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PRIMATE POLONIUM METABOLIC MODELS AND THEIR USE IN ESTIMATION OF SYSTEMIC RADIATION DOSES FROM BIOASSAY DATA*

FINAL REPORT

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FINAL REPORT

to

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EXECUTIVE SUMMARY

A polonium urinary excretion model was derived at New York University Medical Center's Institute of Environmental Medicine (NYUMCIEM) to estimate the systemic radiological dose to workers based on their excretion of polonium in urine over time. This model was developed as part of a limited research program to evaluate polonium urinalysis monitoring results which were accumulated as part of the routine health physics monitoring during the mid-1940s through the early 1970s. The model is independent of the time sequence of exposure, treating each urinalysis result as potentially reflecting a new acute input of ^{210}Po into the urinary compartment. Statistical criteria have been developed to test each data point to determine whether the result represents a new polonium uptake event. The systemic body content of polonium and internal radiation dose are estimated from the urinary output using newly determined metabolic parameters of polonium gleaned from studies of polonium in the non-human primate. The significance of the dose estimates are examined by defining the degree of uncertainty attached to them through comprehensive statistical testing procedures and retrospective quality control considerations.

Many parameters necessary for dosimetry calculations (such as organ partition coefficients and excretion fractions), were evaluated from metabolic studies of ^{210}Po in two species of non-human primates. Four tamarins and five baboons were injected intravenously with ^{210}Po citrate. Excreta and blood samples were collected for up to 203 days post administration for tamarins and up to 91 days post administration for baboons. Baboons were sacrificed by exsanguination at 1 day, 1 week, 2 weeks, 1 month, and 3 months post exposure. Complete necropsies were performed and all excreta and the majority of all organ, skeletal, and tissue samples were analyzed radiochemically for their ^{210}Po content.

Excretion fractions of ^{210}Po in the two species of non-human primates were found to be markedly different from data reported elsewhere in other species, including humans. The tamarin excreted approximately 19.7% of the systemic ^{210}Po in urine and 68.8% in feces. The baboon excreted approximately 37.7% and 55.1% of the systemic ^{210}Po in urine and feces, respectively. These new findings differ with other models which predict that approximately 10% and 90% of polonium will be excreted in urine and feces, respectively. The ^{210}Po excretion rate in the baboon was much more rapid than in the tamarin. The biological half-time of ^{210}Po excretion in the baboon was approximately 15 days while in the tamarin, the ^{210}Po excretion rate was in close agreement with the 50 day biological half-time predicted by ICRP 30.

A thorough review of the polonium urinalysis procedure showed that significant recovery losses resulted when metabolized ^{210}Po (i.e., ^{210}Po which has crossed a biological membrane) was deposited out of raw (i.e., unprocessed) urine. A comparison study was performed to test this finding using urine samples from baboons and tamarins which had been injected with ^{210}Po. Aliquots of baboon and tamarin urine were traced with ^{208}Po, ashed in nitric acid, converted to a chloride solution, and deposited onto a nickel disc in a plating cell while the other aliquots were poured without processing into a plastic cup and deposited onto a copper disc. In some cases, the ^{210}Po recovery using ashed urine samples exceeded that using unprocessed samples by more than one order of magnitude.

Determination of the residual blood volume in all organ and tissue samples was accomplished by labeling red blood cells of the baboon with ^{51}Cr prior to exsanguination. It was then possible to separate sample ^{210}Po measurements into tissue content and residual blood content.

The spleen was by far the organ with the highest post-exsanguination residual blood concentration, with an average of 0.51 ± 0.19 ml/g. The blood-borne polonium added a significant amount of ^{210}Po to the total measured in the spleen, ranging from an additional 23.5% at one day post exposure to 10.4% at 91 days post exposure. The lungs, with 0.23

± 0.05 ml/g, had the next highest concentration of residual blood, which accounted for increases of 28.6% and 7.3% to the polonium content at one day and 91 days post exposure, respectively. Liver and kidneys had residual blood concentrations of approximately 0.1 ml/g. Unlike the spleen and lung, the liver and kidney polonium content were not greatly affected by the addition of blood-borne polonium.

Polonium-210 was found to distribute throughout the soft tissues of the baboon but not with organ partition coefficients for liver, kidneys, and spleen as predicted by the ICRP 30 polonium metabolic model. Fractional distribution of 0.29 for liver, 0.07 for kidneys, and 0.006 for spleen were determined. These three organs did exhibit the greatest ^{210}Po levels on a per gram basis, with kidneys having the highest concentration followed by liver and spleen. Retention times for ^{210}Po in tissues could be described by single exponential functions and had biological half-times ranging from 15 to 50 days.

ABSTRACT

A Polonium metabolic model was derived and incorporated into a Fortran algorithm which estimates the systemic radiation dose from ^{210}Po when applied to occupational urine bioassay data. The significance of the doses estimated are examined by defining the degree of uncertainty attached to them through comprehensive statistical testing procedures.

Many parameters necessary for dosimetry calculations (such as organ partition coefficients and excretion fractions), were evaluated from metabolic studies of ^{210}Po in non-human primates. Two tamarins (on two separate occasions) and six baboons were injected intravenously with ^{210}Po citrate. Excreta and blood samples were collected. Five of the baboons were sacrificed at times ranging from 1 day to 3 months post exposure. Complete necropsies were performed and all excreta and the majority of all skeletal and tissue samples were analyzed radiochemically for their ^{210}Po content.

The ^{210}Po excretion rate in the baboon was more rapid than in the tamarin. The biological half-time of ^{210}Po excretion in the baboon was approximately 15 days while in the tamarin, the ^{210}Po excretion rate was in close agreement with the 50 day biological half-time predicted by ICRP 30. Excretion fractions of ^{210}Po in the non-human primates were found to be markedly different from data reported elsewhere in other species, including man.

A thorough review of the Po urinalysis procedure showed that significant recovery losses resulted when metabolized ^{210}Po (i.e., ^{210}Po which has crossed a biological membrane) was deposited out of raw (i.e, unprocessed) urine. A comparison study was performed to test this finding using urine samples from baboons and tamarins which had been injected with ^{210}Po.

Polonium-210 was found to be distributed throughout the soft tissues of the baboon but not with the partition coefficients for liver, kidneys, and spleen that are predicted by the ICRP 30 metabolic model. A fractional distribution of 0.29 for liver, 0.07 for kidneys, and 0.006 for spleen was determined. Retention times for ^{210}Po in tissues could be described by single exponential functions and had biological half-times ranging from 15 to 50 days.

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1 Introduction

Polonium-210 (^{210}Po) is a naturally occurring 5.3 MeV alpha particle emitter (radiological half-life of 138.4 days) which can also be anthroprogenically produced. In 1943, Monsanto Chemical Company began large scale chemical separation of ^{210}Po from irradiated bismuth metal ingots for the Dayton Project. This work was a major part of the United States government's Manhattan Project, as the ^{210}Po in combination with beryllium was used as a neutron source to initiate the fission reaction for detonation of the atomic bomb (Gilbert 1969).

The goal of this research was to develop a model to estimate systemic dose resulting from occupational exposure to ^{210}Po. In addition, a thorough evaluation of the uncertainty associated with the dose estimate was to be made through comprehensive statistical testing procedures and extensive retrospective quality control considerations. Knowledge of this uncertainty is important for the development of meaningful epidemiological relationships of a dose-response nature.

Early health monitoring data show that some workers were excreting measureable quantities of ^{210}Po in urine and feces (Sheehan 1964a; Silverman 1944; Spoerl 1951). As part of the health monitoring program, workers were required to submit urine samples at frequent intervals, usually on a weekly basis (Spoerl 1950). Results of the ^{210}Po urinalyses were compared to a pre-determined "tolerance limit." Work restrictions were assigned whenever an individual was found to excrete Po in excess of the tolerance limit. The work restriction would be removed whenever the Po level dropped below the tolerance limit. Polonium-210 was processed extensively until 1959, when the program was reduced in scale. The ^{210}Po bioassay program continued into the 1970s. Polonium urinalysis data has been collected for approximately 2000 workers who were monitored during this program, covering a period of about 28 years.

The major route of Po exposure was probably by inhalation (which also involves a significant ingestion component via the mucociliary clearance mechanism), although other routes such as direct ingestion, wounds, and/or by absorption through the skin, cannot be definitively excluded as possible contributors to intake.

Unlike bone seeking alpha emitters, Po translocates from primary deposition sites into the circulatory system and redistributes throughout the soft tissues of the body, effectively resulting in whole body irradiation. Metabolic information on the biokinetics of Po in man was determined to be statistically insufficient to accurately define systemic dose from urine bioassay data. Therefore, a study of the excretion rates, retention times, and distribution of ^{210}Po at various body sites after controlled exposures in non-human primates was performed as a necessary adjunct to the interpretation of historical health monitoring bioassay data. Metabolic parameters determined in this study have been incorporated into a new Po dosimetry model.

2 Literature Review

2.1 Environmental Polonium

Due to the decay of U series nuclides, low levels of ^{210}Po are present naturally in air, water, biota, and foodstuffs. An extensive review of the sources and distribution of environmental ^{210}Po and normal metabolic levels in man has been published by Parfenov (1974).

The average daily dietary intake of ^{210}Po has been estimated to range from 37 to 370 mBq (1 to 10 pCi) per day based on average concentrations of the radionuclide in foodstuffs (Hill 1965). Hill calculated an average intake of 118 mBq (3.2 pCi)/day for individuals in Great Britain and Holtzman estimated an average intake of 67 mBq (1.8 pCi)/day for individuals in the U.S. based on excretion analyses (Holtzman 1963). Excretion of ^{210}Po averaged 70 ± 17 mBq (1.90 ± 0.46 pCi)/day in feces and 23 ± 9 mBq (0.63 ± 0.25 pCi)/day in urine of 12 unexposed men (Holtzman et al. 1976).

Concentrations of ^{210}Po in human tissues have been measured in the U.S., Great Britain, and the Soviet Union (Holtzman 1966; Blanchard 1967; Ladinskaya et al. 1973; Parfenov 1974). Skeletal ^{210}Po concentrations ranged from 1.3-1.5 Bq (35-40 pCi)/kg and exceeded soft tissue ^{210}Po concentrations due to ingrowth and physical trapping of ^{210}Po formed from the decay of ^{210}Pb within the bone matrix. Unlike ^{210}Pb, which has a relatively long half-time in bone, approximately half of the ^{210}Po formed from ^{210}Pb decay is transported to soft tissues and ultimately excreted. Hair had 3.3 Bq (89.5 pCi)/kg ^{210}Po and may be an important means of excretion in addition to the fecal and urinary route. Polonium-210 soft tissue concentrations were greatest in the liver and kidneys. Ladinskaya et al. reported concentrations of 973 and 762 mBq (26.3 and 20.6 pCi)/kg (samples

from adults) and Blanchard reported 537 ± 74 and 418 ± 81 mBq (14.5 ± 2.0 and 11.3 ± 2.2 pCi)/kg (samples from 18 individuals whose ages ranged from 6-78 years) for the two organs, respectively.

Particular attention has been given to the levels of ^{210}Po in tobacco and its hypothesized role as a cofactor in lung cancer production in smokers (Cohen 1978). Reported dose estimates vary, but in general "the doses cover the range from probably insignificant to possibly significant, depending upon the importance of hot spots (BEIR 1988)."

2.2 Metabolism

2.2.1 Route of Exposure

Inhalation

Inhalation of aerosols or particles containing ^{210}Po atoms results in the initial deposition of the nuclide on the lung surfaces. Following such an event, lung epithelia will be irradiated by alpha particles emitted as a result of ^{210}Po decay. In time, the radionuclide may become systemic by one or more mechanisms. During and immediately following exposure, the ionic or soluble Po can be absorbed into the bloodstream. The insoluble and colloidal Po particles are eliminated from the lung with an effective half-time of 18-35 days (Moroz and Parfenov 1972). An exception observed in experiments with rabbits demonstrated a slow phase clearance of only six days following intratracheal administration of the nuclide (Morrow and Della Rosa 1964). Some of these aggregates may break up with time, thereby enabling additional absorption of Po into the blood.

The second mechanism leading to systemic uptake involves transport of particles containing Po up the tracheobronchial tree by means of the "mucociliary escalator," resulting in its eventual presence in the gastrointestinal tract. Subsequently, absorption of Po may occur across the gut membrane.

In their study of ^{210}Po distribution following intratracheal injection in the rat, Thomas and Stannard (1964c) showed that colloidal Po can become incorporated in the tracheobronchial lymph nodes. However, prolonged retention in the lymph nodes does not occur as is often seen for actinides due to rapid dissolution of colloidal particles (Moroz and Parfenov 1972).

Kimball and Fink (1950) reported that 30% of an inhaled aerosol of neutralized Po chloride was retained on the surface of rat lungs 24 hours after exposure. The authors noted that technical difficulties encountered during exposures introduced considerable uncertainty in the data. Rats exposed to a 0.28 *u* MMD ^{210}Po-chloride aerosol in 0.1 *N* HCl had an estimated lung and trachea deposition of 25% of the total dose, with an equal amount of Po found in the gastrointestinal tract following a 5-hour exposure (Berke and DiPasqua 1964). Twenty minute nose-only exposure to a freshly neutralized ^{210}Po aerosol with 0.046 *um* CMD (0.34 *um* MMD) resulted in a mean pulmonary deposition of about 33% in rats, divided equally between the upper and lower portions of the respiratory tract (Casarett 1964b).

Six dogs were exposed to a ^{210}Po chloride carried on a sodium chloride aerosol of CMD 0.04 *um* (Smith et al. 1961). Average deposition in the respiratory tract was 64%, with values ranging from 48-77%. These data are consistent with work done by Morrow et al. (1958), who found an average respiratory deposition of 63% in seven healthy human subjects after inhalation of a sodium chloride aerosol of a similar mean particle size.

Ingestion

A second major route of uptake for Po is through the gastrointestinal tract. Ingestion of contaminated food or water, smoking when one's hands are contaminated, and swallowing Po-containing aerosols after their inhalation will lead to some degree of GI absorption of the radionuclide. Among the heavy elements, Po occupies an intermediate position with regard to absorption; it is absorbed more easily than the actinides, e.g. U and Pu, but less easily than Ra (Moroz and Parfenov 1972).

Two rats exposed via gavage to approximately 18.5 kBq (500 uCi)/kg of freshly neutralized ^{210}Po chloride absorbed 2.4 and 4.8% of the dose (Silberstein et al. 1950a). Following gavage administration of 0.5 kBq (14 uCi)/kg, approximately 3 to 5% of the dose was absorbed by rats (Spoerl and Anthony 1956). Stannard determined average fractional absorption values (f_1 values) of 0.05 for male rats and 0.045 for female rats by balance studies after correcting for the amount of Po assumed to be excreted into the intestine via the bile (Stannard 1954; Stannard 1964a).

Two different chemical forms of Po, a colloidal hydroxide and a soluble citrate, were administered to cats by gavage in a series of experiments (Morrow et al. 1964b). When Po was placed in the stomach, significant amounts were absorbed (0.6 to 1.6%) from the stomach independent of chemical form over a seven hour period. In contrast, significant differences were observed between the two chemical forms when the solution was placed in isolated duodenal loops of the small intestine. Over a ten hour period, absorption was up to forty times greater for the citrate solution. The authors noted that in the stomach, gastric acidity converted the colloidal Po to a soluble form, making absorption comparable to the monomeric citrate form. The percentage of administered

dose absorbed in the cat was less than in the rat, but due to the limited length of time of the cat experiments (7-10 hours), the total amount of absorption may not have been measured.

A male patient hospitalized with chronic myeloid leukemia volunteered to ingest 7 Bq (0.19 nCi) ^{210}Po/kg body weight in drinking water (Silberstein et al. 1950b). Absorption of Po may have reached 10%, although the authors noted that the estimate was largely conjectural and may have been considerably less than this amount.

Skin Absorption

Polonium can penetrate the skin upon contact. A ^{210}Po chloride solution placed on the bottom of the paws of mice was absorbed at the rate of 0.08-0.4% per day (Gorham 1950). Fink (1950) attempted to measure the absorption of Po chloride directly through human skin and concluded absorption occurred at less than 2% per day.

2.2.2 Distribution

In the blood, Po has been shown to be associated almost exclusively with erythrocytes (Campbell and Talley 1954; Thomas 1955; Thomas 1964). Blood from rats and dogs was sampled at four days post injection, with 90% of the Po found associated with the red blood cells (Campbell and Talley 1954). The authors also showed that almost all of the Po in the blood was bound to the globin fraction of hemoglobin. Thomas (1964) showed that following intravenous and oral administration of neutralized Po chloride solution to rats, 84 $\pm$ 11 and 104 $\pm$ 9% of the red cell Po activity were associated with the hemoglobin fractions, respectively, and 87 $\pm$ 8 and 74 $\pm$ 3% of plasma activity were associated with the plasma proteins, respectively. Consistent with the work of Campbell and Talley, the Po associated with the hemoglobin was found bound to the globin. Distribution within the plasma was related to the plasma protein concentrations

as would be expected since the Po affinity is relatively strong for most plasma proteins (Feldman and Saunor 1964; Thomas 1964). Similar results were obtained by Thomas following intravenous administration of Po to rabbits. Thomas also noted that the mode of binding of Po by protein moieties in the blood was not related to the chemical form of the injection solution used.

Polonium forms colloidal aggregates in neutral solution *in vitro* (Finkel et al. 1953). Following intravenous administration or absorption from the gastrointestinal tract, Po will form colloidal complexes with proteins (Moroz and Parfenov 1972). Not surprisingly, Po aggregates are preferentially found in the cells of the reticuloendothelial system (RES) after intravenous administration. Finkel et al. (1953) recovered between 30 and 60% of the retained Po in the liver, spleen, kidneys, and skeleton (the majority of the skeletal Po burden was assumed to be associated with bone marrow) of rats 66 days after intravenous injection of Po chloride.

