble Pu compounds, and no experimental mean value differed from the median for all experiments by more than a factor of eight. The median relative Pu concentration in ovaries was 0.64 (range 0.16 to 3.7) in one human female Pu injection case and 13 animal studies. The new animal data agreed with earlier observations and supported the previously adopted value for the Pu concentration in human gonads (ICRP 1979). However, the median relative Pu concentrations computed for testes and ovaries were 2.3 and 7.0, respectively, for the human adults exposed only to fallout Pu (environmental cases, McInroy et al. 1979; Fox et al. 1980). The ICRP (1986) considered those values, which lie well beyond the ranges for the animal populations, to be unreliable because of large uncertainties in the analyses of the small amounts of Pu in the environmental gonadal samples.

In this report, the experimental animal data for gonadal and total body Pu are expanded by inclusion of previously overlooked reports (Kisilewski and Woodruff

1948; Scott et al. 1948; Ballou 1963) and new data (Miller et al. 1989),<sup>4</sup> and the precision of the fractional gonad Pu concentrations has been improved by computing body Pu at time of death.

New human data have been made available. The U.S. Transuranium Registry<sup>3</sup> provided results of Pu analyses of gonads, soft tissues, and bone specimens obtained at autopsy from 64 male and female Pu workers. The tissue Pu of these occupational cases, which is significantly greater than that of persons exposed only to fallout Pu, can be measured accurately. Four of the occupational cases (males) are killed whole bodies, all of whose tissues and bones were analyzed for Pu. Those four whole-body cases and the completely analyzed skeleton of one female Pu injection case (Langham et al. 1950; Larsen et al. 1978) provide the data needed to refine the estimates of total-body Pu for the occupational and environmental cases, from whom only a few soft tissues and one or two bone specimens were received for Pu analysis.

We have adapted the function, relative Pu uptake (eqn. 1) to predict fractional gonad Pu concentration.

fractional gonad Pu concentration ( $g^{-1}$ )

$$= [\text{Pu}]_G \text{Pu}_B^{-1} \quad (3)$$

where  $[\text{Pu}]_G$  is the Pu concentration in the gonads (Bq  $g^{-1}$ ), and  $\text{Pu}_B$  is the body Pu at death (Bq). Note that the units of eqn. (3) are  $g^{-1}$ .

Data for Ce in animal gonads (NCRP 1978) were also examined to determine whether that model could be generalized to estimate fractional human gonadal concentrations of elements chemically similar to Pu.

## METHODS

### Data and sources

The data used in this analysis, obtained chiefly from published sources, include body and gonad weights of adult male and female subjects, and the whole-body and gonadal Pu at various times after intake of Pu to blood. Body Pu is considered not to include residual Pu at an intramuscular injection site or inhaled Pu retained in the respiratory tract tissues. Body and gonad weights of individual subjects or groups of subjects reported in conjunction with Pu data were pooled and augmented with morphometric data from other sources when needed. If gonad weights were not reported, they were estimated from the reported gonad Pu content and concentration. If only Pu content or Pu concentration were reported, gonad weights were estimated from other morphometric data. Body Pu reported in conjunction with gonad Pu data was used whenever possible. If only gonad Pu data were reported, body Pu at the time of gonadal Pu sampling

<sup>3</sup>P. W. Durbin and N. Jeung, unpublished data.

<sup>4</sup>U.S. Transuranium Registry, P.O. Box 100, Richland, WA 99352.

Square brackets [ ] are used throughout to designate Pu concentration in a tissue; e.g.,  $[\text{Pu}]_G$  is the Pu concentration in gonads in units of radioactivity per unit weight of wet tissue.

was estimated from other reports of Pu retention in that species. The sources of data are as follows:

**Mouse, male:** 100 subjects, six experiments, 17 groups of three to eight. Plutonium-239 citrate was injected intravenously (iv) or intraperitoneally (ip) (11.1 to 370 kBq kg<sup>-1</sup>, 0.3 to 10 μCi kg<sup>-1</sup>); mice were killed 6 h to 348 d after injection (Beechy et al. 1975; Searle et al. 1976; Green et al. 1976; Smith et al. 1976; Ash and Parker 1978; Russell and Lindenbaum 1979). The highest dosages caused progressive testicular atrophy, and control testes weights were used to calculate testes Pu concentration for the high-dosage studies.

**Mouse, female:** 47 subjects, two experiments, groups of four to seven. Plutonium-239 citrate was injected iv or ip (11.1 to 200 kBq kg<sup>-1</sup>, 0.3 to 5.4 μCi kg<sup>-1</sup>); mice were killed 1 to 180 d after injection (Green et al. 1976; Smith et al. 1976).

Data for retention of injected Pu in the body of the mouse (Smith et al. 1976; Durbin and Jeung 1985) were used to estimate body Pu of mice in all the experiments described above. Additional body and gonad weight data for mice were obtained from Durbin (1973). When Pu was injected ip, the Pu content of ovaries was three to ten times greater, and testes Pu was as much as three times greater, than when Pu was injected iv (Smith et al. 1976), suggesting direct entry or adherence to membranes of Pu introduced in the peritoneal cavity.

**Chinese hamster, male:** 43 subjects, groups of five. Plutonium-239 citrate was injected iv (22.2 kBq kg<sup>-1</sup>, 0.6 μCi kg<sup>-1</sup>); hamsters were killed from 1 to 700 d after injection (Brooks et al. 1979).

**Syrian hamster, male:** 30 subjects, groups of four to eight. Plutonium-239 citrate was injected iv (0.74 kBq kg<sup>-1</sup>, 0.02 μCi kg<sup>-1</sup>); hamsters were killed 1 to 30 d after injection (Crawley et al. 1976; Stather and Rodwell 1977). Data for Pu retention in the body were augmented using the results of Stather et al. (1979). Body and gonad weight data for males and females were obtained from Thomas et al. (1979).