Injection solution parameters such as chemical form and pH will determine the degree of colloid present initially, and this will influence early uptake by the reticuloendothelial elements. For example, Casarett (1964a) found Po aggregates in the spleen of rats with an average size of less than 50 atoms when the citrate was administered compared to approximately 500 atoms after administration of a neutral saline solution.

No aggregates were observed in tissue samples after oral administration to both cats and rats (Casarett 1964a). Intestinal absorption of Po in presumably nonaggregate form leads to maximum association with hemoglobin, resulting in a smaller fraction of Po in the cells of the RES and the absence of colloidal aggregates (BEIR 1988). Autoradiographic studies show that the distribution of nonaggregated Po is the same irrespective of the route of administration, the size of the dose, and the chemical form of the Po administered. These studies also show that even after animals received intravenous

solutions with a maximum of large aggregates, less than 20% of the Po content of their soft tissues was contributed by Po contained within large aggregates. It is the nonaggregated Po which is responsible for the delivery of the majority of radiological dose (Casarett 1964a; Stannard and Casarett 1964). Therefore unlike other alpha particle emitters such as plutonium, Po dosimetry need not consider "hot spot" contributions; the average dose to tissue is the pertinent quantity (BEIR 1988).

Once in the bloodstream (following either intravenous administration or after absorption from the lung or gastrointestinal tract), Po distributes throughout the body. While initial accumulation of colloidal aggregates occurs in the RES, the nuclide is found in practically all organs and tissues (Moroz and Parfenov 1972).

In rats, spleen and kidney are the tissues with the highest concentration of Po following single intravenous administration (Fink 1950; Stannard 1964a; Stannard 1964b; Stannard 1988). These sites might therefore be expected to receive some of the highest radiological doses following exposure. Expressed as the percentage of the total administered dose per tissue at one day post intravenous exposure to Po chloride, Fink (1950) found 18% in liver, 14% in muscle, 12% in blood, 11% in skin, 11% in skeleton, 8% in kidneys, 4% in spleen, 2% in lung and less than 1% in testis. Rats administered the nuclide via gavage also had maximum percentages of the total absorbed Po per gram in spleen (2.9%) and kidney (1.2%) ten days post exposure (Fink 1950). Liver, lymph nodes, and bone marrow are other tissues which concentrate Po in excess of the mean tissue concentration.

Polonium was administered intravenously to cats as the citrate and the neutralized hydroxide resulting in similar organ and tissue distribution 7 to 10 hours after exposure

(Morrow et al. 1964b). On a per gram basis normalized to liver Po concentration in a cat exposed to the citrate, the spleen relative concentration factor was highest (3.7), followed by blood (2.9), kidney (2.4), lung (1.9), and small intestine (0.8).

Parfenov and Poluboyarinova (1969) administered Po nitrate subcutaneously to dogs. The kidneys had the highest initial concentration of the nuclide, followed by the lymph nodes > liver > spleen > adrenal gland > lungs > muscle > skeleton. Initially the liver had the highest percentage of the total administered dose per organ with 25.1%. Other tissues and organs with relatively high initial amounts of Po included skeletal muscle (21.0%), blood (13.3%), kidneys (11.8%), skeleton (4%), and spleen and lungs (1.8% each). The biological half-times for Po retention in these tissues ranged from a low of 43 days in the kidney to a high of 75 days in the skeleton.

Mice exposed via intraperitoneal injection of Po were found to have significant ovarian and testicular Po concentrations (Samuels 1966a; Samuels 1966b). Polonium was found in the reproductive tissues of mice after intravenous administration of Po chloride (Finkel et al. 1953). During the first 66 days post exposure, no organ with the exception of the spleen had a higher concentration of the nuclide than the ovaries. Kidney and lymph nodes had Po concentrations similar to the ovaries, which were approximately 2-4 times greater than was the concentration of Po in the liver.

The radiological dose to the testis may be augmented by the fact that Po clearance from that organ may be slower than from most organs and tissues. Relative to other tissues, the concentration of Po in rat testis steadily increases as a function of time (Fink 1950).

Fink (1950) measured the Po content of the tissues of a volunteer subject who died from acute lymphatic leukemia six days after receiving Po chloride. The liver had the highest tissue concentration of Po (21.0% of the injected dose per kg organ weight)

followed by spleen (17.0%), kidneys (13.6%), testes (4.3%), and lung (4.1%). In terms of total Po per tissue, the liver contained 43% of the injected dose, followed by kidneys (5.0%), spleen (4.1%), blood (3.9%), and lungs (2.5%). The author believed that the liver values were inaccurately high due to the assay of what was possibly a non-representative aliquot. However, studies with the baboon (described in Sections 3 and 4) indicate that Po distribution in the liver is uniform. With the exception of the liver, these data are in good agreement with the percentage of intravenously injected dose seen in rat organs and tissues (Fink 1950).

2.2.3 Retention

The rate of biological clearance of Po from the various organs is best described by exponential functions with one or two loss constants (Stannard, 1964b). Long term distribution studies with the rat showed that Po is lost from most tissues via a rapid early phase followed by a slower phase of varying duration and half-time. An exception to this general rule was noted for the testis, where clearance occurred as a single exponential with a half-time of approximately 153 days. Composite biological half-times for Po in rats include 11 days for liver, 31 days for spleen, 38 days for kidney, and 31 days whole body. A summary of biological half-times for various organs and tissues following intravenous Po administration is presented in Table 2.1.

In contrast to the kinetics observed in the rat testis (Stannard 1964b), data from Samuels (1966b) can be used to estimate a 27 day biological half-time for Po in mice testis. These data were collected from 30-140 days post intraperitoneal injection. Retention of Po in the kidneys over the same test period could be represented by a 50 day biological half-time. The retention curves appear in Figure 2.1. The Po half-time estimates for these organs are admittedly only approximations, as only six points are

available for the regression analysis and the first measurement was not made until 30 days post exposure. Additional error is introduced by assuming single exponential kinetics for the two organs in the absence of data prior to day 30 and by using average testis and kidney weights for mice (Ivanyi et al. 1972; Foster et al. 1983) to estimate total organ Po content. Nevertheless, the retention curves fit to these data do qualitatively suggest that the radiological dose imparted from the Po to the testes might only be a factor of 2-4 less than the kidney dose.

Polonium biological organ retention half-times of approximately 35 days appear consistently throughout the literature. Where data describing early as well as long-term elimination are available (such as following inhalation exposure to the dog and rat), rapid phase clearance with half-times of a few days followed by the 30-40 day slow phase have been observed.

2.2.4 Excretion

Excretion of Po has been characterized for a number of animal species as well as for man. Elimination of Po from the body begins almost immediately following exposure. A large percentage of the nuclide is excreted in a rapid phase via the digestive tract when exposure is by the ingestion or inhalation routes. The liver has been shown to play a significant role in the removal of systemic Po via the bile to the feces (Fink 1950).

Fifty per cent of the inhaled dose was excreted by dogs during the first three days post exposure, principally via the feces (Smith et al. 1961). Total excretion by the rat following inhalation exposure was not quite as rapid, with approximately 23% of the total dose recovered in excreta during the first ten days (Berke and DiPasqua 1964). The authors measured a cumulative fecal-to-urine ratio of 6.6 after 60 days for systemic Po after exposure via the inhalation route. Casarett (1964b) collected 82% of the total dose

in excreta after "nose-only" inhalation exposure to rats over 30 days, with at least 60 percent having been collected during days 1-10 post exposure. Fecal-to-urine Po ratios peaked through days 1-4 at a value slightly under 30 before decreasing to ratios ranging from 10-13 beyond day five.

A similar Po excretion pattern is followed after oral administration of Po. Almost 40% per day of the administered dose was excreted by rats via the fecal route during the first two days, with levels dropping precipitously to less than 0.1% per day by day seven (Fink 1950). Urinary output of Po was an order of magnitude greater during the first ten days after the ingestion exposure than following intravenous exposure. Fecal-to-urine ratios after the ingestion exposure were similar to the 10-13 range measured following inhalation exposure, although ratios during the first few days post exposure were not nearly as high.

Consideration of absorbed Po in urine after oral administration resulted in markedly different excretion fractions when compared to the other routes of exposure. The percentage of urinary output of Po by rats was much higher with the exception of day one, with an average fecal-to-urine ratio of approximately two (Stannard 1964a). This same trend was also noted by Spoerl and Anthony (1956). Polonium excretion curves fit to data presented by Stannard (1964a) following intravenous administration of Po chloride to male rats can be used to estimate a fecal-to-urine ratio equal to 10 (shown in Fig. 2.2). Over-all fecal-to-urine ratios for systemic Po through 60 days in the rat have been given as 6.6 for inhalation, 3.3 for oral, 13.3 for intratracheal, and 13.0 for intravenous exposures (Berke and DiPasqua 1964).

Human occupational and controlled exposures to Po have been summarized by Jackson and Dolphin (1966). A mean effective half-time of 31.4 days for Po excreted in urine was reported for 18 individuals occupationally exposed (Naimark 1948; Naimark

1949). When Po urinalysis data from 17 more workers was included in the analysis, a mean effective half-time of 34 days was calculated (Spoerl 1951). Excreta samples from two exposed workers were measured after a defective Po-Be source ruptured (Foreman et al. 1958). Polonium excretion could be characterized by a two compartment exponential model for both feces and urine. Fecal excretion occurred with a rapid phase half-time of 0.6 days followed by a 19.6 day slow phase. Initial Po urine excretion occurred with a 0.75 day half-time, followed by a slow phase with a 37 and 47 day half-time for the two individuals. The ratio of ^{210}Po excreted in feces to that excreted in urine decreased with time, with values greater than 100 for the first week decreasing to approximately 10 five months after the accident. Similar kinetics were reported by Sheehan (1964a), who measured a mean effective half-time of 33 days (43 day biological) in two accident cases and by Taylor (1970), who measured a mean effective half-time of 37 days (50 day biological) for 7 individuals accidentally exposed to ^{210}Po.

Potential exposure to six workers was caused by the escape of 259 MBq (7 Ci) from a Po-Be source (Callihan and Ross 1952). All urinalysis measurements for Po were below the lower limit of detection, but analyses of one worker's feces did indicate that some intake had occurred. Rapid elimination of Po continued through the first four days post exposure, followed by clearance with an approximate effective half-time of 25 days.

As part of the work done at the University of Rochester Manhattan Project, four patients hospitalized with generalized lymphosarcoma or chronic myeloid leukemia were injected with tracer amounts of ^{210}Po chloride (Fink 1950). Excretion data were reported and have been widely referenced as evidence that Po retention kinetics in humans are similar to those determined from animal experiments. Since patient #2 died six days following the administration of Po, only data from patients 1, 3, and 4 have been examined here. The daily percentages of Po excreted in the urine are given in Table 2.2.

The Po urinary excretion data for the three patients are shown in Fig. 2.3. The data were fit using a weighted nonlinear least squares regression method which will be detailed in Section 3.4. The urinary excretion parameters are listed in Table 2.3.

Urinary excretion half-times of 30-50 days have been determined in the majority of animal experiments for Po. The data presented by Fink would result in a similar urinary half-time for Po only if the data from the three individuals (or four by including case #2) were combined prior to least squares regression to the single exponential model. However, an analysis of covariance test examining the log transformed bioassay results indicates that the data sets from the three individuals cannot be grouped together. The statistical procedure rejects the hypothesis that the intercepts of the urinary Po excretion curves are equal, $p < 0.01$. The biological half-time estimates range from a low of 13.9 days to a high of 32.0 days, although these differences are not statistically significant. These data are admittedly limited in number, but they indicate that urinary excretion of systemic Po in man may be more rapid than is predicted by the animal data presented in the literature.

The urinary excretion functions regressed to the urinary ^{210}Po data for the three human volunteers can be used to estimate the urinary excretion fraction for systemic Po. The resultant fractions range from 0.02-0.05, which are in reasonably good agreement with the urinary ^{210}Po excretion fraction in rats based on the data of Fink (1950) and Stannard (1964a; 1964b).

The Po excretion data of two workers who were believed to have been exposed to the nuclide via absorption through the skin have also been examined via regression analysis. On August 28, 1944, a male supervisor in an electrodeposition laboratory handled a foil containing an estimated 44.4 MBq (1.2 Ci) of ^{210}Po. Daily urine sampling and weekly fecal sampling for Po began immediately and continued for 64 days

(Silverman 1944). Urinary and fecal Po effective half-times were determined to be 27.9 ± 1.3 days (34.9 days biological) and 24.2 ± 2.4 days (29.3 days biological), respectively (Fig. 2.4).

A female technician at Mound Laboratory in Miamisburg, Ohio was involved in an incident in which a Po solution was accidently splashed on her face. Unpublished urine, feces, and blood Po bioassay data reveals relatively rapid excretion rates for the nuclide (Spitz 1987). As shown in Fig. 2.5, ^{210}Po in urine was excreted with a 12.0 ± 1.6 day half-time (13.1 day biological) and fecal Po was excreted with a 23.7 ± 9.3 day half-time (28.6 day biological). Fig. 2.6 shows that the ^{210}Po retention in the whole blood had a 17.7 ± 0.9 day half-time (20.3 day biological). Only nine blood measurements were made over several months following the accident, compared to 38 urine measurements and 16 feces measurements.

2.2.5 Species Differences

The overall distribution and excretion patterns for Po among the species described in the literature reveal many similarities. One notable exception is the metabolism of the nuclide observed in the rabbit. Fink (1950) injected one rabbit with a solution of Po chloride and noted that while fecal excretion was consistent with that observed in the rat, urinary excretion of Po was significantly greater. After 10 days, 35% of the injected dose had been excreted via the urine by the rabbit, compared to only 0.91% by the rat in the same time period. The tissue distribution differences mirrored the relatively high urinary output of Po. Many of the rabbit soft tissues had lower concentrations of Po, and the loss from tissues proceeded at a faster rate than in other species. One notable exception was the rabbit kidney, which had three times the Po concentration to that of the rat on a per gram basis.

Similar differences in rabbit metabolism of Po were observed following intratracheal administration (Morrow and Della Rosa 1964). Retention in the lung can be described by an initial rapid phase followed by a slower phase. Fecal excretion of Po was consistent with that observed in the rat, but urinary excretion of the nuclide was again much greater in the rabbit. During the initial 30 days post exposure, the rabbit excreted 30% of the administered dose in urine. The rat excreted only 2% of the administered dose in urine during 70 days post exposure (Thomas and Stannard 1964c). The overall rabbit excretion half-time for Po was 20 days compared to the 30 days for the rat.

In contrast to the rapid rate of Po excretion by the rabbit, the rate of excretion of the radionuclide by the dog was slow compared to other species, regardless of the route of administration (Stannard and Smith 1964). The greatest difference occurred after intravenous exposure. The difference was only reflected in the rate of Po excretion. The urine-to-fecal excretion ratio for the dog was not different than for the rat.

Polonium content and retention in tissues of various species exhibit some variability, but the overall relationship (i.e., ratios) between levels in the different organs is relatively constant (Moroz and Parfenov 1972). Liver, spleen, kidneys and lymph nodes are the tissues with the highest Po concentrations in all species, although most of the organ data in the literature was generated without consideration of the contribution of the organ's residual blood Po to the total organ burden. Since Po tends to associate strongly with erythrocytes and plasma proteins, "blood-free" Po organ burdens would provide the most accurate means of comparing Po distribution.

2.3 Toxicity and Pathology

2.3.1 Acute

Acute toxicity of Po has been studied in a number of animal models. In a pilot study, Fink (1950) determined an $LD_{50/30}$ of 1.1 kBq (30 uCi)/kg in Wistar-Rochester rats following intravenous administration. Additional study resulted in an $LD_{50/20}$ of 1.6 kBq (43 uCi)/kg and an $LD_{50/40}$ of 1.0 kBq (27 uCi)/kg. These data are similar to those of Davis (1950a), who measured $LD_{50/20}$ values of 1.6 kBq (43 uCi)/kg and 1.3 kBq (36 uCi)/kg in male and female Sprague-Dawley rats, respectively. Similar lethality was observed in CF#1 female mice, with a reported $LD_{50/30}$ of 1.4 kBq (36.5 uCi)/kg (Finkel et al. 1953). The CFW strain of mice was found to be somewhat more resistant to the lethal effects of Po. Spoerl and Anthony (1956) measured average $LD_{50/20}$ values of 3.0 and 3.7 kBq (80 and 100 uCi)/kg for males and females, respectively. At Mound Laboratory, lifespan shortening in dogs, cats, and rabbits following intravenous administration of Po was also studied. $LD_{50/20}$ values of 2.6 kBq (70 uCi)/kg in the dog and rabbit and 2.5 kBq (69 uCi)/kg in the cat were determined (Davis and Jolley 1951; Davis et al. 1952).

Della Rosa and Stannard (1964) studied acute toxicity of Po in the rat following oral, intratracheal, and intraperitoneal administration, and compared their data with the effects observed by others after intravenous administration. Their work established that the tissue differences resulting from the various exposure routes do not alter the lethal effects of Po, although lethality took longer to develop following intraperitoneal exposure.

As a toxic agent with widespread distribution in the body, Po has numerous degenerative effects. These include sclerotic changes in blood vessels (particularly in the testes and kidneys), atrophy of lymph nodes, pancreas, thymus, spleen, and bone marrow,

involution of growing cartilage, general arteriosclerosis, and hypoplastic and hyperplastic changes in pulmonary lymphoid tissue (BEIR 1988). Cowden (1952) noted that the kidneys, gonads, lymphoid tissue, and blood were the organs in rats most sensitive to the ionizing radiation of Po.

At dosage levels ranging from 33.3 Bq to 1.3 kBq (0.9 to 35 uCi)/kg ^{210}Po chloride administered intravenously, kidneys showed consistent degenerative changes. At 100 days post exposure, renal lesions were observed in rats receiving the 33.3 Bq (0.9 uCi)/kg dose. Casarett (1964c) found enlarged, swollen, distorted epithelial cells in some of the proximal convoluted tubules in rats 42 days after exposure to 185 Bq (5 uCi)/kg. Cortical arterioles had thickened walls due to swollen endothelial cells. At 37 Bq (1 uCi)/kg, these changes were also observed in rats, but not until the period from 250 to 445 days post exposure. Casarett noted that while vascular changes may not be observed during the early stages, ischemia may result from radiation induced arterial spasm prior to the advent of conspicuous vascular change. He concluded that the early development of pale kidneys was indicative of an early reduction in the renal blood supply.

Hematological and pathological effects of Po on gastrointestinal, reproductive, reticuloendothelial, and various other tissues of rats have been reported (Cowden et al. 1950; Zipf 1950). The effects of Po on experimental animals at various acute dose levels have been summarized and partially reproduced here in Table 2.4 (Spoerl and Anthony 1956).

2.3.2 Chronic

Casarett (1964c; 1964d) studied and compared the pathological changes induced by both the single and multiple intravenous administration of Po to rats of the Wistar strain. No direct effects of Po were observed in the liver. This is in contrast to studies where

Sprague-Dawley rats injected biweekly with 74 Bq (2 uCi)/kg developed hyperplasia of bile-duct epithelium with fatty degeneration and fibrosis and necrosis of liver-cord cells (Spoerl and Anthony 1956). Rats administered 74 Bq (2 uCi)/kg ^{210}Po chloride intravenously at 14-day intervals showed a general pattern of lesions similar to that resulting from single doses of 296 Bq (8 uCi)/kg (Cowden and Zipf 1951). However, the lesions appeared at a faster rate and proceeded ultimately to greater severity, which the authors attributed to an ever increasing dose rate in conjunction with the presence of subacute lesions. Nephrosclerotic changes resulted from single doses of 370 Bq (10 uCi)/kg and in the multiple dose group receiving 56 Bq (1.5 uCi)/kg/month, although the damage was less severe in the latter group. Dose estimates at these two exposure levels are comparable.

Damage to the hematopoietic tissues was similar regardless of the dose regimen with one exception. In multiple dose experiments only, marked hemorrhage of the spleen was common. Hypoplasia and atrophy of seminiferous epithelium resulted in rats of both experimental groups. However, onset of the condition was more rapid in the single dose animals.

Pulmonary hemorrhage and edema resulted from administration of high doses of Po. Rats receiving 3.7 Bq (0.1 uCi)/kg/month developed obstructive pulmonary emphysema, but rats in the higher dose groups (11.1 and 56 Bq/kg/month) did not develop this disease. Marked atrophy of pulmonary lymphatic tissue occurred in the high dose animals.

A common measure of an agent's toxicity is the degree of life-span shortening which results following exposure. When the Po body burden was maintained in rats at 1.85 Bq (0.05 uCi)/kg, the resultant life-span shortening was not significant (Stannard et al. 1964). At higher doses, however, a linear relationship exists between dose and

life-span shortening, with a slope of approximately 4.3 weeks of life-span shortening per 37 Bq (1 uCi)/kg. Unlike gamma or x-radiation, fractionating the dose over many exposure episodes does not reduce the life-span shortening effectiveness of Po. Applicable to both the single and multiple exposure situations, this supports the observation that the alpha radiation emitted from Po produces a high degree of irreversible damage (Blair 1964). Stannard et al. (1964) estimated that alpha particles emitted from Po have a relative biological effectiveness (RBE) of 20 based on their life-span shortening data. Samuels (1966b) suggested that the RBE of Po may be as high as 50 based on oocyte destruction induced on Harvard Swiss-Wistar mice following intraperitoneal injection.

Blair (1964) found the life-span shortening effect of Po to be equal to that of plutonium and about five times as great as radium. Finkel (1953) described the relative toxicity of some alpha particle emitters as follows: 7:3:2:1:1 corresponding to ^{239}Pu:^{210}Po:^{232}U:^{233}U:^{226}Ra.

Male rats exhibited an increased incidence in malignant tumors of all types at multiple intravenous ^{210}Po doses of 0.85, 3.7, and 11.1 Bq (0.023, 0.1, and 0.3 uCi)/kg/month (Casarett 1964b). Carcinogenic effects of Po could not be established for individual malignancies. Interestingly, a carcinogenic effect of Po was not seen in females due at least in part to a reduction in the incidence of mammary carcinoma with increasing dose and shorter survival time. Casarett noted that the increasing ovarian atrophy resulting from increased doses may have a role in the reduction of cancer incidence, since normal ovarian function favors the development of mammary neoplasms in rats. A similar carcinogenic effect of Po in Sprague-Dawley rats was not observed (Spoerl and Anthony 1956). Many tumors were observed in their study population (36% of the rats developed tumors), but the incidence was not significantly greater than that of the control group.

The carcinogenic effect of Po on the rat lung was observed after intratracheal administration of 37 and 74 Bq (1 and 2 uCi) per lung (Dusan et al. 1977). The incidence of tumors was enhanced when the Po was administered in conjunction with quartz dust, which increases Po retention and therefore increases dose to pulmonary tissue. Multiple intratracheal instillations totaling from 5.6-111 Bq (0.15-3 uCi) ^{210}Po resulted in malignant lung tumors in 47 to 91% of exposed Syrian golden hamsters (Little et al. 1973). Tumor frequency was greater when a lower but relatively uniform dose was delivered to lung tissue compared to when a higher dose was delivered to a small volume of tissue. The carcinogenic effect of single intratracheal instillations of ^{210}Po in saline was enhanced by subsequent instillations of Po free saline, indicating the importance of noncarcongenic secondary factors in the expression of radiation-induced lung cancer (Little et al. 1985).

2.3.3 Clinical Effects In Man

Little data has been reported describing clinical effects of Po-induced injury in man. Workers who had estimated body burdens of 37-185 Bq (1-5 uCi) ^{210}Po developed hematologic changes, asthenia, functional impairment of the liver, kidneys, and reproductive organs, and changes in protein, carbohydrate, and pigment metabolism (Kozlova and Omelianenko 1963). Two episodes have been described whereby adolescents came in contact with a ruptured Po-Be source. In one incident, four individuals had estimated ^{210}Po body burdens ranging from 18.5-399.6 Bq (0.5-10.8 uCi) (Guskova et al. 1964). Radiation sickness was not observed over an 18 month period, but changes in liver function (increased blood levels of bilirubin) and kidney function (decreased flow of renal plasma) occurred. Following the second incident, ten children with estimated ^{210}Po

body burdens ranging from 7.4-259 Bq (0.2-7 uCi) showed no clear changes in general health over a four year period, although some impairment of the protein-forming function of the liver beginning at 21 months was observed (Shantyr et al. 1969).

Three chemists inadvertantly exposed to a ^{210}Po aerosol sustained estimated maximum doses of 4.8 Bq (0.13 uCi)/kg, 7.0 Bq (0.19 uCi)/kg, and 42.2 Bq (1.14 uCi)/kg, corresponding to body burdens of 10, 11.8, and 88.1 uCi, respectively (Naimark 1948). No evidence of kidney damage was found. Subclinical depression of the hematopoietic system was suspected for the two individuals receiving the higher doses, although the data were considered insufficient to support the findings. Clinical observations were made 15 years after four individuals inhaled ^{210}Po which had escaped from a Po-Be source resulting in body burdens ranging from 5.6-49.2 Bq (0.15-1.33 uCi) (Jialiu et al. 1982). The general conditions of the patients were good and no obvious abnormalities were discovered. However, small spots were observed on the lens epithelia of two of the individuals. These may be related to the ^{210}Po exposure since cataracts and other degenerative changes of the eye have been reported in dogs (Markelov et al. 1964; Volkova 1961) and rats (Sproul et al. 1964) which had been exposed by various routes.

2.4 Epidemiology

The mortality of more than 22,000 British workers employed by the Atomic Weapons Establishment has been studied (Beral et al. 1988). Of the 638 individuals who had been monitored for Po exposure at some point during their employment, an excess standardized mortality ratio ($p=0.03$) was determined for cancer of the kidney, although it was based on only three deaths. It should be noted that many individuals in the cohort were monitored for internal contamination by more than one radionuclide, and that two of the three individuals who died from kidney cancer were also monitored for uranium.

To date, no epidemiological studies of a dose-response nature have been published on the health effects caused by Po exposure. The Mound Laboratory cohort is the largest group of persons occupationally exposed to ^{210}Po. The dosimetry data which can be generated with the model developed from this research will be used by epidemiologists at the Los Alamos National Laboratory in their ongoing investigation of mortality among the Mound employees.

TABLE 2.1 EXPERIMENTAL DATA ON THE BIOLOGICAL RETENTION OF ^{210}PO IN VARIOUS TISSUES FOLLOWING INTRAVENOUS ADMINISTRATION*

Tissue	Biological Half-Time (days) Species			
	Rabbit	Rat	Mouse	ICRP 30
Kidney	18	38	43	50
Liver	11	11	43	50
Spleen	8	31	18	50
Lung	8	47	23	
Muscle	-	38	42	
Blood	-	56	-	
Skeleton	-	23	-	
Lymph Nodes	-	56	-	
Reference	Moroz and Parfenov 1972	Stannard 1964b	Finkel et al. 1953	ICRP 1979

* adapted from Moroz and Parfenov 1972

TABLE 2.2 URINARY EXCRETION OF PO BY HUMAN SUBJECTS*

Days Post	Per Cent Injected Dose Excreted Per Day		
	Subject 1	Subject 3	Subject 4
1	0.2	0.090	0.069
2	0.048	0.125	0.063
3	0.056	0.153	---
4	0.038	0.146	0.056
5	0.031	---	0.064
6	0.030	0.059	0.060
7	0.021	0.157	0.052
8	0.033	0.086	0.053
9	---	0.080	0.044
10	---	0.103	---
11	---	0.077	0.044
12	---	---	0.040
13	---	0.059	0.038
14	---	0.080	---
15	---	0.070	---
16	---	0.069	---
17	---	0.070	---
18	---	0.056	---
39	---	0.043	---
43	0.016	---	---
70	---	0.021	---

* data from Fink (1950)

TABLE 2.3 URINARY PO EXCRETION PARAMETERS IN MAN*

Patient	Half-Time** (days ± se)	P-value	Intercept (%ID/day ± se)	P-value
1	32.0 ± 2.4	< 0.05	0.04 ± 0.01	< 0.05
3	27.9 ± 0.6	< 0.05	0.11 ± 0.01	< 0.05
4	13.9 ± 0.5	< 0.05	0.07 ± 0.01	< 0.05

*data from Fink (1950)
**Biological

TABLE 2.4 SUMMARY OF EFFECTS OF PO ON EXPERIMENTAL ANIMALS*

Dose (kBq/kg)	Animal	Lethality	Histo-pathological	Hemato-logical	Gross
1.85-3.7	cat, dog, rabbit, mouse	LD_{50}, 20 days: 2.96 kBq/kg	massive tissue destruction	severe loss of lymphocytes, WBC, RBC, hemoglobin	weight loss, lethargy, death
1.30-1.67	rat	LD_{50}, 20 days: 1.48 kBq/kg	massive tissue destruction	severe loss of lymphocytes, WBC, RBC, hemoglobin	weight loss, lethargy, death
0.37-1.1	rat	LD_{50}, 50-250 days	rapid kidney damage	moderate to severe loss of WBC, effects on RBC and hemoglobin as rat is dying	weight loss
0.04-0.4	rat	LD_{50}, 300-500 days	slow kidney damage	early WBC reduction followed by recovery	moderate weight loss
0.02-0.04	rat	10-20% reduced life span, male only	occassional mild kidney and/or thyroid lesions	none	none
0.01	rat	none	none	none	none

*adapted from Spoerl and Anthony (1956)

Figure 2.1 Retention of ^{210}Po in testes and kidneys of mice following intraperitoneal exposure to a weakly acidic Po solution (data from Samuels 1966b).

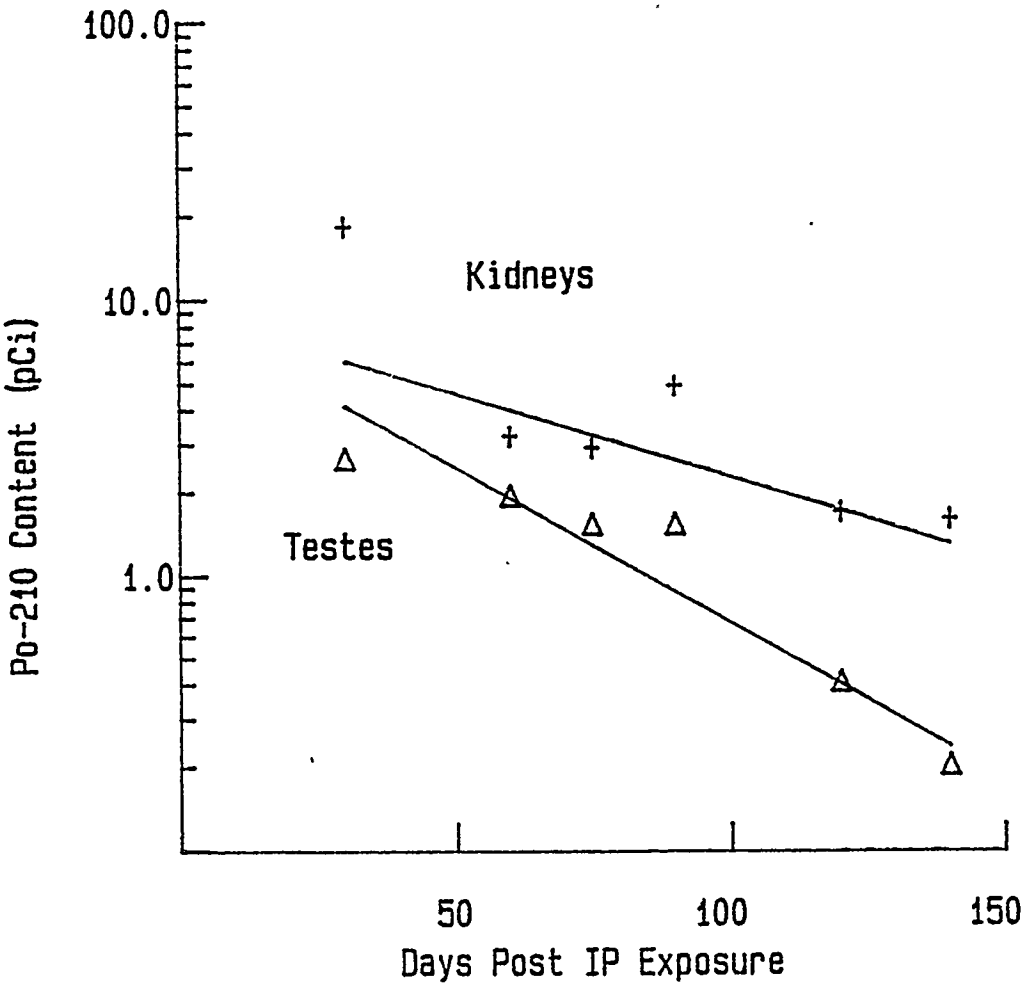


Figure 2.2 Urinary and fecal excretion of Po by rats following intravenous administration of ^{210}Po chloride (curves fitted to data presented by Stannard 1964 a).

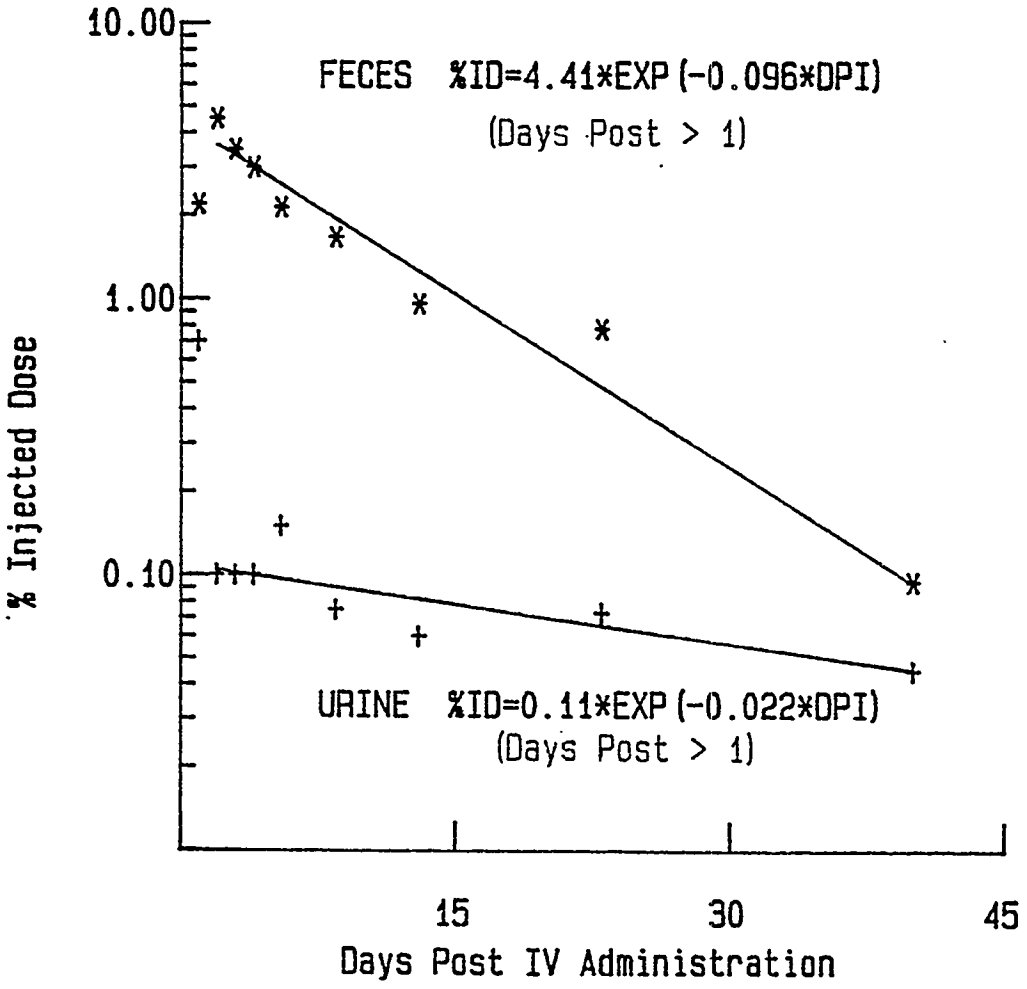


Figure 2.3 Urinary ^{210}Po excretion by man from three volunteers after IV administration of Po chloride (data from Fink 1950).