**Rat, male:** 92 subjects, three experiments, groups of two to six. Plutonium-239 citrate or nitrate was injected iv or intramuscularly (im) (70 to 185 kBq kg<sup>-1</sup>, 1.9 to 5 μCi kg<sup>-1</sup>); rats were killed from 1 to 420 d after injection (Kisielewski and Woodruff 1948; Scott et al. 1948; Taylor 1977).

**Rat, female:** 87 subjects, four experiments, 20 groups of three to six. Plutonium-239 citrate or nitrate was injected iv (3.7 to 3330 kBq kg<sup>-1</sup>, 0.1 to 90 μCi kg<sup>-1</sup>), or <sup>241</sup>Pu citrate was injected iv (50 MBq kg<sup>-1</sup>, 1.35 μCi kg<sup>-1</sup>); rats were killed 1 to 146 d after injection (Ballou 1963; Seidel and Volf 1972; Priest 1977; Taylor 1977).

The body Pu used to compute fractional Pu concen-

tration from the gonadal data of Taylor (1977) was estimated from other experiments performed in the same laboratory with rats of the same strain and age (Taylor et al. 1961; Taylor and Bensted 1969). Additional body and gonad weight data were obtained from Durbin (1973).

**Rabbit, male and female:** 17 male and 8 female subjects, two experiments, results for individual subjects. Plutonium-239 nitrate was injected iv or im in 21 rabbits (46 kBq kg<sup>-1</sup>, 1.1 to 1.4 μCi kg<sup>-1</sup>); rabbits were killed 1 to 365 d after injection. Plutonium-238 citrate was injected iv in four rabbits (11.1 kBq kg<sup>-1</sup>, 0.3 μCi kg<sup>-1</sup>), and pairs of rabbits were killed at 4 and 106 d.<sup>†</sup>

**Monkey, male:** 12 subjects; results for individual rhesus or cynomolgus monkeys. Plutonium-238 citrate was injected iv or im in eight monkeys (11.1 kBq kg<sup>-1</sup>, 0.3 μCi kg<sup>-1</sup>); monkeys were killed 7 to 552 d after injection (Durbin et al. 1985).<sup>‡</sup> Four cynomolgus monkeys inhaled <sup>239</sup>Pu nitrate to achieve initial lung burdens of 3.1 to 37 kBq (0.1 to 1.0 μCi); pairs of monkeys were killed at 4 and 45 d after exposure (Brooks et al. 1980).

**Monkey, female:** 17 subjects, results for individual rhesus or cynomolgus monkeys. Plutonium-239 citrate was injected iv or im (11.1 kBq kg<sup>-1</sup>, 0.3 μCi kg<sup>-1</sup>); monkeys were killed 1 to 1100 d after injection (Durbin et al. 1985).

Additional body and gonad weight data were available for 12 male and 21 female monkeys.<sup>‡</sup>

**Beagle dog, male and female:** 31 male and 31 female subjects; results for individual subjects. Plutonium-239 citrate was injected iv at dosages less than 11.1 kBq kg<sup>-1</sup> (0.3 μCi kg<sup>-1</sup>); dogs died or were killed 1 to 5394 d after injection (Miller et al. 1989). Whole-body Pu was calculated from the retention equation published by Slover et al. (1972). Additional gonad weight data were made available for 204 male and 198 female dogs, 3287 ± 1594 and 3517 ± 1501 d of age, respectively.

**Human, male occupational and injection cases:** 62 well-characterized subjects, including 55 partial autopsies<sup>§</sup> (estimated body Pu ≥ 0.83 Bq), four completely analyzed willed bodies of former Pu workers (McInroy et al. 1989)<sup>\*\*</sup> and three hospital patients, who were injected iv with <sup>239</sup>Pu citrate (Langham et al. 1950). The Pu-injected cases died of their diagnosed illnesses 4 to 450 d after injection; most of the occupational cases (exposed primarily by inhalation) died more than 20 y after intake of the major fraction of their Pu burdens. An estimated body Pu greater than 0.83 Bq was selected as the criterion for a "suitable" occupational case because, in addition to liver, the Pu analyses of the testes and the bone specimens were statistically reliable (McInroy et al. 1979).

The detailed and complete Pu analyses of the skeletons of the four willed bodies (McInroy et al. 1989)<sup>\*\*</sup>

<sup>†</sup> F. W. Brieger, Radiobiology Division, University of Utah School of Medicine, Salt Lake City, UT 84112. Unpublished data.

<sup>‡</sup> Partial autopsy defines those cases from whom a limited number of soft-tissue and bone samples were obtained at routine pathology autopsies and subsequently analyzed for Pu. For the occupational cases, the specimens included gonads, liver, lungs, pulmonary lymph nodes, and two or three 50- to 200-g samples of bone (usually vertebral wedge, rib,

sternum). For the environmental cases, the autopsy sample set usually consisted of liver, lungs, pulmonary lymph nodes, kidneys, gonads (in about one-half of the cases), and one bone sample, most often vertebral wedge (less often, rib or both vertebral wedge and rib were obtained).

<sup>§</sup> F. McInroy, unpublished data.

<sup>\*\*</sup> Unpublished data from the U.S. Transuranium Registry.

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and one female Pu injection case (Langham et al. 1950; Larsen et al. 1978) provide data for the Pu concentration ( $Bq\ g^{-1}$  wet weight) in individual bones and bone parts and the whole skeleton at intervals after Pu intake to blood ranging from 1.5 to many years (Table 1). The ratios of the Pu concentration in the whole wet skeleton to those in samples of wet rib, sternum, and thoracic and lumbar vertebral bodies (structurally equivalent to the vertebral wedge samples obtained from the partial autopsies) are  $0.80 \pm 0.08$ ,  $0.98 \pm 0.21$ , and  $0.78 \pm 0.24$ , respectively. If the mass of the wet skeleton is assumed to be 10 kg for the four males and 6.8 kg for the female (ICRP 1974), the Pu wet weight concentration ratio that we calculated from the data in Table 1 for ribs ( $[Pu]_{SK} / [Pu]_{R}$ ) yields a closer estimate of the measured skeletal Pu than the other two bone specimens separately or averaged, or the average of all three specimens.

The residual soft-tissue masses (tissues other than

liver and respiratory tract) of the four willed bodies contained  $0.10 \pm 0.05$  of the total body Pu (McInroy et al. 1989):

Total-body Pu for the 55 male occupational and three male injection cases, which were partial autopsies, was estimated, assuming that the wet weights of the adult male liver and whole skeleton are 1.8 and 10 kg, respectively (ICRP 1974), as:

$$Pu \text{ in liver } (Bq) = 1.8 [Pu]_{L}$$

$$Pu \text{ in skeleton } (Bq) = 0.80 \times 10 [Pu]_{SK}$$

$$Pu \text{ in whole body } (Bq) = 1.1 (Pu_{L} + Pu_{SK})$$

if no rib samples were received.

$$Pu \text{ in skeleton } (Bq) = 0.5 (0.78 [Pu]_{L} + 0.98 [Pu]_{ST})$$

where  $[Pu]_{L}$ ,  $[Pu]_{SK}$ ,  $[Pu]_{L}$ , and  $[Pu]_{ST}$  are the measured

Table 1. Tissue weights and Pu analytical data for whole bodies of four occupationally exposed males and skeleton of one female injected with Pu.<sup>a</sup>

Case No.	212	193	213	208	HP-4	Mean $\pm$ SD
Body weight (kg)	76.6 <sup>b</sup>	67.6 <sup>b</sup>	56.4 <sup>b</sup>	39.4 <sup>c</sup>	55.5	
Testes weight (g)	60.6	14.4	38.3	29.4		35.7 $\pm$ 19.3
Skeleton weight (g) <sup>d</sup>	10703	8691	9048	8407	3332	
Pu in tissues (Bq)						
Liver	85.7	46.6	47.6	35.7	...	
Skeleton	112.6	51.2	172.9	88.4	5823	
Soft tissues <sup>e</sup>	6.8	16.6	24.2	17.0		
Testes	0.10	0.0167	0.154	0.06		
Total Pu <sup>d</sup>	205.2	116.4	245.0	141.2		
Pu concentration in bones ( $Bq\ g^{-1}$ wet tissue)						
Whole skeleton	0.0105	0.0059	0.019	0.0105	1.75	
Ribs	0.0143	0.0064	0.0236	0.0101	2.15	
Vertebral bodies-thoracic, lumbar	0.0142	0.0054	0.0195	0.018	3.26	
Sternum	0.0105	0.0047	0.0171	0.0135	2.25	
Pu concentration ratio ( $[Pu]_{SK} / [Pu]_{bone}$ )						
Skeleton/ribs	0.732	0.92	0.81	0.743	0.814	0.804 $\pm$ 0.075
Skeleton/vertebral bodies	0.741	1.08	0.98	0.512	0.537	0.784 $\pm$ 0.244
Skeleton/sternum	1.50	1.25	1.12	0.773	0.776	0.985 $\pm$ 0.208
Pu concentration <sup>f</sup>	$8 \times 10^{-6}$	$1 \times 10^{-5}$	$1.6 \times 10^{-5}$	$1.0 \times 10^{-5}$		$1.25 \times 10^{-5} \pm 4.4 \times 10^{-6}$

<sup>a</sup>Summaries of the four U.S. Transuranium Registry cases appear in McInroy et al. (1989); Pu injection case reported by Langham et al. (1950) and Larsen et al. (1978).

<sup>b</sup>Weight of tissues recovered at autopsy.

All weights are for fresh or rehydrated tissue.

<sup>c</sup>Soft tissue and whole body do not include respiratory tract.

<sup>d</sup> $[Pu]_{SK} = W_{SK} [Pu]_{SK}$

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Pu concentrations ( $\text{Bq kg}^{-1}$ ) of wet liver, rib, vertebral wedge, and sternum, respectively.

Testes weights were available for all 64 "suitable" occupational cases, but body weights were reported for only 28 of these cases. Testes weights, and in some cases body weights also, were available from an additional 46 "unsuitable" occupational partial-autopsy cases, for whom the Pu analyses are not yet complete or for whom the estimated body Pu is less than 0.83 Bq.

**Human, male environmental cases:** Among 717 individuals exposed to Pu only from worldwide weapons-testing fallout, for whom Pu analyses of some tissue and bone specimens are available, 231 provide data for Pu concentration in testes (McInroy et al. 1979). Testes weights only are available for an additional 82 cases (Pu analyses not completed); body weights are available for only 175 of the male cases. Inhalation is considered to be the predominant mode of entry of fallout Pu in the bodies of the general population (Bennett 1974). The environmental series consists of persons exposed to fallout Pu in adulthood who died 14 to 23 y after the start of worldwide fallout in 1954 (5 to 18 y after the peak Pu concentration in surface air, in 1963) (Bennett 1974).

In the environmental series, liver is the only systemic organ that consistently yielded a statistically valid Pu measurement (lung and pulmonary lymph nodes are considered to be outside the body for the purposes of this analysis). The net Pu counting rates of nearly all the testes samples and many of the bone specimens were zero, or if positive, were less than the minimum reporting level (based on sample weight, total Pu counts collected, and counting statistics). The Pu concentrations of those specimens are statistically uncertain. Few individual sets of tissue samples provided statistically reliable Pu analytical results for testes and a bone specimen in addition to liver.

For the environmental cases, overall median values of Pu concentrations in liver ( $0.025 \text{ Bq kg}^{-1}$ , 701 male and female cases) and vertebral wedge ( $0.012 \text{ Bq kg}^{-1}$ , 325 male and female cases) were reported (McInroy et al. 1979). Fox et al. (1980) determined that the concentrations of Pu in the internal organs other than gonads were not different for males and females, and the overall median Pu concentrations could be applied to both sexes. The median Pu concentration in testes, which were obtained from the data for 231 cases (McInroy et al. 1979), is  $0.0042 \text{ Bq kg}^{-1}$ , and the 16th to 84th percentile range is 0 to  $0.0245 \text{ Bq kg}^{-1}$ .