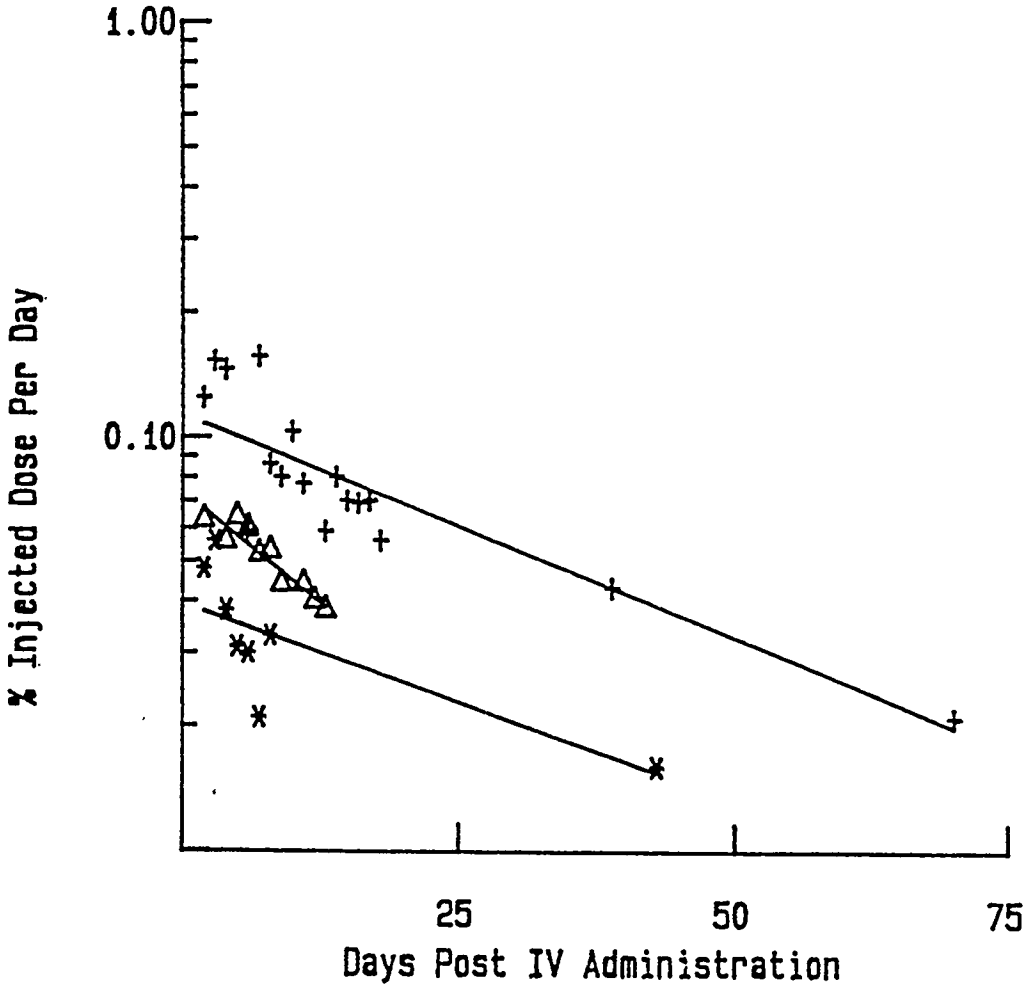


Figure 2.4 Urinary and fecal excretion of Po by a male who had handled a foil contaminated with approximately 44.4 MBq (1.2 Ci) of ^{210}Po (curves fitted to data presented by Silverman 1944).

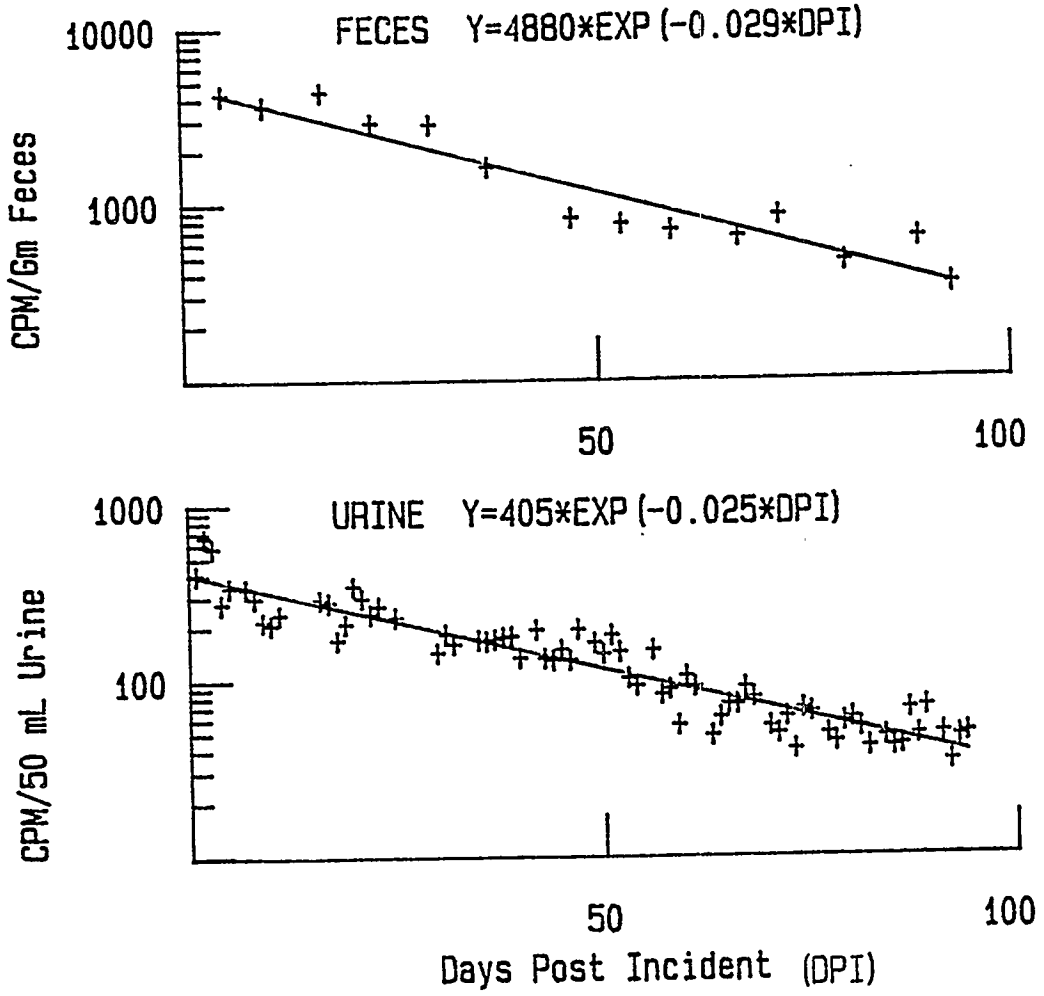


Figure 2.5 Urinary and fecal excretion of Po by a female who was splashed with a solution containing ^{210}Po (curves fitted to unpublished data obtained from Spitz 1987).

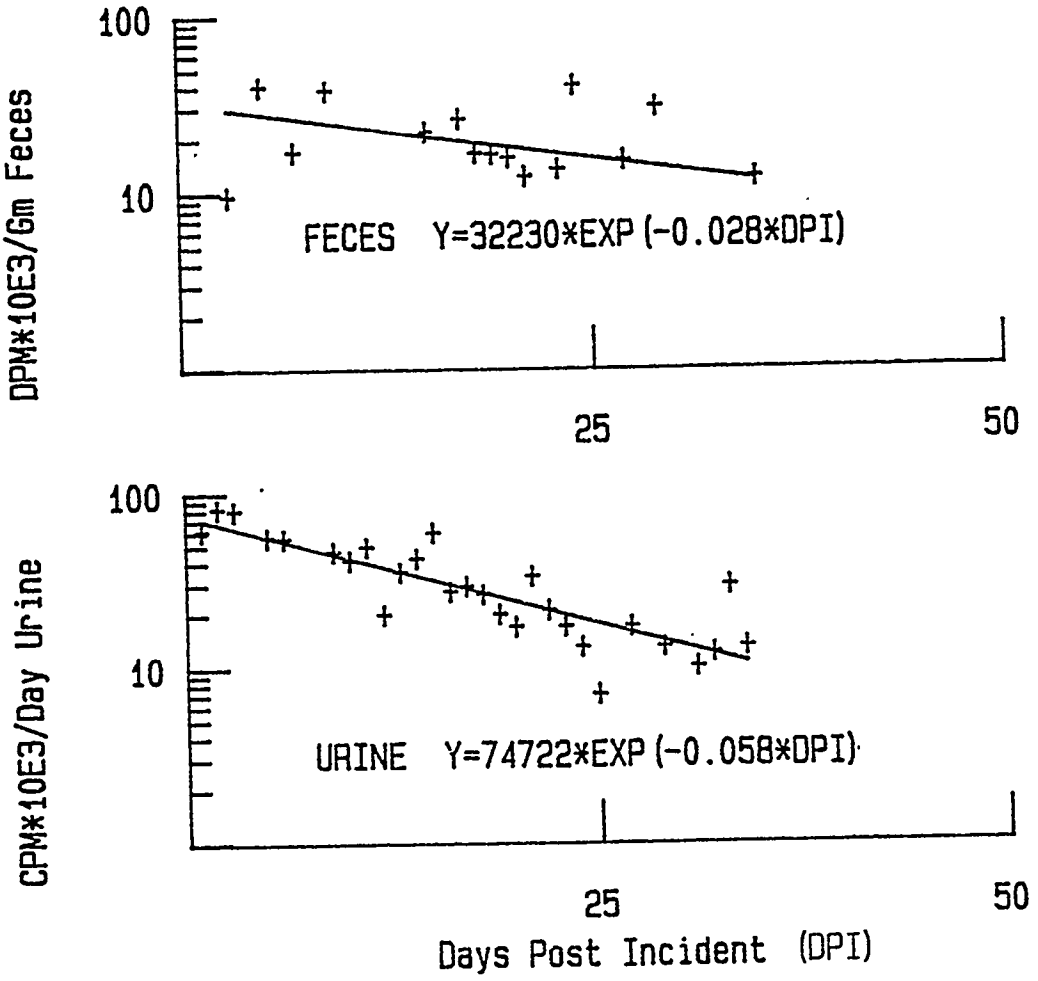
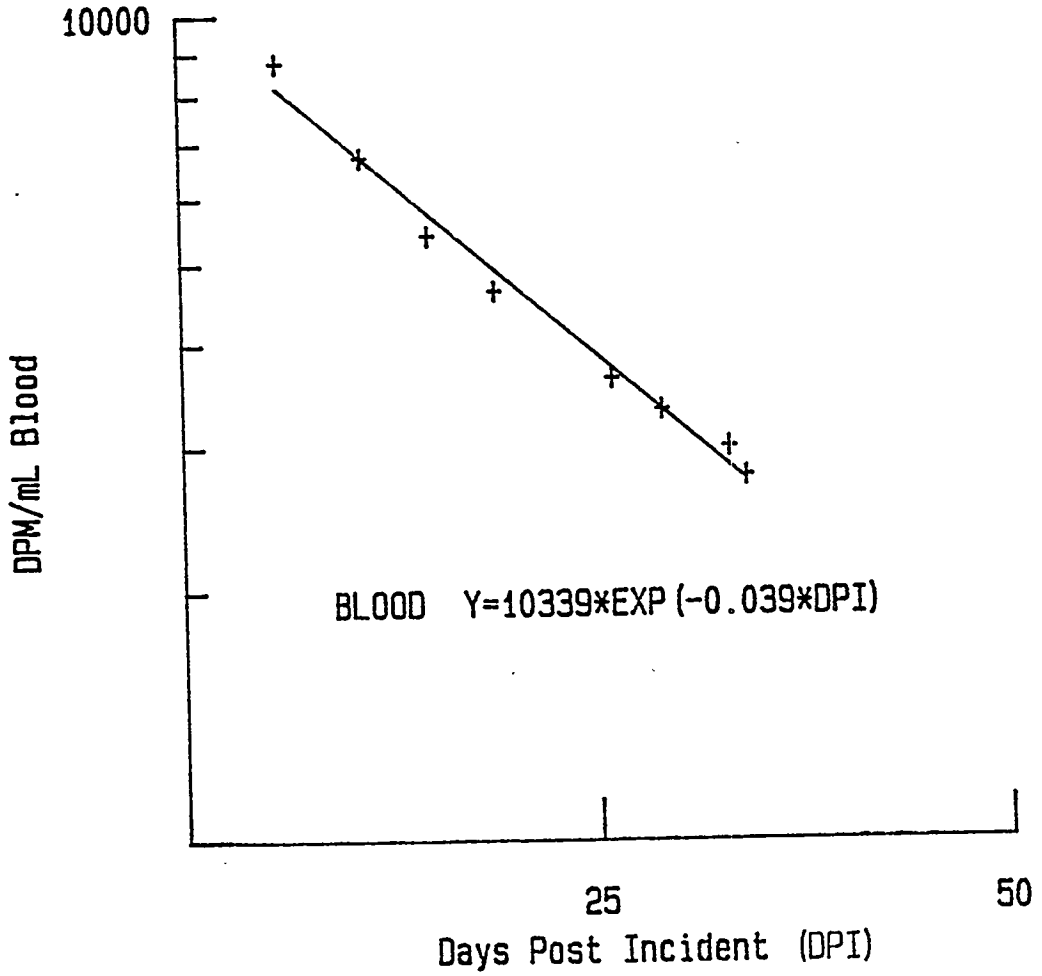


Figure 2.6 Retention of ^{210}Po in the blood of a female who had been splashed with a solution containing an unknown but significant quantity of the radionuclide (curve fitted to unpublished data obtained from Spitz 1987).



3 Experimental Methods

3.1 Rationale For Using Non-human Primates

Studies of Po metabolism in any non-human primate species have not been previously reported. The excretion rates, retention times, and distribution of ^{210}Po within and among various body sites after controlled exposures in baboons and tamarins were determined and utilized in the Po dosimetry model described in Section 5.

The assumption that kinetics and branching fractions observed in the baboon are applicable to humans is based on genetic considerations, anatomical similarities between the two species, and the body of literature recognizing the physiological parallelism which exists in many areas. These include metabolic comparability in relevant areas of hematology, blood chemistry, reproduction, endocrinology, and the metabolism of pharmacological drugs (Vagtborg 1967). In addition, biokinetic studies of radionuclides have shown that baboons are similar to man with regard to retention and excretion patterns for those bone-seeking actinides with relatively long half-times (Cohen and Wrenn 1972) as well as for the shorter lived actinide curium (Cohen et al. 1983).

3.2 Mode of Exposure

The metabolic studies of Po in non-human primates consisted entirely of animals exposed via intravenous administration. The usefulness of utilizing this route of exposure have been eloquently stated by Fink (1950, p.40):

"...it permits the introduction and immediate wide dispersal within the body of a definite amount of material at a definite time and thus gives results that are ordinarily more easily interpretable than in the case of experiments in which indefinite amounts of material may

gradually continue to enter the general circulation over indefinite periods of time. The interpretation of the results of experiments in which more commonly encountered routes of entry are employed is then made easier by the groundwork of intravenous experiments available for comparison. Similarly, single doses were used to facilitate the execution of the experiments and the interpretation of results."

There are, however, some obvious limitations to intravenous metabolic studies. Unlike inhalation or ingestion, the intravenous route is not the most frequently encountered exposure route (except for the occasional wound accident) for man. Injected ^{210}Po does not pass through a biological membrane such as the lung or gastrointestinal lining prior to entering the blood. Consequently, results from intravenous studies are highly dependent on the physicochemical form of the Po injected. However (as will be discussed in the next section), the form of ^{210}Po used in these studies represents to as great a degree as possible that which would pass through a membrane following deposition in an external organ.

3.3 Injection Solution

The physicochemical form of a material significantly affects its biological behavior. As discussed in Sections 2.1.1 and 2.1.2, some metabolic parameters observed in previously published studies of Po showed differences when a soluble solution (e.g., Po citrate) was compared to a colloidal solution (e.g., neutralized Po chloride).

The colloidal properties of Po were studied by filtering solutions through molecular filters under various conditions (Morrow et al. 1964a). Drastic changes in filterability were produced by altering the ionic strength and the complexing agent. In general, solutions with noncomplexing constituents such as NaCl-NaOH were less than 10% filterable at pH 6-8 while greater than 90% filterable when the solution pH was dropped

to 2 or raised to 10. Addition of complexing agents such as sodium citrate or sodium carbonate produced almost complete filterability of Po. It has been concluded from one study that filterability of Po is greatly enhanced by citrate (Feldman and Saunor 1964). The authors further conclude that in tracer concentrations of Po in blood, about 75% is bound to citrate.