We assume the following: (1) the tissue weights of the males are those of reference man (1.8 kg liver, 10-kg skeleton, ICRP 1974); (2) the Pu concentration in the wet vertebral wedge sample is 0.78 times the average Pu concentration in the whole wet skeleton (see Table 1 and description of occupational cases); and (3) 10% of the Pu in the body is in soft tissues other than liver. We consider that those conversion factors, derived from the whole-body occupational cases, are applicable to the environmental cases because the mode and temporal patterns of the Pu exposure are generally similar for the two groups. The median liver, skeleton, and total-body Pu of these

male cases is then 0.045, 0.095, and  $0.154 \text{ Bq}$  of Pu, respectively.

**Human, female occupational cases:** Partial autopsies were available for five female employees in Pu facilities\* and one female Pu injection case (Langham et al. 1950). The criterion of an estimated body Pu greater than 0.83 Bq was met by one occupational case and the injection case. The Pu concentration in ovaries was statistically reliable for only one occupational case and the one injection case. For the four other cases, several of the Pu analyses of bone specimens were also statistically unreliable. However, these six cases were considered worth including because none of the ovary Pu values was zero, and the body Pu, ovaries Pu, and the fractional Pu concentration in ovaries could be calculated for each individual.

**Human, female environmental cases:** Among 78 females for whom ovaries weight was reported, only 39 Pu analyses of ovaries were available (McInroy et al. 1979). Body weights were available for 36 female cases. The mean age of the 78 cases was  $59.8 \pm 18.3 \text{ y}$ . Only 26 of these cases were premenopausal (less than 52 y). The overall median value of the Pu concentration in ovaries, which we obtained from the published data for 39 cases, was  $0.0175 \text{ Bq kg}^{-1}$  with a 16th to 84th percentile range from 0 to  $0.09 \text{ Bq kg}^{-1}$ . The net Pu count of ovaries was statistically reliable for only two cases, and one of those may have been contaminated.

If the median Pu concentrations in liver and vertebral wedge samples for the environmental cases (see above) are combined with the tissue masses for reference woman (1.4-kg liver, 6.8-kg skeleton, ICRP 1974), the Pu content of female liver, skeleton, and whole body is estimated to be 0.035, 0.064, and  $0.109 \text{ Bq}$ , respectively.

**Ce; male and female rats, guinea pigs, rabbits, dogs, swine, male mice, female cats:** One to five subjects per group; Ce chloride or citrate was injected parenterally; some dogs inhaled  $^{144}\text{CeCl}_2$ ; animals were killed 2 to 4 d after injection (NCRP 1978). Cerium in the body at death is considered to be the same as Ce injected because prompt excretion of Ce is negligible in that short postinjection interval.

#### Data presentation

In the tables and figures, gonad and body weights are presented as arithmetic mean  $\pm$  standard deviation (SD; Fisher 1954), which was calculated from data for individuals or from grouped data weighted for group size when individual measurements were not reported. Gonadal Pu, recalculated from original sources, is expressed as the fractional gonad Pu concentration,  $[\text{Pu}]_G/\text{Pu}_B^{11}$ . Fractional gonad Pu concentration, which incorporates individual variations in gonad weight, gonadal Pu, body Pu, and time after Pu intake, is not normally distributed. It approaches but is not exactly lognormal. Therefore, we have expressed fractional gonad Pu concentration as the geometric mean (median), and the variability of the collected measurements as the 16th to 84th percentile range. The percentile range was used rather than the geometric standard deviation ( $\sigma_G$ ) because the distributions of the

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Table 2. Adult body and testes weights and fractional testes Pu concentrations.<sup>a</sup>

Species	Body weight <sup>b</sup> (kg)	Testes weight <sup>c</sup> (g)	Fractional Pu concentration <sup>d</sup> [Pu] <sub>t</sub> · Pu <sub>t</sub> <sup>-1</sup>
Mouse	0.031 <sup>e</sup>	0.23 ± 0.042	5.2 × 10 <sup>-3</sup> (3.6 × 10 <sup>-3</sup> - 8.2 × 10 <sup>-3</sup> )
Chinese hamster	0.032	2.0	9.5 × 10 <sup>-4</sup> (5.1 × 10 <sup>-4</sup> - 8.5 × 10 <sup>-4</sup> )
Syrian hamster	0.133 ± 0.016	2.2 ± 0.06	2.3 × 10 <sup>-2</sup> (2.1 × 10 <sup>-2</sup> - 2.6 × 10 <sup>-2</sup> )
Rat	0.25	2.9 ± 0.28	8.6 × 10 <sup>-4</sup> (5.6 × 10 <sup>-4</sup> - 1.4 × 10 <sup>-3</sup> )
Rabbit	2.5 ± 0.7	8.0	4.4 × 10 <sup>-5</sup> (2.3 × 10 <sup>-5</sup> - 1.6 × 10 <sup>-4</sup> )
Monkey	7.0 ± 2.0	39.0 ± 1.4	2.7 × 10 <sup>-3</sup> (7.6 × 10 <sup>-4</sup> - 5.8 × 10 <sup>-3</sup> )
Beagle dog	10	20.9 ± 5.4	1.9 × 10 <sup>-3</sup> (8.4 × 10 <sup>-4</sup> - 3.4 × 10 <sup>-3</sup> )
Human-reference man	70	35	1.0 × 10 <sup>-3</sup>
Occupational Pu cases	69.0 ± 16	42.0 ± 22	6.2 × 10 <sup>-4</sup> (1.8 × 10 <sup>-4</sup> - 2.2 × 10 <sup>-3</sup> )
Environmental Pu cases	69.0 ± 14	35.0 ± 16	3.1 × 10 <sup>-3</sup>

<sup>a</sup>Data sources and management are described in Methods.