Three ^{210}Po solutions were used to investigate the retention by the blood and distribution among the reticuloendothelial system (RES) tissues of colloidal Po in rats (Thomas and Stannard 1964a): (1) neutral NaOH (pH of 7); (2) 0.15 *M* citrate; and (3) acid diluted with 0.5 *N* HCl. Initial disappearance from the blood of ^{210}Po in the acid and citrate solutions was much slower than in the neutralized solution. However, as shown in Figure 3.1, the rate of ^{210}Po loss from the blood was slower for the neutralized solution after the initial clearance of the nuclide. The rapid initial blood loss of neutralized ^{210}Po was reflected in the corresponding uptake by the RES tissues relative to the citrate and acidified solutions. As shown in Table 3.1, only 13.7% of the ^{210}Po was recovered in the RES tissues from the citrate solution compared to 62.3% and 38.9% for the two neutralized solutions (aged 4 months and 15 days, respectively) at 20 minutes post injection. The relatively high RES tissue ^{210}Po content would be expected since the radionuclide exists predominantly in a colloidal state after neutralization of the solution (Morrow et al. 1964a; Thomas and Stannard 1964b).

The criteria for selection of a Po injection solution for use in the non-human primate metabolic studies were as follows:

(1) A chemical matrix which would keep Po in a stable, "soluble" form in order to emulate the diffusible state of Po across biological membranes.

(2) A chemical matrix which would be compatible with and non-toxic to blood constituents.

(3) Solution pH which was comparable to previous Po studies.

(4) A solution which was ultrafilterable (0.22 uM) to ensure a pyrogen and colloidal free medium.

(5) A solution which was reproducible and easy to prepare.

The citrate solution best meets the specified criteria. Its capacity to emulate a diffusible state of ^{210}Po capable of crossing biological membranes was exhibited in cats (Morrow et al. 1964b). When colloidal ^{210}Po solutions were administered via gavage, the acidic environment in the stomach caused ^{210}Po aggregates to break up and hence become available for absorption to the same extent as soluble ^{210}Po citrate. Ionic Po or soluble complexes are most likely the principle forms absorbed (Stannard and Casarett 1964); once entering the circulation from the gastrointestinal tract, the chemical form played only a secondary role in Po organ distribution and excretion. Morrow et al. (1964a) concluded that "The citrate complex appears to be a form of Po compatible with biological use that will be relatively free of colloid on administration." The procedure for preparation of the ^{210}Po citrate solution for intravenous administration to non-human primates is described in Appendix C.

3.4 Metabolic Studies of ^{210}Po In Non-human Primates

Two adult female tamarins (Saquinus labiatus) were each given single intravenous injections of ^{210}Po citrate in the femoral vein on two separate occasions (Table 3.2). Excreta collections were made daily for a period of 90 days post injection after the first injection and for 14 days after the second injection. A few urine and fecal samples from tamarin #T504 were also collected approximately 200 days post injection. Urine samples

were acidified with concentrated HCl and fecal samples were dried prior to storage and analysis. Infrequent blood samples were taken from T500 and T504; entire blood samples were analyzed.

Six female adult baboons (Papio anubis) were exposed to ^{210}Po as the citrate via single injection into the femoral vein. Doses were chosen which would be both chemically and radiologically non-toxic. Baboons B806 and B1046 were injected with approximately 37 Bq (1 uCi)/kg (compared with the 7.4-11.1 Bq/kg injected into the other baboons) so as to permit radiochemical determinations of ^{210}Po in bioassay samples and tissues at times as great as 90 days post exposure. Injection data is summarized in Table 3.3.

The tamarins were housed on site at New York University Medical Center (NYUMC) while the baboons were housed at the Laboratory for Experimental Medicine and Surgery in Primates (LEMSIP) of the NYUMC. All animals were maintained in individual cages positioned over excreta collectors constructed from wood, wire mesh, and plastic lining. Wastes fell through the floor bars of the cages onto the wire mesh surface. The plastic liner was extended beneath the wire mesh. A hole was cut in the center of the plastic to funnel the urine into a collecting basin. Fecal material remained on the wire mesh and was easily transfered into plastic cups.

Urine and fecal samples were collected daily (urine only from B514). Urine samples were acidified with 1 mL of concentrated HCl per 100 mL of urine (to retard the loss of Po to container walls) and then stored for analysis. Feces samples were dried in plastic cups and stored for analysis.

Urine samples were analyzed using a procedure modified from that originally developed for water, vegetation, soil, and Microsorban filters at the U.S. Department of Energy's Environmental Measurements Laboratory (EML 1983). The modifications

involved changes in plating times and temperature. The procedure (summarized in Appendix A) uses a 50 mL aliquot of sample spiked with ^{208}Po tracer which is wet ashed with concentrated HNO_3. Once digested, the sample is dissolved in 100 mL of 0.5 *N* HCl and a 10 mL aliquot is transfered to a plating cell. The plating cell (Fig. 3.2) consists of an inverted 30 mL polypropylene bottle with the bottom removed and a screw cap-mounted base. A 2.22 cm diameter disc punched from a 0.64 mm Ni sheet is placed in the cap. The bottle is screwed into the cap forming a leak-free seal with the disc, and the 10 mL sample solution is poured into the inverted bottle. Approximately 10 mL of 0.5 *N* HCl is added to the plating cell along with 1 mL of saturated ascorbic acid, reducing Fe^{+3} which interferes with the spontaneous deposition of Po (Hursh 1958).

A glass stirring paddle suspended from an electric motor capable of maintaining at least 100 rpm is suspended in the solution. Each sample is stirred for two hours. Polonium is spontaneously deposited on one side of the Ni disc. The disc is removed, rinsed with water and ethanol and counted with a 300 mm^2 silicon surface barrier solid state detector. The 5.15 MeV and 5.3 MeV alpha peaks of ^{208}Po and ^{210}Po, respectively, are resolved using a 1024 channel multichannel analyzer (MCA). The recovery fraction is directly determined for each sample using the ^{208}Po tracer.

The procedure used at Mound Laboratory for determining the ^{210}Po level in urine was duplicated. A comparison of the urinalysis method (which includes addition of ^{208}Po tracer and wet ashing prior to spontaneous deposition) with the direct deposition method used at Mound was then performed to test the effect of radiochemical procedure on recovery. A description of the study and the results are the subject of Section 5.1.

The analytical procedure for the determination of ^{210}Po in fecal samples is the same for the tamarin and baboon samples, with one exception. While the entire mass of a tamarin fecal sample is wet ashed in concentrated HNO_3, the baboon fecal samples have

to be homogenized using a Spec Ball Mill Shaker prior to taking a 10-15 gram aliquot for analysis. The samples are wet ashed to dryness and brought to a volume of 100 mL in dilute HCl. A 10 mL aliquot is taken, traced with a suitable amount of ^{208}Po, reduced to dryness and brought back up to 100 mL volume in dilute HCl prior to plating.[1]

Whole blood samples (10 mL heparinized) were drawn periodically post injection. On average, samples were taken from each animal (depending on scheduled sacrifice time) at 1 hour post injection, and then daily over the first week followed by weekly and then monthly sampling. Four blood samples were drawn from B1060 during the first hour post injection so as to accumulate the data necessary to describe the rapid phase kinetics exhibited by Po in the blood.

Hematocrits were taken and then blood samples were separated into cellular and serum constituents by ultracentrifugation. One mL aliquots of red cells and plasma were spiked with ^{208}Po tracer, wet ashed with concentrated HNO_3, and converted to a 1 *N* HCl solution prior to plating of Po onto Ni discs. Radiochemical procedures for the analyses of ^{210}Po in bioassay samples are given in Appendix A.

With the exception of B514, all of the baboons were sacrificed as part of the Po distribution study. Baboons were sacrificed at 1 day, 1 week, 2 weeks, 1 month, and 3 months post exposure. All sacrifices were carried out by exsanguination. Complete necropsies were conducted immediately following death, with all soft tissues and organs removed and individually weighed. Thorough disarticulation of the skeletons were then carried out. The entire skeleton of B1046 (the first animal to be sacrificed) was analyzed radiochemically as were aliquots of muscle samples taken from various areas of the body;

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1 At the outset of the study, a few samples were homogenized and split. An entire aliquot was traced with ^{208}Po prior to wet ashing. The other aliquot was ashed, diluted and then traced. The comparison showed that no ^{210}Po was lost during the initial wet ashing process.

concentration of ^{210}Po in skeleton and muscle were seen to be relatively consistent. Therefore, the total skeletal ^{210}Po burdens of the other four animals were calculated based on the activity measured in the right femur, and the total muscle ^{210}Po burdens were calculated by multiplying the average concentration of two or three samples taken from different areas of the body by the entire muscle mass.

Soft tissues and skeleton samples were stored in a freezer. Radiochemical analysis of all major organs were performed in addition to the skeletal and muscle samples. The radiochemical procedure utilized was similar to those described above for the other types of bioassay samples. Wet ashing in concentrated HNO_3 preceded spiking with a suitable quantity of ^{208}Po tracer. Samples were brought to dryness, converted to a 1 *N* HCl solution and plated onto Ni discs prior to alpha spectrometry.

Residual Blood Study

Polonium exhibits a relatively long retention time in the blood (Fink 1950; Stannard 1964b). It was considered possible therefore that analyses of tissues for ^{210}Po content would be artificially high due to the presence of some ^{210}Po in the residual blood contained within the tissue or organ mass, even after exsanguination. To account for this possibility, residual blood measurements were made for all soft tissue and skeletal samples by utilizing the following modified ^{51}Cr red blood cell labeling technique (Frank et al. 1979): A 5 mL blood sample was drawn from each baboon approximately 24 hours prior to exsanguination. The red blood cells were separated and labelled with 0.7-4.6 kBq (20-125 uCi) ^{51}Cr. The labelled red cells were incubated for 30 minutes and refrigerated overnight. After removal of the culture media, the red cells were washed several times with sterile saline. The 10 mL aliquot of labelled blood was drawn into a syringe and reinjected into the animal about 10 minutes prior to exsanguination. Further details of the procedure appear in Appendix B.

Chromium-51 emits a 325 keV gamma ray with an abundance of 9.83%. All of the baboon samples were counted for this photon with an 8" x 4" NaI(Tl) detector in the whole body counting facility prior to ^{210}Po analysis (a typical spectrum appears in Figure 3.3). The gamma rays emanating from the blood collected during exsanguination were counted to quantify the blood ^{51}Cr concentration. Tissue sample counts of the 325 keV ^{51}Cr gamma were then used to quantify the volume of blood contained within the sample mass. The concentration of ^{210}Po in the blood at time of death was determined radiochemically. Tissue sample ^{210}Po measurements could then be separated into tissue content and residual blood content. The results from the residual blood procedure appear in Section 4.4.3.

3.5 Counting System Descriptions

Two types of alpha radiation detection systems were used for these studies. Polonium deposited spontaneously onto Ni discs from all bioassay samples were counted with 300 mm^2 silicon surface barrier solid state detectors and analyzed by a 1024-channel per spectrum multichannel analyzer (MCA). A low background alpha/beta proportional counter was used for tracer and injection solution calibration and to count Po deposited on Cu discs out of raw urine as part of the study on the duplication of the Mound Laboratory procedure.

Gamma counting of the ^{51}Cr labelled erythrocytes in baboon organ and tissue samples was done with an 8" x 4" NaI(Tl) detector in the graded Z shielded whole body counting facility. Spectral analysis was accomplished using a MCA.

3.6 Data Handling

Polonium-210 excretion and organ retention data were analyzed on a microcomputer via either the weighted nonlinear or linear least squares regression technique available on MicroTSP[2] software. Nonlinear regression is an iterative technique which determines the best fit function (as defined statistically by the function with the minimum sum of squares of residuals). It can be used on both linear and nonlinear data. Partial derivatives are computed on initial parameter estimates and data are regressed to those derivatives. The sum of squares of the residuals is calculated. The parameter estimates are then altered slightly in an attempt to improve the fit and the process repeats, driving eventually to the parameter estimates resulting in the minimum sum of squares of the residuals (Draper and Smith 1981).

For some data sets, a linear regression performed on the log transformed data resulted in a sum of squares of the residuals which was lower than that from the nonlinear model. A comparison of the regression statistics (such as the standard error of the regression and standard errors of the parameter estimates) from both the linear and nonlinear techniques provided the basis for the selection of the best statistical regression.

In regression analysis, the assumption is made that all observations have equal variance (Neter and Wasserman 1974). The variance in bioassay data is influenced by the variance associated with the analytical procedure, the count rate error and most importantly by the biological variance. The assumption of heteroscedasticity is incorrect for the data sets generated in the study of Po metabolism in non-human primates. The statistics generated by a least squares procedure are biased as a result of the unequal variances in the data. When regressing data to the function $Y=k \cdot exp[-lambda \cdot X]$, the

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2 MicroTSP was developed and is currently distributed by Quantitative Micro Software, Irvine, California.

best fit curve tends to lie closest to the high data points so as to minimize the sum of squares of the residuals. But these data points have the largest biological variance; they should therefore be given less relative weight in determining the line of best fit.

A weighting series may be applied to the data prior to performing the regression to obtain parameter estimates with minimum variance.[3] The weighting series used for the majority of the metabolic data was based on the assumption that the variances are proportional to the "predicted" excretion or retention model. Briefly, the applicable function is regressed to the unweighted data. The weighting series is then generated from the residuals squared for each datum and its corresponding "predicted" value. MicroTSP calculates the mean of the weighting series and then multiplies both the dependent (e.g., cpm/mL urine, per cent injected Po/day, organ Po content, etc.) and independent (e.g., days post first sample date, days post injection, etc.) variable by the ratio of the weighting series to its mean (Hall and Lilien 1987). The function is then regressed to the "weighted" data to determine the model parameter estimates and the least squares curve.

3.7 Quality Control

Counting system paramaters such as background count rate and detection efficiency were routinely monitored throughout the study period. Backgrounds were usually run overnight in the alpha spectrometry chambers and averaged 0.02 ± 0.01 cpm ^{210}Po for 154 measurements. A total of 46 reagent blank samples were processed; they averaged 0.04 ± 0.03 cpm ^{210}Po. The detection efficiency was maintained by calibration with a ^{208}Po standard traceable[4] to the National Bureau of Standards. A relatively high activity

3 The data weighting technique utilized was modified from a technique described by Skrable et al. 1988.

4 The ^{208}Po standard was plated from Standard Reference Material #4327 which had a specific activity of 77 Bq/g $\pm$ 1.4%.

^{241,243}Am source (10548 dpm) was also utilized to check the detection efficiencies. The efficiency of all three silicon surface barrier detectors was consistent, averaging 0.28 $\pm$ 0.005 cpm per dpm.

The alpha proportional counter had an average background count rate equal to one cpm. The efficiency was maintained with the ^{208}Po standard as well as electroplated ^{239,240}Pu standards prepared by the United States Department of Energy's Environmental Measurement Laboratory. Alpha detection efficiency averaged 0.52 $\pm$ 0.01 cpm per dpm.

The 2.06 E-3 efficiency of the NaI (Tl) gamma detector was determined in the 320-350 keV region with a ^{133}Ba stick source in a meter arc geometry (source purchased from the New England Nuclear Corporation). Background count rates were collected prior to sample counting and averaged 268.4 $\pm$ 10.9 cpm. The lower limit of detection (Altshuler and Pasternack 1963; Pasternack and Harley 1971; Harley 1986) for all counting systems are listed in Table 3.4.

Blood and excreta samples collected from tamarins and baboons prior to administration were assayed to determine the average natural levels of ^{210}Po. The background count rates were then subtracted from samples collected post injection to accurately calculate the percentage of administered dose in bioassay samples.

TABLE 3.1 TOTAL PO RECOVERED IN THREE ORGANS OF THE RETICULOENDOTHELIAL SYSTEM AND PER CENT OF THIS TOTAL IN EACH ORGAN*

Solution injected	Total recovered Po in RES (% dose)	% of Total in each organ Lung	Liver	Spleen
Neutral #1	62.3	47.4	41.6	11.1
Neutral #2	38.9	7.0	89.2	3.9
Acid	22.2	32.9	56.1	11.1
Citrate	13.7	13.8	70.6	15.5

* Tissues analyzed at 20 minutes after injection.
Neutral #1, aged 4 months; neutral #2, aged 15 days.
from Thomas and Stannard 1964a, p. 19.

TABLE 3.2 TAMARINS USED IN STUDY OF PO METABOLISM

Tamarin	Injection Date	Body Weight (kg)	Dose (Bq/kg)	Days on study
T500	1/30/87	0.549	87.7	90
T504	1/30/87	0.550	94.4	90
T500	5/12/88	0.583	12.6	14
T508	5/12/88	0.440	13.7	14

TABLE 3.3 BABOONS USED IN STUDY OF PO METABOLISM

Baboon	Injection Date	Body Weight (kg)	Dose (Bq/kg)	Days on study
B1054	4/01/87	10.1	9.62	1
B156	4/01/87	11.0	8.88	7
B1060	6/22/87	16.6	8.14	14
B1046	1/31/87	13.0	29.6	30
B806	1/31/87	13.0	28.9	91
B514	2/02/88	16.5	5.55	80

TABLE 3.4 LOWER LIMITS OF DETECTION (LLD)

	Detector		
	Silicon alpha spec.	Alpha proportional	8" x 4" NaI(Tl)
Counter Efficiency	0.28	0.52	2.06 E-3
Counter Bkg. (cpm)	0.02 ± 0.01	1 ± 0.5	268 ± 11
Radiochemical Yield	0.8	0.8	--
Reagent Blank (cpm)	0.04 ± 0.04	1	--
LLD (100 min.) (mBq)	5.8[a]	18.3[a]	44.3 Bq[b]
LLD (30 min.) (mBq)	10.3[a]	33.3[a]	109.3 Bq[b]

[a]
$$LLD = \frac{2 \cdot 1.645}{t \cdot Eff \cdot Yield} \sqrt{(bkg + blk\ counts) + (SEM_{bkg})^2 + (SEM_{blk})^2}$$

[b]
$$LLD = \frac{2 \cdot 1.645}{t \cdot Eff} \sqrt{(bkg\ counts) + (SEM_{bkg})^2}$$

where:

alpha and beta = 0.05
t = time (min)
Eff = detector efficiency (cpm/Bq)
Yield = radiochemical recovery determined with tracer
bkg = single background count
blk = single reagent blank count
SEM = standard error about the mean of multiple measurements

Fig. 3.1 Disappearance of ^{210}Po from the blood of rats. The neutralized (colloidal) form disappeared rapidly prior to the onset of sampling and then proceeded at a slower rate than did the acidified and citrated forms (from Thomas and Stannard 1964a, p. 18).

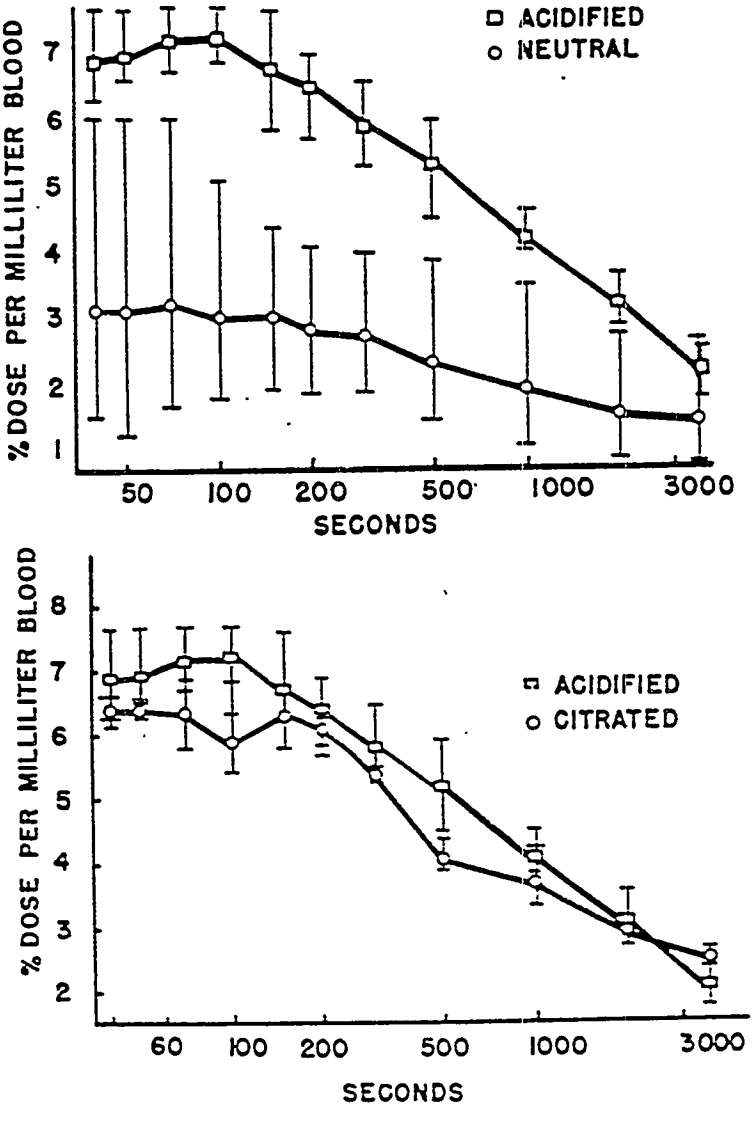


Fig. 3.2 Plating cell used to deposit Po onto Ni.

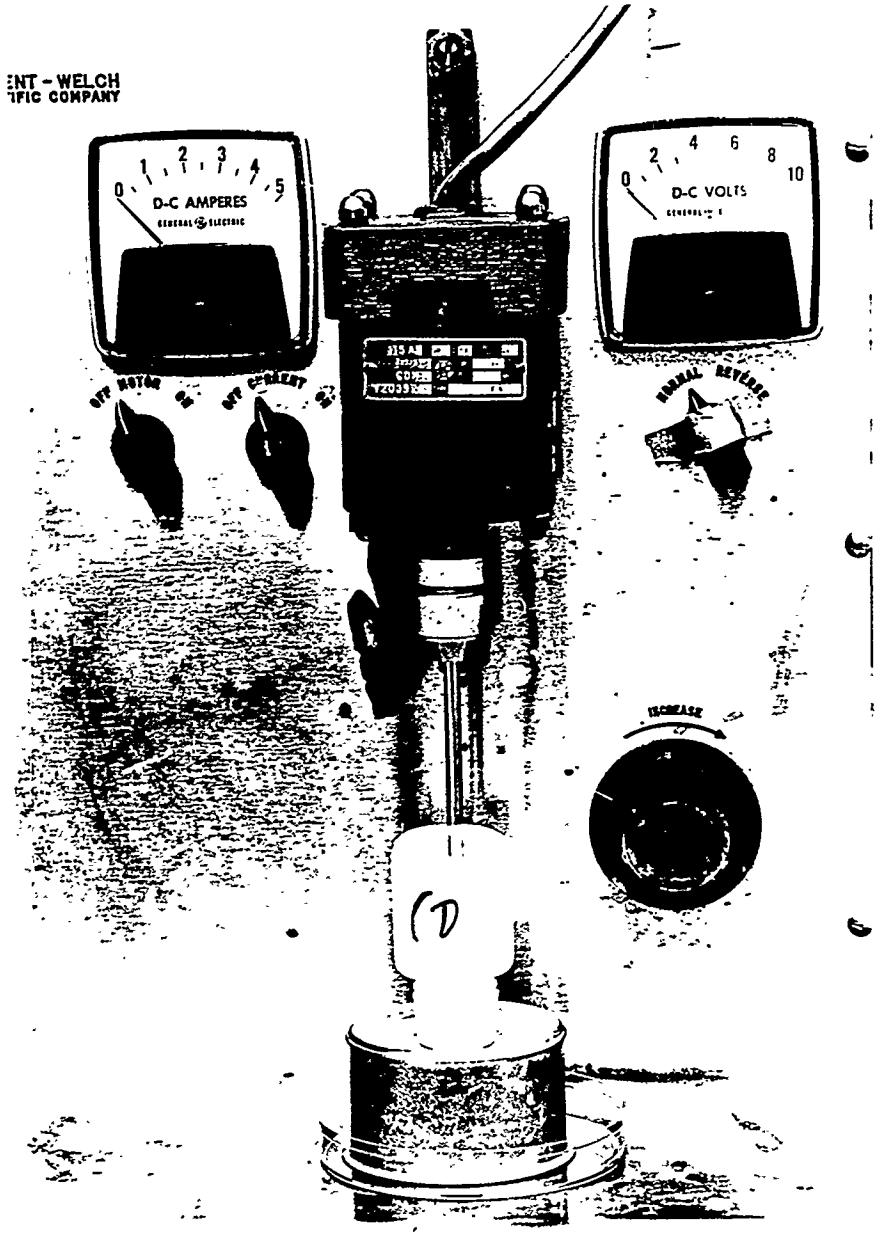
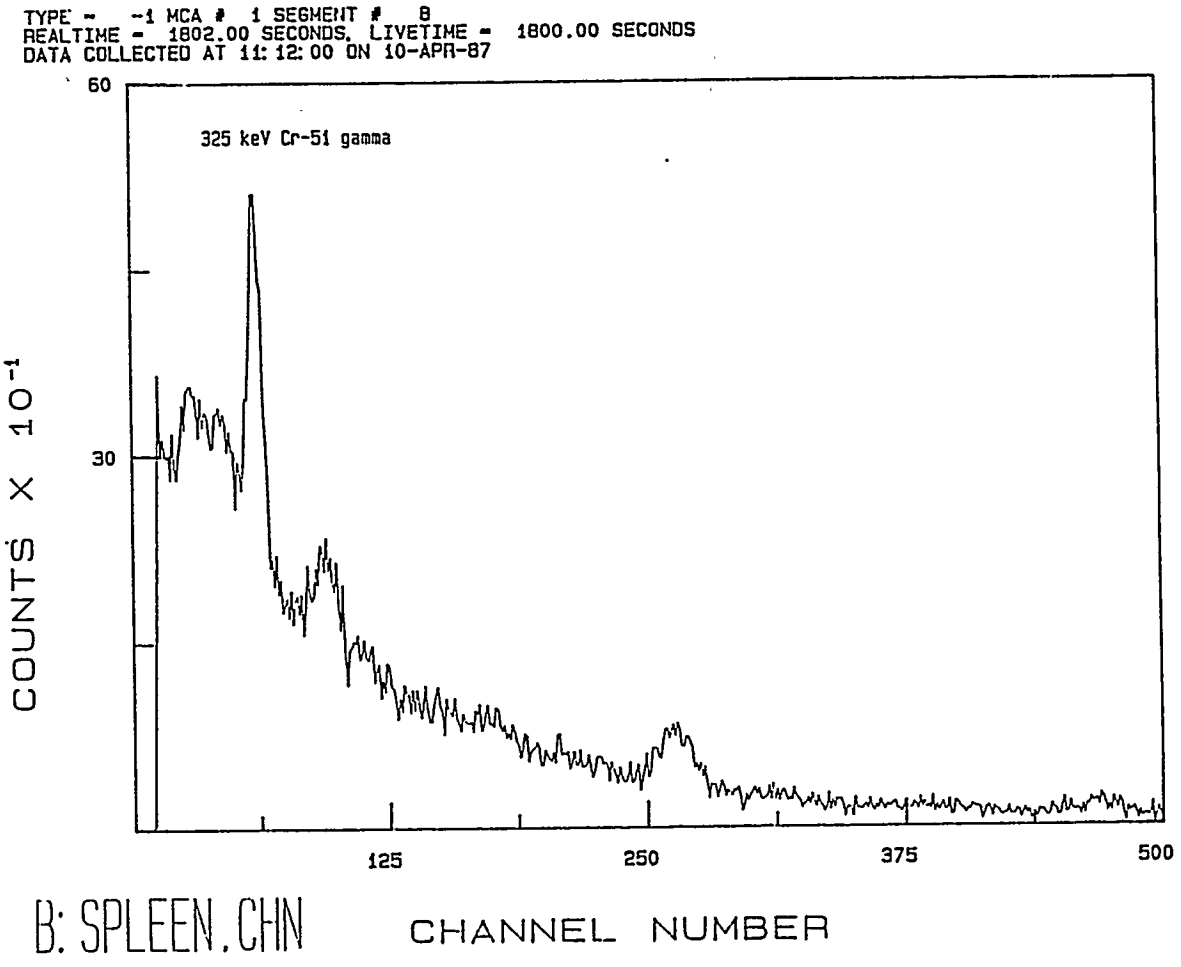


Fig. 3.3 Typical ^{51}Cr gamma spectrum from an 8" by 4" NaI(Tl) detector used to determine the volume of residual blood in tissue samples.



4 Excretion and Distribution of Po in Non-human Primates

The data presented below which describe excretion and distribution of ^{210}Po in tamarins and baboons have been adjusted for radioactive decay and consequently represent biological mechanisms only. The "effective" values which incorporate both the biological and physical decay are used in the Po dosimetry model presented in Section 5. Since the amounts of injected Po were high relative to counter background and reagent blank count rates, the relative errors on excreta, blood, and tissue samples ranged from 2-10 percent of the actual measurement.

4.1 Excretion

Tamarins

Urinary Po excretion in the tamarin is best described by single exponential kinetics with a biological half-time of 45.2 $\pm$ 2.1 days over 203 days (Figure 4.1). The total urinary Po output, based on the least squares curve, is 19.7 $\pm$ 1.1% of the injected dose.

Ninety consecutive daily fecal samples plus an additional five samples from 195-205 days post injection were collected. Feces samples from T504, T508, and T500 (second injection only) were analyzed.

Polonium-210 excretion in feces is best described by a single exponential during the initial 205 days post exposure with a biological half-time of 54.3 $\pm$ 3.9 days (Figure 4.2). The excretion curve predicts that a total of 68.8 $\pm$ 28.8% of the injected dose is excreted via the feces (assuming that the single exponential clearance continues to infinity).

Baboons

Excretion of Po by the baboon is characterized by single exponential kinetics through 90 days. (The excretion data from both species of non-human primates appear in Appendix D.) Excretion via both urine and feces proceeded more rapidly than expected.

That is, most of the available human occupational Po data as well as metabolic studies with other animal species indicate biological excretory half-times of approximately 50 days for Po. Figures 4.3a and 4.4a show that Po was excreted by the baboon with biological half-times of 15.6 $\pm$ 1.5 days for urine and 14.4 $\pm$ 2.5 days for feces. As can be seen in Figures 4.3b and 4.4b, the curves describing Po excretion by the baboon are only slightly changed when the concentration of Po (i.e., activity of ^{210}Po per gram urine or feces), rather than the daily output, are examined. The biological half-time estimate is reduced for both pathways, to 12.4 and 13.6 days for urine and feces, respectively. Therefore it would appear that the volume of excreta does not influence the ^{210}Po kinetics for either urine or feces. Regression analysis for the fecal data does not include Po recovered during the first four days post injection due to the extreme variability observed in the fecal Po output during this initial period. All of the baboons (with the exception of B806) eliminated a large quantity of the administered dose (12-14%) on either day 2,3, or 4 of the experiment.

The Po fecal-to-urine output ratio in baboons was markedly different from data reported elsewhere for other species, including the limited data for humans. The urinary excretion function parameters show that 37.7 $\pm$ 4.0% of the injected activity is excreted via the urine. Total fecal Po excretion is 55.1 $\pm$ 11.2% of the injected dose, resulting in a fecal-to-urine ratio of 1.5 $\pm$ 0.3. Table 4.1 presents a summary of excretion parameters found in this study for non-human primates following intravenous administration of Po citrate. In contrast, earlier studies conducted at the University of Rochester discussed in Section 2.1.4 estimate a fecal-to-urine ratio of ten following intravenous administration of Po. Likewise, Foreman et al. (Foreman et al. 1958) indicated that Po content recovered in feces was at least ten times the Po content recovered in urine after two workers were occupationally exposed to ^{210}Po.

An examination of the blood and fecal data from B806 (sacrificed at 91 days post injection) suggests that as much as half of the ^{210}Po in the syringe was inadvertantly injected into the femoral muscle. For example, at ten minutes post injection, the blood from each of the other exposed animals contained 50-70% of the injected dose. On the other hand, the Po in the blood of B806 accounted for only 37.8% of the injected dose at that time. To a lesser degree, B156, with 52.9% of the injected dose present in the blood at ten minutes, and B1054, with 50.0% of the injected dose present at ten minutes, may also have received some intramuscular administration. Retention measurements of the nuclide in the blood of B806 indicates that, for the first week, Po levels did not decline significantly after the completion of an initial rapid phase. The blood Po level was relatively constant from day 2 (14.8% of the injected dose) to day 14 (11.9% of the injected dose). It could be that the slower than expected clearance of the Po from the blood was due to a slow and constant absorption of ^{210}Po from the muscle into the blood.

The B806 excretion pattern of ^{210}Po in feces during the first few days after exposure also support the possibility of a combination of intravenous and intramuscular administration. An immediate and precipitous drop in fecal content consistently followed peak fecal Po output during days 2-4 for the three other studied baboons. Polonium-210 output in the feces of B806 followed a different pattern during the first week. A large (12-14%) daily maximum excretion was not noted in B806's feces, as was the case for B156 and B1046. Rather, levels ranging from 1.1-3.8% of the injected dose were found in fecal samples collected from day 2 through day 8 post injection, with levels increasing daily from day 4 through day 7 post injection. Continued input of Po into the bloodstream during the first few days (presumably from the muscle deposit) could account for the observed fecal excretion pattern during this time period.

Due to the possibility that B806 was exposed via both the intravenous and intramuscular routes, its Po excretion data were compared to the data from the other exposed baboons via an analysis of covariance test. For both the urinary and fecal excretion data, there were no statistically significant differences found between either the slopes (i.e., biological half-times) or the intercepts of the excretion functions ($p > 0.05$). Therefore, the B806 excretion data were combined with the data from the other baboons for the determination of the Po urinary and fecal excretion functions.

4.2 Distribution

4.2.1 Blood

Tamarins

A total of 13 blood samples were drawn from the tamarins on study for ^{210}Po metabolism. Two samples were taken minutes after injection and samples were also drawn at 1, 2, 5, 6, 21, 133, 149, and 202 days post injection. These samples are sufficient to estimate a two phase exponential retention of Po by the blood using the nonlinear least squares method (Figure 4.5). An early rapid phase retention with a half-time of 12.1 ± 1.4 minutes continues until the Po blood level is reduced to approximately 20% of the injected dose. A later slow phase then follows with a 37.3 ± 15.5 day half-time. These parameters give an approximation of the retention of Po in the tamarin blood since the total number of samples was limited. It is possible that the slow phase described may actually be an intermediate phase with a half-time somewhat more rapid than 37.3 days followed by an additional phase with a longer retention half-time. Total blood volume is estimated to be 7% of body weight.

Baboons

Approximately all of the injected Po was recovered in the baboon excreta, blood, and tissue samples. Table 4.2 lists the material balance of the injected dose. (Determination of the total quantity of ^{210}Po excreted in urine and feces for B806 was estimated by extrapolation of the previously derived curves since some of the samples were not analyzed.)