<sup>b</sup>Arithmetic mean ± standard deviation, SD = (dev. in %).

<sup>c</sup>Median (50th percentile) and (16th to 84th percentile range).

<sup>d</sup>When no SD is shown, only one value was given in reference representing all subjects.

logarithms of individual values around the medians are not symmetrical. A single value is shown without a range or SD when only one published value, representing all subjects, was available.

Tables 2 and 3 contain representative values for gonad and body weight and fractional gonadal Pu concentrations of adult males and females, respectively, of several laboratory animal species, reference man and woman (ICRP 1974), and the male and female occupational and environmental cases whose autopsy tissue samples were analyzed for Pu. Measured body weights and fractional gonadal Ce concentrations of several laboratory species are collected in Table 4.

The straight lines through the data points in Figs. 1 through 3 were fitted by least-squares regression of the

logarithms. All of the relevant animal data were used to fit each line.

## RESULTS AND DISCUSSION

The equations of the regression of log testes or ovaries weight (g) on log body weight (kg), and the correlation coefficients of the regression lines (*r*) for the animals, are: T (g) = 6.5BW<sup>0.64</sup> (*r* = 0.9136) and O (g) = 0.19BW<sup>0.76</sup> (*r* = 0.9151), respectively.

The slopes of the fitted regression lines of gonad weight on body weight (not shown) are less than 1.0, indicating that, unlike the parenchymatous organs, the gonads are not a constant fraction of body weight (Brody 1945). Extrapolation of the testes and ovaries weight

Table 3. Adult body and ovaries weights and fractional ovaries Pu concentrations.<sup>a</sup>

Species	Body weight <sup>b</sup> (kg)	Ovaries weight <sup>c</sup> (g)	Fractional Pu concentration <sup>d</sup> [Pu] <sub>o</sub> · Pu <sub>o</sub> <sup>-1</sup>
Mouse	0.026 <sup>e</sup>	0.012 ± 0.003	5.0 × 10 <sup>-3</sup> (2.4 × 10 <sup>-3</sup> - 1 × 10 <sup>-2</sup> )
Syrian hamster	0.13 ± 0.014	0.039 ± 0.007	...
Rat	0.20	0.062 ± 0.012	4.5 × 10 <sup>-3</sup> (2.1 × 10 <sup>-3</sup> - 6.4 × 10 <sup>-3</sup> )
Rabbit	3.2 ± 0.8	0.60	2.2 × 10 <sup>-4</sup> (9.8 × 10 <sup>-5</sup> - 1.5 × 10 <sup>-3</sup> )
Monkey	5.4 ± 2.1	0.45 ± 0.20	1.0 × 10 <sup>-4</sup> (7 × 10 <sup>-5</sup> - 1.9 × 10 <sup>-4</sup> )
Beagle dog	10	1.28 ± 0.56	4.6 × 10 <sup>-5</sup> (2.4 × 10 <sup>-5</sup> - 1 × 10 <sup>-4</sup> )
Human-reference woman	58	11.5	1.0 × 10 <sup>-3</sup>
Occupational Pu cases	47.0 ± 8	17.0 ± 1	1 × 10 <sup>-3</sup> (9.5 × 10 <sup>-4</sup> - 4.4 × 10 <sup>-3</sup> )
Environmental Pu cases (all)	63.0 ± 17	8.2 ± 6.1	8 × 10 <sup>-3</sup>
Environmental Pu cases (<52 yr)	63.0 ± 22	12.2 ± 8	

<sup>a</sup>Data sources and management are described in Methods.

<sup>b</sup>Arithmetic mean ± standard deviation, SD = (dev. in %).

<sup>c</sup>Median (50th percentile) and (16th to 84th percentile range).

<sup>d</sup>When no SD is shown, only one value was given in reference representing all subjects.

Table 4. Adult body weight and fractional Ce concentrations in animal gonads.\*

Species	Body weight (kg)	Fractional gonad Ce concentration [Ce] <sub>g</sub> · Ce <sup>-1</sup>	
		Testes	Ovaries
Mouse	0.025	3.0 × 10 <sup>-7</sup>	...
Rat	0.16 (F), 0.25 (M)	4.7 × 10 <sup>-7</sup>	2.9 × 10 <sup>-7</sup>
Guinea pig	0.45	1 × 10 <sup>-6</sup>	5.7 × 10 <sup>-7</sup>
Rabbit	3.0	2.7 × 10 <sup>-6</sup>	3.6 × 10 <sup>-6</sup>
Cat	3.4		4.4 × 10 <sup>-6</sup>
Oog	10	2.8 × 10 <sup>-6</sup>	2.7 × 10 <sup>-6</sup>
Miniature swine	70	5.7 × 10 <sup>-6</sup>	1.0 × 10 <sup>-5</sup>

\*Data from NCRP (1978)

curves for the animals overestimates the median adult human testes weight, and the weight curve for the animals underestimates the adult human ovaries median weight by a factor of about 2.8.

The fractional testes and ovaries Pu concentrations are shown in Tables 2 and 3, respectively. The fractional gonad Pu concentrations shown for the animals are not all the same as previously published values (Stather and Rodwell 1977; Thomas et al. 1985; ICRP 1986) because new data have been added (rats), uncertain data from

several Pu inhalation experiments in dogs have been replaced by more reliable data from a large Pu-injection study (Miller et al. 1989), and in all cases, default values for Pu (i.e., amount of Pu injected) have been replaced by better estimates of the body Pu at death.

The fractional gonad Pu concentrations shown for the male and female environmental cases and the male occupational cases are not the same as those previously published (Thomas et al. 1985; ICRP 1986). The Pu analytical data for gonads and the median values for [Pu]<sub>g</sub>

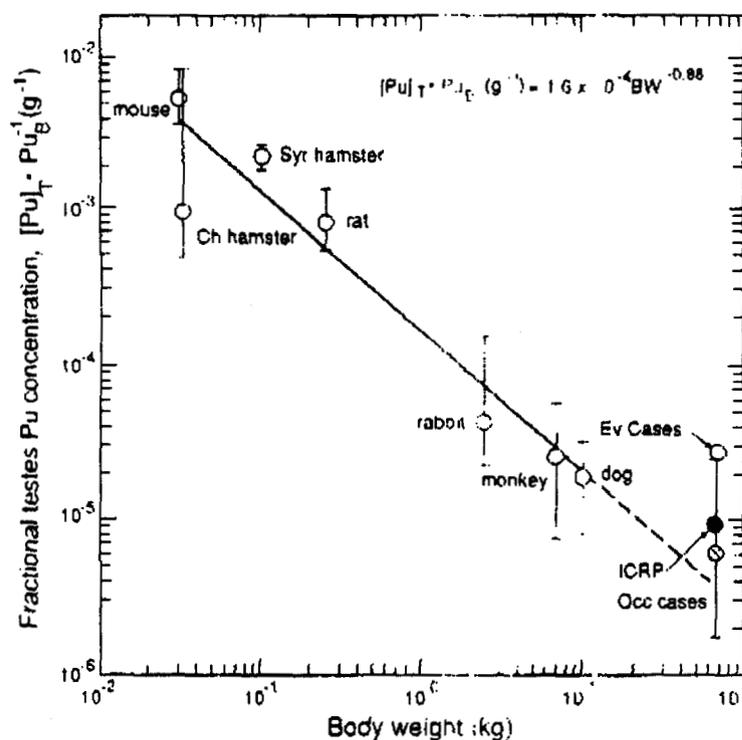


Fig. 1. Fractional testes Pu concentrations as a function of body weight of some laboratory animals and adult men (seven species,  $r = -0.9552$ ). Syr = Syrian; Ch = Chinese (hamster); Ev = environmental; Occ = occupational (exposure); ICRP = International Commission on Radiological Protection (ICRP 1979). See text for explanation of terms in equation.

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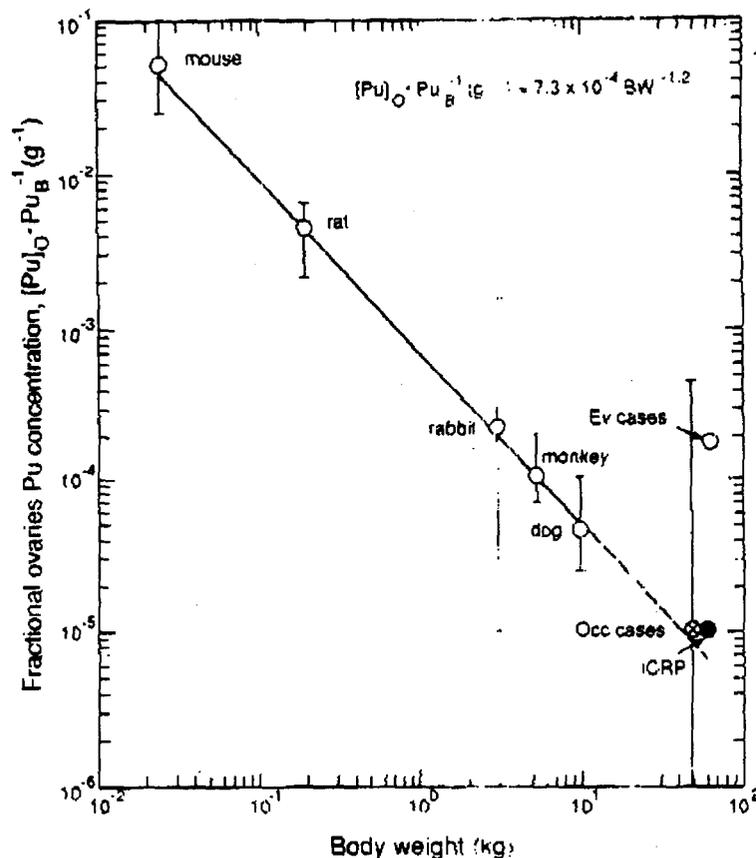


Fig. 2. Fractional ovaries Pu concentration as a function of the body weight of some laboratory animals and adult women (five species,  $r = 0.9995$ ). Ev = environmental; Occ = occupational (exposure); ICRP = International Commission on Radiological Protection (ICRP 1979). See text for explanation of terms in equation.

and  $[Pu]_{SK}$  used were taken only from the published case reports (McInroy et al. 1979). The size and structure of the set of occupational cases used in this report differ from those in earlier reports because we added some new unpublished cases and omitted as unsuitable some previously published cases whose estimated  $Pu_B$  was less than 0.83 Bq. Furthermore, the conversion factors we used to compute  $[Pu]_{SK}$  from  $[Pu]_R$  or  $[Pu]_I$ , and to compute  $Pu_B$  from  $Pu_I$  and  $Pu_{SK}$  (see Methods section) differ somewhat from those used by Thomas et al. (1985), who used  $[Pu]_{SK} = 0.65[Pu]_I$ , and  $Pu_B = Pu_I + Pu_{SK}$ . Our conversion factors also differ from those used by the ICRP (1986),  $[Pu]_{SK} = 0.65[Pu]_I$ , and  $Pu_B = 0.8(Pu_I + Pu_{SK})$ . Our calculated values for  $Pu_B$  are about 10 and 30% greater, respectively, than those that would be obtained using the conversion factors of the ICRP (1986) and Thomas et al. (1985).

The distributions of the fractional gonad Pu concentrations about their median values are surprisingly small, considering the diversity of the animal experiments and the ranges of ages, gonadal weights, and postexposure intervals of both the animal and human subjects. Except

for the Chinese hamster, the 16th and 84th percentile values of the fractional testes Pu concentration differed by no more than a factor of four from median values. Except for the rabbits and the female occupational cases, the ranges of fractional ovaries Pu concentration differed from the respective median by no more than a factor of two.