Figures 4.6 and 4.7 show the retention of ^{210}Po citrate in the blood of baboons. It is clear from these curves that differences exist among animals in the percentage of Po remaining in the blood at the beginning of the slow phase. The blood Po levels of B156 (7 day study) and B1060 (14 day study) drop to approximately 11% of the injected dose during the initial rapid phase, with Po leaving the blood with a half-time of 38.7 $\pm$ 6.0 minutes. The slow phase follows with a half-time of 8.4 $\pm$ 3.1 days. Rapid phase kinetics cannot be determined for the other animals due to the lack of early blood samples drawn during the first day post exposure. Slow phase retention of Po in the blood of B1046 (30 day study) is controlled by similar kinetics as noted for B156 and B1060, with a half-time of 12.5 $\pm$ 2.7 days. However, twice as much of the injected dose is still present in the blood at the onset of the slow phase. Of course, differences observed among the blood retention curves may also be partially due to portions of the administered Po being injected intramuscularly. As with the tamarin, these data are not sufficient to determine whether there is an additional, slower phase of Po retention in the blood.

The blood ^{210}Po data for B806 is separated graphically into plasma and red blood cell content for the samples taken through day 21. After completion of the rapid phase clearance, the red cell fraction contains 3-4 times more total Po than the plasma. On a weight basis, red cell Po concentration exceeds that of plasma by a factor of 5.5. Slow

phase Po clearance commences with 16.6% of the injected dose estimated in the circulatory system. The loss of ^{210}Po from the plasma and red cells is consistent with the 19.1 $\pm$ 2.5 day retention half-time observed for total blood Po, a rate almost double that exhibited for Po clearance from the blood of the other baboons. This longer retention in the blood of B806 may be indicative of a sustained or continuous input of Po into the bloodstream from the deposit believed to have been injected into the femoral muscle.

4.2.2 Tissues

While measureable levels of Po were recovered in all organs assayed, distribution was clearly not uniform throughout the soft tissues. The distribution data for ^{210}Po in baboon tissues appears in Table 4.3. Kidney and liver cells accumulated the most ^{210}Po, with concentrations in excess of 0.1 percent injected dose per gram wet weight of tissue during the first week post injection. The concentration of ^{210}Po in the spleen was of an intermediate level, containing approximately one-third that determined in the kidney and liver. The lung, adrenal gland, and pancreas had ^{210}Po concentrations approximately one-tenth that of kidney and liver.

The expressions which describe the change in the content of tissues are referred to as "retention functions." This terminology is often used interchangeably with the loss of material from a tissue. A true retention function describes the temporal retention of material by the cellular mass of the tissue which certainly is affected by Po being recycled among all organs and soft tissues. However, this study of the biokinetics of ^{210}Po in the baboon was not intended to account for recycling between compartments via the circulatory system.

Stannard (1964b) described the retention of Po in various tissues of the rat as consisting of a rapid and slow phase. In that study, exponential kinetics for biological loss were assumed and composite half-times were derived by combining data from the two phases. Retention of ^{210}Po by baboon tissues in this study is best described by using a single phase exponential model. These curves for baboon tissues are shown in Figures 4.8, 4.9, 4.10, and 4.11. Partition coefficients (i.e., the fraction of the administered Po initially deposited in an organ) and retention half-times are given in Table 4.5. Loss of ^{210}Po from the liver proceeds more rapidly than from all other tissues, with a half-time of 15.4 days. Kidney, spleen, pancreas, and skeleton comprise an intermediate group with half-times ranging from 25-35 days. Lungs, ovaries, and thyroid lose ^{210}Po more slowly, exhibiting retention half-times of 45-50 days.

As noted by Stannard (1964b), there is a shift in the tissue distribution pattern of ^{210}Po with time because loss rates vary among tissues. In Table 4.4, ^{210}Po content of each organ or tissue is expressed as the percent of the body content on a per organ and per gram wet tissue weight basis. The changes in the relative distribution of ^{210}Po with time can be seen graphically for some tissues in Figures 4.12 (on a per gram wet weight basis). The spleen and skeleton retain a relatively constant fraction of the body content. The percentage of the Po body content found in the pelt undergoes a dramatic increase, climbing from 5% at day 1 to greater than 50% at day 91. This results from the pelt maintaining 5-7% of the administered Po throughout the study period while the levels of the radionuclide declined in all other tissues. A similar trend is also observed to a lesser extent in the ovaries and brain. The kidney undergoes an increase in percentage of Po body content during the initial 30 days post injection before falling off between day 30 and day 91. The muscle contains an increasing percentage of the body content through the first 30 days. However on a wet weight basis, the concentration of Po in muscle

tissue is relatively constant over that period. The increase in total muscle Po may only reflect the differences in the total muscle mass of the study animals. The fraction of the body content present in the blood first drops and then remains relatively constant through 30 days. The relative increase in the fraction of the body content reported for the blood of the rat from day 30 to day 400 post injection (Stannard 1964b) was not observed in the baboon during the 91 day study period.

4.3 Residual Blood Study

Exsanguination is never 100% efficient in removing the volume of blood from the circulatory system. In metabolic studies with cats, exsanguination removed 50-93% of the total blood volume (Morrow et al. 1964b). Nevertheless, all of the tissue ^{210}Po contents presented in the previous section can be considered as "blood-free" measurements. If significant quantities of measured Po were resident within the "residual" blood volume of the sample and not within the cells of the tissue itself, an accompanying overestimation of the organ Po content would result. The exact origin of an emitted alpha particle (i.e., whether the Po atom is actually located in blood vs. a tissue cell of an organ) is important for dosimetry.

Thomas (1955) constructed a crude model in an attempt to estimate the fraction of alpha radiation damage in tissue due to Po carried by erythrocytes. For example, depending on the diameter of the blood vessels contained within the spleen, 17-44% of the effective dose may be contributed by blood-borne Po. Using data from Stannard (1964a), Thomas showed that 86% of all alpha energy expended in the body was contributed by blood-borne Po after single gavage administration, but only 14% was contributed by blood-borne Po after intravenous administration.

Consideration of Po distribution following its intravenous administration to the baboon does not include any contribution of effective dose to tissue from blood-borne Po. Certainly alpha energy from blood-borne Po will irradiate soft tissue in some cases. However, it is assumed that much of the 14% of the total alpha energy estimated by Thomas to have originated in the blood will be dissipated intravascularly. A further reduction in tissue dose from blood-borne Po results from the geometric distribution of alpha particles emitted from within blood cells bathing the tissue surfaces.

The residual blood data for baboon tissues are summarized in Tables 4.6, 4.7, and 4.8. Table 4.6 gives the blood concentration of ^{51}Cr and the measurement of total blood volume. Table 4.7 lists several organ weights and the concentration of residual blood within those organs after exsanguination. Table 4.8 gives the contribution of blood-borne Po to organ Po burdens for a number of organs. As would be expected, much of the ^{210}Po measured in bone marrow samples was due to residual blood Po. The ^{210}Po content of the lungs and spleen were reduced by approximately 25% for the initial days post injection to account for the blood-borne Po. The contributions of blood-borne Po in other organs, such as the liver and kidneys, were not as significant as that observed for the spleen and lung tissue.

4.4 Discussion

4.4.1 Excretion

Differences were found in the Po excretion fractions and half-times for the two species of non-human primates. The tamarin excretes approximately 20% of the injected dose via the urine (to infinity) with a 45.2 day half-time. In comparison, the baboon excretes 38% of the injected amount via the urine (to infinity) with a 15.6 day half-time.

These data indicate a possible species difference in the metabolism of Po. Both non-human primate species differ from rats with respect to Po excretion. As discussed in Section 2, rats excrete a total of 5-10% of systemic Po in the urine, which is significantly different than both species of non-human primates examined in this research.

The tamarin excretes 69% of the injected ^{210}Po in feces, while the baboon excretes 55% in feces. These estimates do have large relative errors associated with them (approximately 20-40%), and any species difference in total ^{210}Po fecal excretion cannot be shown to be statistically significant. Regardless, the ^{210}Po fecal-to-urine ratio observed in the non-human primates following intravenous injection (ranging from 1.5-3.5) is significantly lower than for rats, which was reported to be equal to 10 (Berke and DiPasqua 1964).

The urinary and fecal ^{210}Po excretion data in the non-human primates suggest the existence of a long term phase of Po excretion which could not be adequately characterized during 90 days of study. At 90 days post injection, the daily urinary Po elimination constant[5] is estimated to be 0.004 day^{-1} (corresponding to a 160 day biological half-time). Similarly for the tamarin, the urinary Po elimination constant at 90 days post injection is estimated to be 0.002 day^{-1} (corresponding to a 300 day biological half-time). The composite elimination rates in both species are much more rapid over the entire 90 day period. Estimates of total ^{210}Po excreted by both routes (which can be predicted from the integrated single exponential excretion functions) total 89% and 93% for the tamarin and baboon, respectively. Likewise, re-evaluation of data presented by Fink (1950)

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5 Estimated daily urinary elimination constant can be estimated:

$$\lambda = A_t / BB_t$$

where,
A_t = daily quantity of polonium eliminated prior to sacrifice
BB_t = body burden at time of sacrifice

indicate that 89% of the intravenously administered ^{210}Po was excreted by a human volunteer based on the sum of the integrated single exponential urinary and fecal excretion functions. A relatively small percentage of Po excreted with a longer half-time might describe some or all of the 7-10% of the administered dose unaccounted for by the single phase excretion functions. Study of Po metabolism in rats over long term periods (e.g., in excess of 400 days) indicated that loss of Po from most tissues and the whole body does indeed include a slow phase component (Stannard 1964b).

It is possible that a portion of the body burden is excreted in hair. Ladinskaya et al. (1973) reported ^{210}Po concentrations in human hair to be higher than ^{210}Po soft tissue and skeletal concentrations in persons exposed solely to environmental levels of the nuclide. The baboon pelt samples contained from 5-7% of the injected dose, corresponding to 5% of the body content on day one post injection and 53% of the body content on day 91 post injection. This trend was also seen in dogs following inhalation exposure to Po, as the percentage of body content in the pelt increased steadily from 11% on day 28 to 51% on day 149 post exposure (Smith et al. 1961). The majority of activity was found in the hair follicles. Unfortunately, the baboon samples assayed were not separated into the hair, skin, and fat components which comprise the pelt.

4.4.2 Blood Retention

The retention of ^{210}Po in the blood of the five baboons in the study exhibited similar kinetics, although some differences were found with regard to the percentage of the administered dose remaining in the circulatory system at the conclusion of the initial rapid phase. The slow phase commenced within a few hours post injection, with approximately 11% of the injected activity in the blood of B156 and B1060, 17% in the blood of B806, and 22% in the blood of B1046. These data may reflect normal biological

variability or perhaps a radiation dose effect since B806 and B1046 received 3-4 times higher doses of ^{210}Po than did the other two animals. Another possibility for the differences observed in early Po retention is the relative amounts of the administered dose which were accidentally injected intramuscularly.

The clearance of Po from the blood may be more rapid in the baboon than in the tamarin. However, the longer retention half-time measured in tamarin blood (37 days) is based on too few samples to warrant a conclusive comparison. Nevertheless, the blood Po retention half-time differences between the species appear to be reflected in the urinary excretion half-time differences. The initial rapid phase for both species appears similar, with the blood Po level falling to approximately 20% of the injected dose in the tamarin and to 11-22% in the baboon.

4.4.3 Tissue Distribution and Retention

Polonium has often been described as a soft tissue seeker which distributes throughout the whole body (Fink 1950; Spoerl and Anthony 1956; Stannard 1964a; ICRP 1979). For the most part, the baboon data support this generalized description of ^{210}Po distribution.

The tissue ^{210}Po distribution in the baboon was generally similar to distribution data reported in other species (especially the rat). Liver, kidney, and spleen were the tissues with the greatest ^{210}Po concentrations. However, the spleen ^{210}Po content was much lower in the baboon than in the rat and somewhat lower than in the mouse on a percent injected dose per organ basis (Stannard and Smith 1964). Two factors may have contributed to this difference: 1. The injection solution administered to the baboon was free of Po aggregates whereas the Po chloride solutions used in previous metabolic studies in other species did consist largely of Po aggregates. The spleen (as well as other RES tissues)

would be expected to remove aggregates from the bloodstream. An injection solution free of aggregates was essential to best approximate the metabolic behavior of systemic Po following occupational exposure. 2. To a lesser extent, the baboon tissue data are "blood-free" measurements. Subtracting the residual blood ^{210}Po from the spleen assays. resulted in an approximate 25% reduction in the measured spleen ^{210}Po content.

The excretion rate of ^{210}Po in feces is almost identical to the rate of loss of ^{210}Po from the liver, with half-time estimates of 14.4 days and 15.4 days, respectively. These kinetics support the assumption that the entire liver ^{210}Po content is excreted in the feces via the biliary pathway. This suggests that a significant amount of Po is recycled to the liver by the circulatory system since a total of 55% of the administered dose is excreted in baboon feces compared to the only 30% of the administered dose initially found in the liver.

Retention of ^{210}Po in various baboon tissues exhibited half-times ranging from 15-50 days. In general, the tissue retention kinetics observed in the baboon were similar to the other species studied previously, especially the rat. Differences in tissue processing, injection solution composition, and dosage levels make a more rigorous comparison of distribution and retention difficult to quantify.

4.4.4 Residual Blood

Residual blood Po contributed significantly to the organ Po measurement of some organs under certain circumstances. The measurement of red blood cells labeled with ^{51}Cr revealed that significant amounts of activity were added to the gross organ Po measurements of the spleen, lungs, heart, skeletal muscle, and bone marrow. The time from exposure to sacrifice was most important, as the amount of blood-borne Po was

greatest when the blood Po concentration was still high. The completeness of the exsanguination procedure, the route of administration, and the chemical form of Po also influence the relative contribution of blood-borne Po to the total organ Po content.

Morrow et al. (1964b) accounted for the amount of blood-borne Po in cat tissue samples by comparing the blood volume recovered to reported organ blood volumes and estimating the quantity of blood remaining in each sample. The authors concluded that addition of the blood-borne Po to the blood-free tissue Po content seven hours after intravenous administration of Po citrate would add 66% to the spleen, 83% to the liver, 72% to the lung, and 49% to the kidney.

Thomas and Stannard (1964c) estimated that blood-borne Po in rat organs following intratracheal administration when blood Po is highest relative to total Po (day 62) accounts for decreases of 10.2% in spleen, 37.5% in liver, and 5.3% in kidneys. They assumed removal of only one-third total blood volume at sacrifice.

TABLE 4.1 EXCRETION OF PO BY NON-HUMAN PRIMATES

Species	Study Period (days)	Biological Half-time (days ± se)	Excretion fraction (± se)
Tamarin:			
Urine	203	45.2 ± 2.1	0.20 ± 0.03
Feces	203	54.3 ± 3.9	0.69 ± 0.29
Baboon:			
Urine	91	15.6 ± 1.5	0.38 ± 0.04
Feces	91	14.4 ± 2.5	0.55 ± 0.11

TABLE 4.2 MATERIAL BALANCE OF INJECTED PO

	Percent Injected Dose (± 1 sd)				
	B1054	B156	B1060	B1046	B806
Sacrifice Time (days)	1	7	14	30	91
Feces	0.4 ± 0.01	26.7[a] ± 0.3	22.4 ± 0.3	41.6 ± 0.2	54[b] ± 0.2
Urine	1.0 ± 0.1	13.3 ± 0.1	17.2 ± 0.1	25.1 ± 0.1	36[b] ± 0.1
Blood	20.5 ± 0.5	5.7 ± 0.1	4.3 ± 0.1	3.7 ± 0.04	0.6 ± 0.02
Soft Tissues	63.8 ± 1.2	35.1[c] ± 0.6	27.1[c] ± 0.3	18.6[c] ± 0.1	2.4[c] ± 0.03
Muscle[d]	6.6 ± 0.5	8.2 ± 0.4	6.4 ± 0.2	8.7 ± 0.1	1.0 ± 0.09
Pelt[d]	5.2 ± 0.4	6.6 ± 0.4	6.9 ± 0.2	lost	5.6 ± 0.5
Skeleton[e]	4.8 ± 0.3	5.7 ± 0.3	4.8 ± 0.1	4.1 ± 0.04	1.0 ± 0.06
TOTAL	102 ± 1.4	101 ± 0.9	89 ± 0.6	102 ± 0.4	101 ± 0.6

[a] Day 4 sample was lost. Polonium-210 content was estimated.
[b] Polonium content of some samples from day 60-80 were estimated.
[c] Polonium content of large intestine (and contents) was estimated.
[d] Value estimated from %ID/gm (mean of 3 samples) * gm (total)
[e] Entire skeleton of B1046 was analyzed.
Other values estimated:
Skeletal ^{210}Po = Femur ^{210}Po content / 0.0329
Right femur of B1046 constituted 3.29% of the skeletal ^{210}Po burden.

TABLE 4.3 BABOON ORGAN AND TISSUE PO CONTENT

	Percent injected dose/organ or tissue[a]				
Baboon #	B1054	B156	B1060	B1046	B806
Days on Study	1	7	14	30	91
Tissue					
Blood	20.5	5.6	4.3	3.7	0.59
Liver	33.2	19.3	15.3	6.3	0.48
Kidney	7.2	4.4	4.8	4.3	0.57
Spleen	0.95	0.40	0.39	0.24	0.05
Lung	1.8	0.78	0.42	0.75	0.22
Ovary	0.03	0.03	0.01	0.04	0.01
Thyroid	0.09	0.01	0.003	0.01	0.002
Adrenal Gland	0.10	0.02	0.03	--	0.004
Pancreas	0.30	0.24	0.17	0.20	0.02
Brain	0.06	0.29	--	0.55	0.28
GI tract[b]	18.8	8.3[c]	5.1[c]	4.6[c]	0.7[c]
Muscle[d]	6.6	8.2	6.4	8.7	1.0
Skeleton[e]	4.8	5.3	4.8	4.1	1.0
Pelt[d]	5.2	6.6	6.9	--	5.6
	Percent injected dose/gm				
Blood	0.027	0.007	0.004	0.004	0.0008
Liver	0.105	0.105	0.059	0.026	0.003
Kidney	0.129	0.103	0.082	0.083	0.014
Spleen	0.035	0.025	0.018	0.021	0.003
Lung	0.015	0.009	0.006	0.008	0.002
Ovary	0.011	0.015	0.005	0.008	0.003
Thyroid	0.073	0.008	0.004	0.003	0.002
Adrenal Gland	0.039	0.011	0.010	--	0.001
Pancreas	0.018	0.018	0.008	0.011	0.001
Brain	0.0005	0.002	--	0.003	0.002
GI tract	--	--	--	--	--
Muscle[d]	0.002	0.002	0.0007	0.001	0.0002
Skeleton[e]	0.002	0.002	0.002	0.002	0.0003
Pelt[d]	0.005	0.005	0.003	--	0.004

[a] 2-10% relative range of errors

[b] Sum of stomach, small and large intestines (with contents).