The general trend of declining fractional gonad Pu concentration with increasing gonad and body weight is demonstrated in Figs. 1 and 2, confirming that the fractional gonad Pu concentrations are inverse and approximately linear functions of body weight, as suggested by Slather and Rodwell (1977).

Extrapolation of the curves in Figs. 1 and 2 to the body weights of reference man (70 kg) and woman (58 kg) predicts fractional Pu concentrations in adult testes and ovaries of  $4 \times 10^{-6}$  and  $7 \times 10^{-6}$  g<sup>-1</sup>, respectively. The extrapolated fractional testes Pu concentration for man is 67% of the value we obtained for the male occupational cases, 40% of the recommended value (ICRP 1979, 1986), and 5% of the value we calculated from the environmental data. The extrapolated fractional ova-

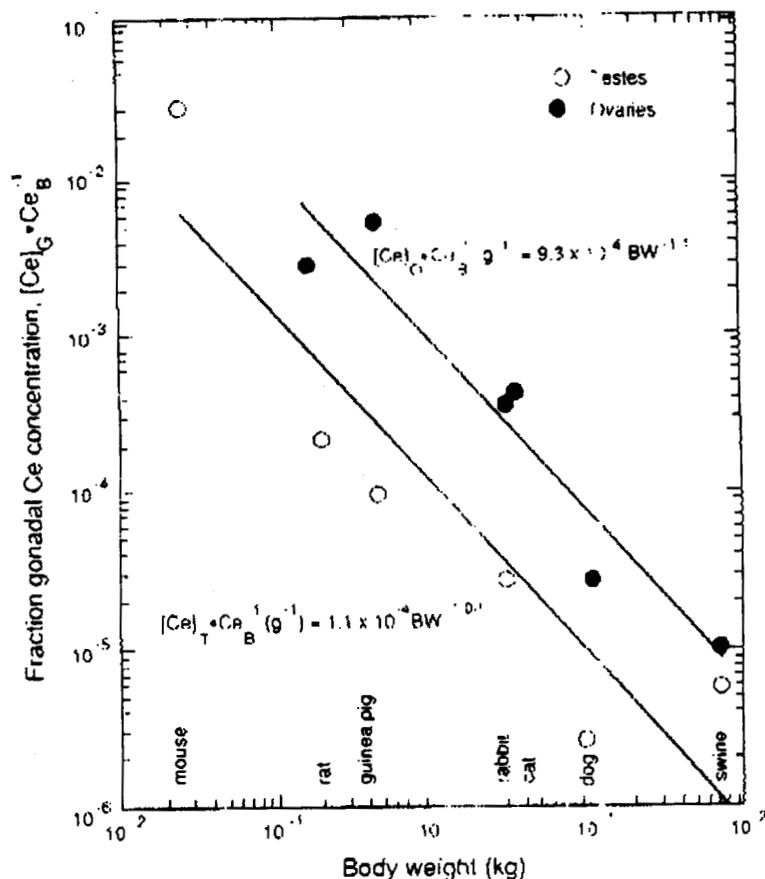


Fig. 3. Fractional testes and ovaries Ce concentrations as functions of body weight of some laboratory animals (testes, six species,  $r = 0.9212$ ; ovaries, six species,  $r = 0.9490$ ). See text for explanation of terms in equation.

ries Pu concentration for human females is 80% of the value we obtained for the six occupational cases, 70% of the recommended value (ICRP 1979, 1986), and 4.4% of the value we calculated from the environmental data.

The animal data for fractional testes and ovaries Ce concentrations are plotted as functions of body weight in Fig. 3. Extrapolation of the Ce curves to the body weights of reference man and woman yields fractional Ce concentrations of  $1.1 \times 10^{-4} \text{ g}^{-1}$  in testes and  $1.1 \times 10^{-5} \text{ g}^{-1}$  in ovaries, close to the measured values for the miniature swine.

The trends of declining Ce concentration in testes and ovaries with increasing body weight are the same as for Pu, even though not all the same species are represented in the two data sets. The parameters of the regression lines are similar. The intercept at  $\text{BW} = 1 \text{ kg}$  of the Ce curve is about twice that of the Pu curve, but the scatter of the Ce data points is large, and the intercepts are not significantly different. The regression lines of fractional testes Pu and Ce concentrations are also similar. The slope of the Ce curve is 1.3 times that of the Pu curve, and the intercept of the Pu curve at  $\text{BW} = 1 \text{ kg}$  is 1.7 times that of the Ce curve. However, the scatter of both sets of testes

data about their respective regression lines is large, and the two sets of data overlap; the curves are not significantly different ( $F$ -test, Neter and Wasserman 1974).

The regression lines of fractional concentrations of Pu and Ce in testes and ovaries are all similar to each other. The four slopes,  $-0.88$  and  $-1.1$  for Pu and Ce in testes, respectively, and  $-1.2$  and  $-1.1$  for Pu and Ce in ovaries, respectively, are not significantly different from one another. The intercepts at  $\text{BW} = 1 \text{ kg}$  for ovaries,  $7.3 \times 10^{-4}$  and  $9.3 \times 10^{-4} \text{ g}^{-1}$  for Pu and Ce, respectively, are five and eight times greater than the intercepts of the respective testes curves,  $1.6 \times 10^{-4}$  and  $1.1 \times 10^{-4} \text{ g}^{-1}$ . If the gonad data for Pu and Ce in the animals are combined, the coefficient of the average ovaries curve is six times larger than that of the average testes curve, and the difference is statistically significant ( $p < 0.01$ ,  $F$ -test, Neter and Wasserman 1974).

#### SUMMARY AND CONCLUSIONS

1. The fractional concentrations of Pu and Ce in testes and ovaries of laboratory animals are inverse and approximately linear functions of body weight. The four

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regression lines of fractional Pu and Ce concentration in testes and ovaries expressed as logarithmic functions (fractional gonadal nuclide concentration =  $aRW^b$ ) have similar slopes. The intercept at BW = 1 kg for the regression of fractional concentration of Pu and Ce in ovaries is six times greater than for the fractional concentration of the two nuclides in testes—a statistically significant difference. A single value,  $1 \times 10^{-5} \text{ g}^{-1}$ , for the fractional gonadal concentration of actinides or lanthanides is probably not appropriate for both testes and ovaries.

2. The fractional gonadal nuclide concentration model adequately describes the uptake of Ce as well as that of Pu in both ovaries and testes. It seems reasonable to generalize the model to estimate gonadal concentrations of chemically similar elements—multicharged cations that hydrolyze at low pH, form stable complexes with biological ligands, and are associated mainly with macrophages in the connective tissue matrix of the gonads.

3. Extrapolation of logarithmic regression lines of fractional testes and ovaries Pu concentrations for the animals to reference man and reference woman body weights yields human values which agree reasonably well with the recommended value of  $1.0 \times 10^{-5} \text{ g}^{-1}$  (ICRP 1979, 1986) and with the median measured values for the occupational cases. The agreement between the gonadal data for Ce

and Pu in both testes and ovaries of animals lends support to the ICRP practice of substituting gonadal Pu values in the metabolic models of other actinides for which there are no gonadal data. That agreement suggests further that gonadal Ce and Pu values are reasonable substitutes for human gonadal concentrations of elements with principal III and IV oxidation states.

4. The fractional Pu concentrations in human testes and ovaries that we calculated for the environmental cases lie close to the 84th percentiles for the occupational cases, and they are more than 10 times larger than the values extrapolated from animal data. These large discrepancies reinforce the view that the Pu analyses of the environmental human gonad and bone samples are probably inaccurate (ICRP 1986), and a more sensitive analytical method is needed to insure that statistically reliable analyses are obtained from samples containing Pu at environmental levels.

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## REFERENCES

- Ash, P.; Parker, T. The ultrastructure of mouse testicular interstitial tissue containing plutonium-239 and its significance in explaining the observed distribution of plutonium in the testes. *Int. J. Radiat. Biol.* 34:523-536; 1978.
- Balfou, J. E. Comparative toxicity of Pu<sup>239</sup> and Pu<sup>240</sup>. In: Hanford biology research annual report for 1962. HW-76000. Richland, WA: Hanford Laboratory; 1963:11-17.
- Beechy, C. V.; Green, D.; Humphreys, E. R.; Searle, A. G. Cytogenetic effects of plutonium-239 in male mice. *Nature* 256: 577-589; 1975.
- Bennett, B. G. Environmental pathways of transuranic elements. In: Wachholz, B. W., ed. *Plutonium and other transuranium elements: Sources, environmental distribution and biomedical effects*. U.S. Atomic Energy Commission, Springfield, VA: National Technical Information Service; 1974:131-154.
- Brody, S. *Bioenergetics and growth*. Baltimore, MD: Reinhold Publishing Co.; 1945:575-663.
- Brooks, A. L.; Diel, J. H.; McClellan, R. O. The influence of testicular microanatomy on the potential genetic dose from internally deposited <sup>239</sup>Pu citrate in Chinese hamster, mouse, and man. *Radiat. Res.* 77:292-301; 1979.
- Brooks, A. L.; Mewhinney, J. W.; Redman, H. C.; Guilmette, R. A.; McClellan, R. O. Distribution, retention, and early cytogenetic damage in cynomolgus monkeys following inhalation of <sup>239</sup>Pu(NO<sub>3</sub>)<sub>6</sub>. In: *Inhalation Toxicology Research Institute Annual Report, LMF-84*. Albuquerque, NM: Inhalation Toxicology Research Institute; 1980:153-157.
- Crawley, F. E. H.; Humphreys, E. R.; Stather, J. W. A comparison of 239-plutonium in soft tissues and skeleton of mice, rats and hamsters. *Health Phys.* 30:491-493; 1976.
- Durbin, P. W. Metabolism and biological effects of the transplutonic elements. In: Hodge, H. C.; Stannard, J. N.; Hursh, J. B., eds. *Uranium, plutonium, transplutonic elements*. Handbook of experimental pharmacology, vol. 36. Berlin, Germany: Springer-Verlag; 1973:739-896.
- Durbin, P. W.; Jeung, N. Kinetics of plutonium deposition in the mouse. In: *Biology and Medicine Division Annual Report 1983-1984, LBL-18393*. Berkeley, CA: Lawrence Berkeley Laboratory; 1985:56-59.
- Durbin, P. W.; Jeung, N.; Schmidt, C. T. <sup>239</sup>Pu(IV) in monkeys. Washington, D.C.: U.S. Nuclear Regulatory Commission; NUREG/CR-4355; 1985.
- Fisher, R. A. *Statistical methods for research workers*, 12th edition, revised. New York, NY: Hafner Publishing Co.; 1954.
- Fox, T.; Tietjen, G. L.; McInroy, J. F. Statistical analysis of a Los Alamos Scientific Laboratory study of plutonium in U.S. autopsy tissue. *Health Phys.* 39:877-892; 1980.
- Green, D.; Howells, G. R.; Humphreys, E. R.; Vennart, J. Radiation dose to mouse testes from <sup>239</sup>Pu. In: Jee, W. S. S., ed. *The health effects of plutonium and radium*. Salt Lake City, UT: J. W. Press; 1976:21-31.
- Green, D.; Howells, G.; Vennart, J.; Watts, R. The distribution of plutonium in the mouse ovary. *J. Appl. Radiat. Isotopes* 28:497-501; 1977.
- International Commission on Radiological Protection. Report on amendments to the recommendations of the International Commission on Radiological Protection (ICRP). *Radiology* 70:261-262; 1958.
- International Commission on Radiological Protection. Report of ICRP committee II on permissible dose for internal radiation. *Health Phys.* 3:1-380; 1959.
- International Commission on Radiological Protection. *The metabolism of compounds of plutonium and other actinides*. Oxford, England: Pergamon Press; ICRP Publication 19; 1977.

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