[c] Large intestine ^{210}Po content was estimated.

[d] Value estimated from %ID/gm (mean of 3 samples) * gm (total)

[e] Entire skeleton of B1046 was analyzed. Other values estimated:
Right femur of B1046 constituted 3.29% of the skeletal ^{210}Po burden.
Skeletal ^{210}Po = Right femur ^{210}Po content / 0.0329

TABLE 4.4 PERCENT OF PO BODY CONTENT IN BABOON TISSUES

	Percent body content/organ or tissue[a]				
Baboon #	B1054	B156	B1060	B1046	B806
Days on Study	1	7	14	30	91
Tissue					
Blood	20.3	9.2	8.7	10.3	5.5
Liver	32.7	31.4	31.0	17.4	4.5
Kidney	7.1	7.1	9.8	12.0	5.3
Spleen	0.9	0.6	0.8	0.6	0.4
Lung	1.8	1.3	0.8	1.2	2.1
Ovary	0.03	0.05	0.03	0.17	0.07
Thyroid	0.09	0.02	0.01	0.01	0.02
Adrenal Gland	0.10	0.04	0.06	--	0.04
Pancreas	0.3	0.4	0.4	0.5	0.2
Brain	0.06	0.5	--	1.4	2.6
GI tract[b]	18.5	13.5[c]	10.4[c]	12.7[c]	6.4[c]
Muscle[d]	6.5	13.4	12.8	24.1	9.7
Skeleton[e]	4.7	8.5	8.9	11.4	8.9
Pelt[d]	5.1	10.8	14.1	--	53.0
	Percent body content/gm				
Blood	0.03	0.01	0.01	0.01	0.007
Liver	0.11	0.17	0.12	0.07	0.02
Kidney	0.13	0.17	0.17	0.23	0.13
Spleen	0.03	0.04	0.04	0.06	0.03
Lung	0.01	0.01	0.01	0.02	0.02
Ovary	0.01	0.02	0.01	0.04	0.03
Thyroid	0.07	0.01	0.01	0.01	0.03
Adrenal Gland	0.04	0.02	0.02	--	0.01
Pancreas	0.02	0.03	0.02	0.03	0.01
Brain	0.0005	0.003	--	0.01	0.02
GI tract	--	--	--	--	--
Muscle[d]	0.002	0.003	0.001	0.004	0.001
Skeleton[e]	0.002	0.003	0.003	0.005	0.003
Pelt[d]	0.005	0.008	0.01	--	0.04

[a] 2-10% relative range of errors
[b] Sum of stomach, small and large intestines (with contents).
[c] Large intestine ^{210}Po content was estimated.
[d] Value estimated from %ID/gm (mean of 3 samples) * gm (total)
[e] Entire skeleton of B1046 was analyzed. Other values estimated:
Right femur of B1046 constituted 3.29% of the skeletal ^{210}Po burden.
Skeletal ^{210}Po = Right femur ^{210}Po content / 0.0329

TABLE 4.5 DISTRIBUTION OF SYSTEMIC PO IN SELECTED ORGANS OF THE BABOON

Organ	Partition Coefficient ± se	Biological Half-time (days ± se)	r^2 of the regression
Liver	0.29±.01	15.4±0.6	0.99
Kidneys	0.07±.01	24.5±3.0	0.95
Spleen	0.006±.002	24.9±3.0	0.95
Pancreas	3E-3±4E-4	24.7±2.2	0.95
Adrenal Gland	5E-4±6E-6	25.2±6.3	0.83
Skeleton	0.06±0.003	33.8±2.7	0.97
Lungs	0.009±.005	44.9±18.0	0.66
Ovaries	3E-4±2E-5	48.2±22.8	0.61
Thyroid	7E-5±6E-6	49.5±31.2	0.56

TABLE 4.6 ^{51}Cr BLOOD LABELING RESULTS

Baboon	Body Weight (kg)	^{51}Cr Blood Concentration (Bq/ml±sd)	Total Blood Vol. (ml±sd)
B1054	10.1	0.59 ± 0.10	749.8±45.5
B156	11.0	3.96 ± 0.42	785.1±29.1
B1060	16.6	0.70 ± 0.06	1162*
B1046	13.0	1.98 ± 0.02	970.1±6.4
B806	13.0	6.06 ± 0.62	782.1±32.4

* volume estimated to be 7% of body weight; majority of the activity in the syringe did not enter bloodstream

TABLE 4.7 BABOON ORGAN WEIGHTS AND RESIDUAL BLOOD CONCENTRATION

Organ	N	Weight (g±sd)	Residual Blood (mL/g±sd)
Liver	5	241.22±46.11	0.10±0.04
Kidneys	5	50.10±8.31	0.11±0.02
Spleen	4	17.08±7.20	0.51±0.19
Lungs	5	94.55±19.74	0.23±0.05
Heart	5	54.42±6.17	0.05±0.02
Brain	4	143.50+19.51	0.01±0.00
Pancreas	5	17.70±2.77	0.03±0.02
Adrenal	4	2.68+0.42	0.19±0.11
Muscle	21	---	0.01±0.00
Bone-Femur	3	87.48±5.20	0.01±0.01
Bone Marrow	19	---	0.06±0.09
Pelt	4	1229.7±92.3	0.01±0.00

TABLE 4.8 RESIDUAL BLOOD ^{210}PO CONTRIBUTION TO VARIOUS TISSUES

Organ	Days Post Injection	Percent ID (Gross)	Percent ID (Corrected)	Percent Difference
Liver	1	33.9	33.2	2.1
	7	19.4	19.3	0.6
	14	15.4	15.3	1.1
	30	6.4	6.3	1.3
	91	0.5	0.5	2.7
Kidneys	1	7.4	7.2	2.6
	7	4.4	4.4	0.7
	14	4.9	4.8	0.5
	30	4.4	4.3	0.7
	91	0.6	0.6	0.7
Spleen	1	1.2	0.9	23.5
	7	0.5	0.4	16.9
	14	0.4	0.4	11.4
	30	0.3	0.2	13.1
	91	0.05	0.05	10.4
Lungs	1	2.3	1.8	28.6
	7	0.9	0.8	20.9
	14	0.5	0.4	17.3
	30	0.8	0.7	12.2
	91	0.2	0.2	7.3
Heart	1	0.6	0.4	36.0
	7	0.4	0.3	5.4
	14	0.1	0.1	4.1
	30	0.2	0.2	6.6
	91	0.06	0.05	10.0
Bone Marrow[a]	1	0.005	0.002	125.4
	7	0.004	0.003	28.4
	14	0.014	0.013	6.3
	30	0.024	0.022	9.0
	91	0.002	0.002	7.0

[a] Bone marrow extracted from right femur. Considerable variation in sample sizes.

Figure 4.1 Tamarin Urinary ^{210}Po Excretion

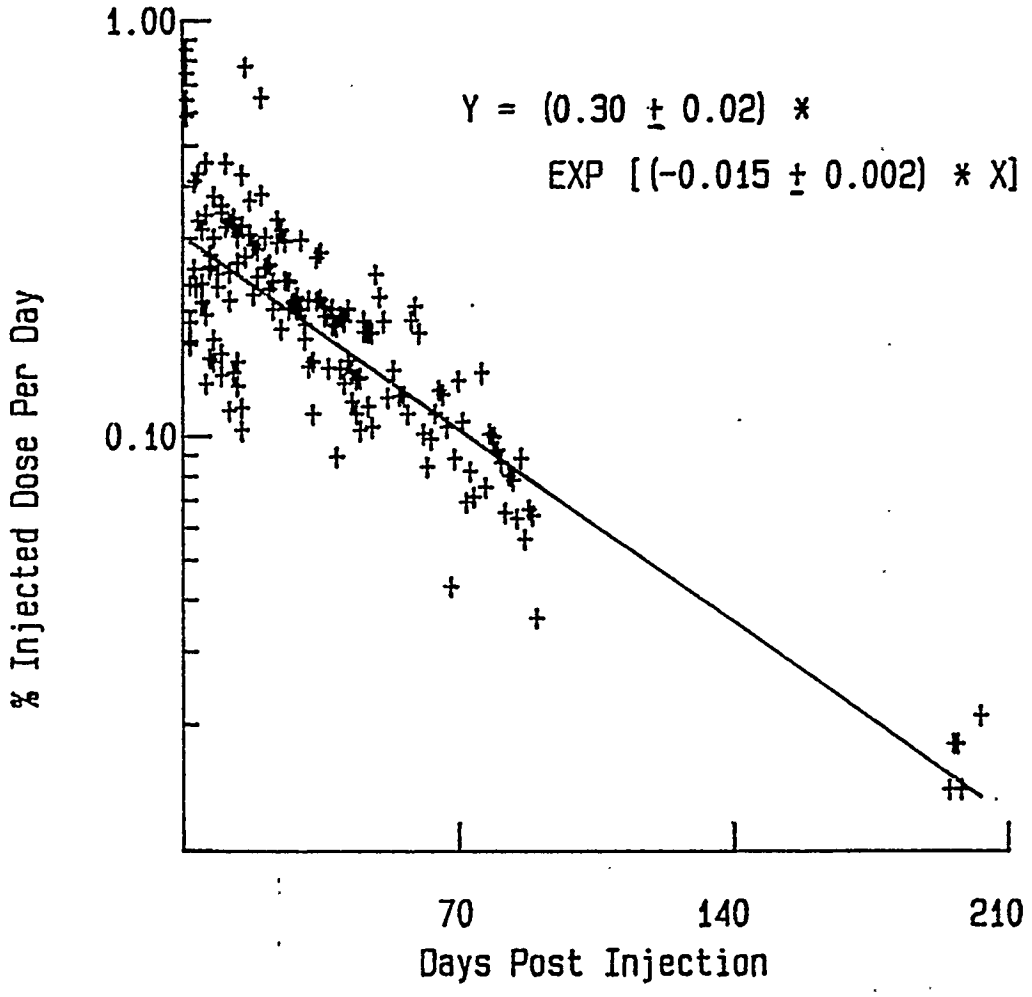


Figure 4.2 Tamarin 504 Fecal ^{210}Po Excretion

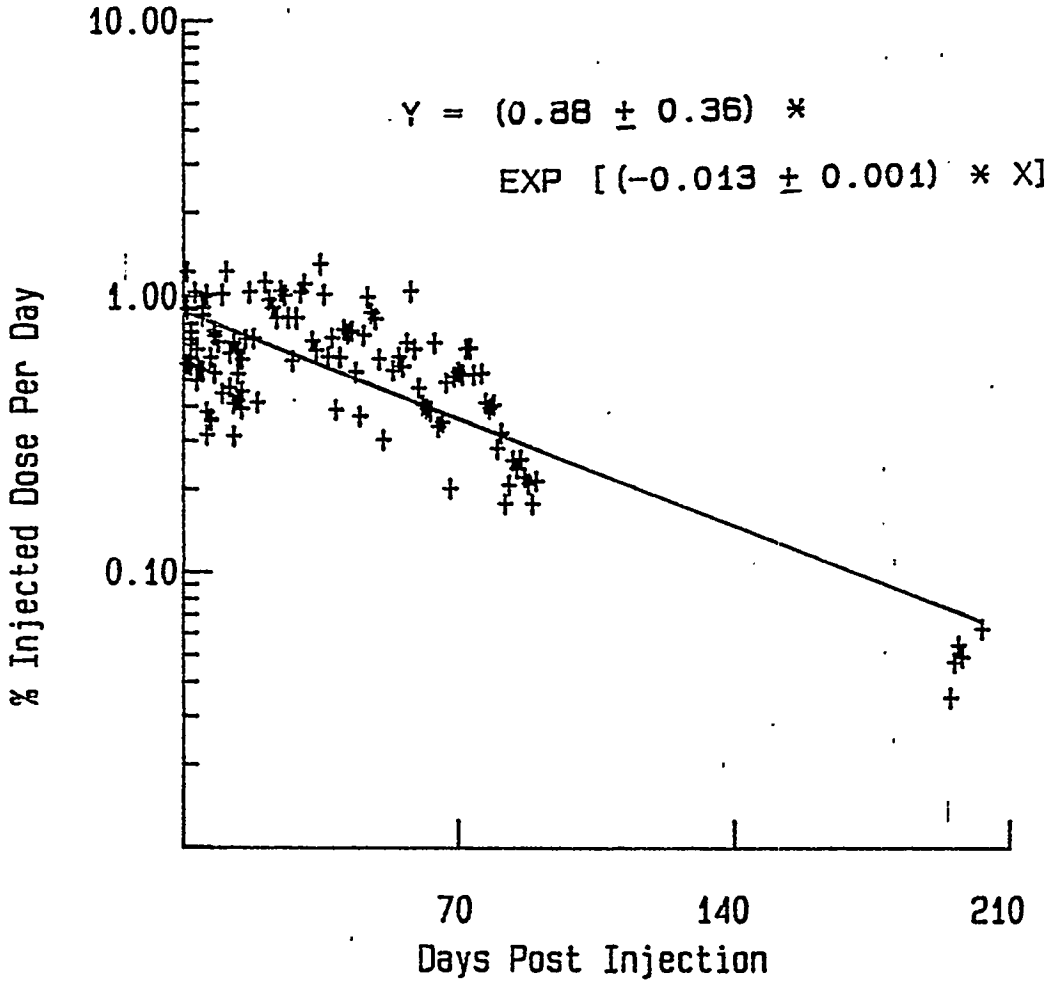


Figure 4.3 Baboon Urinary ^{210}Po Excretion

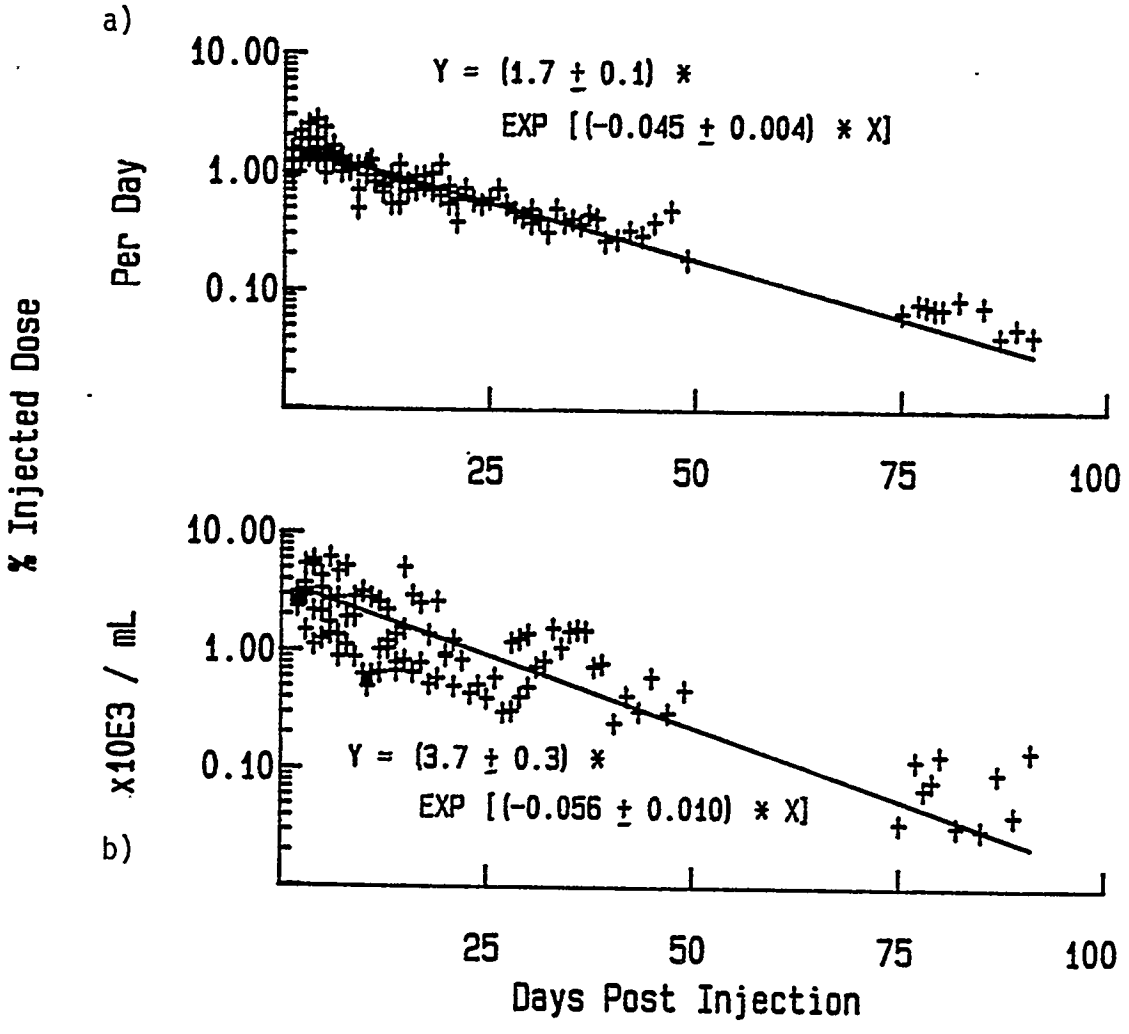


Figure 4.4 Baboon Fecal ^{210}Po Excretion

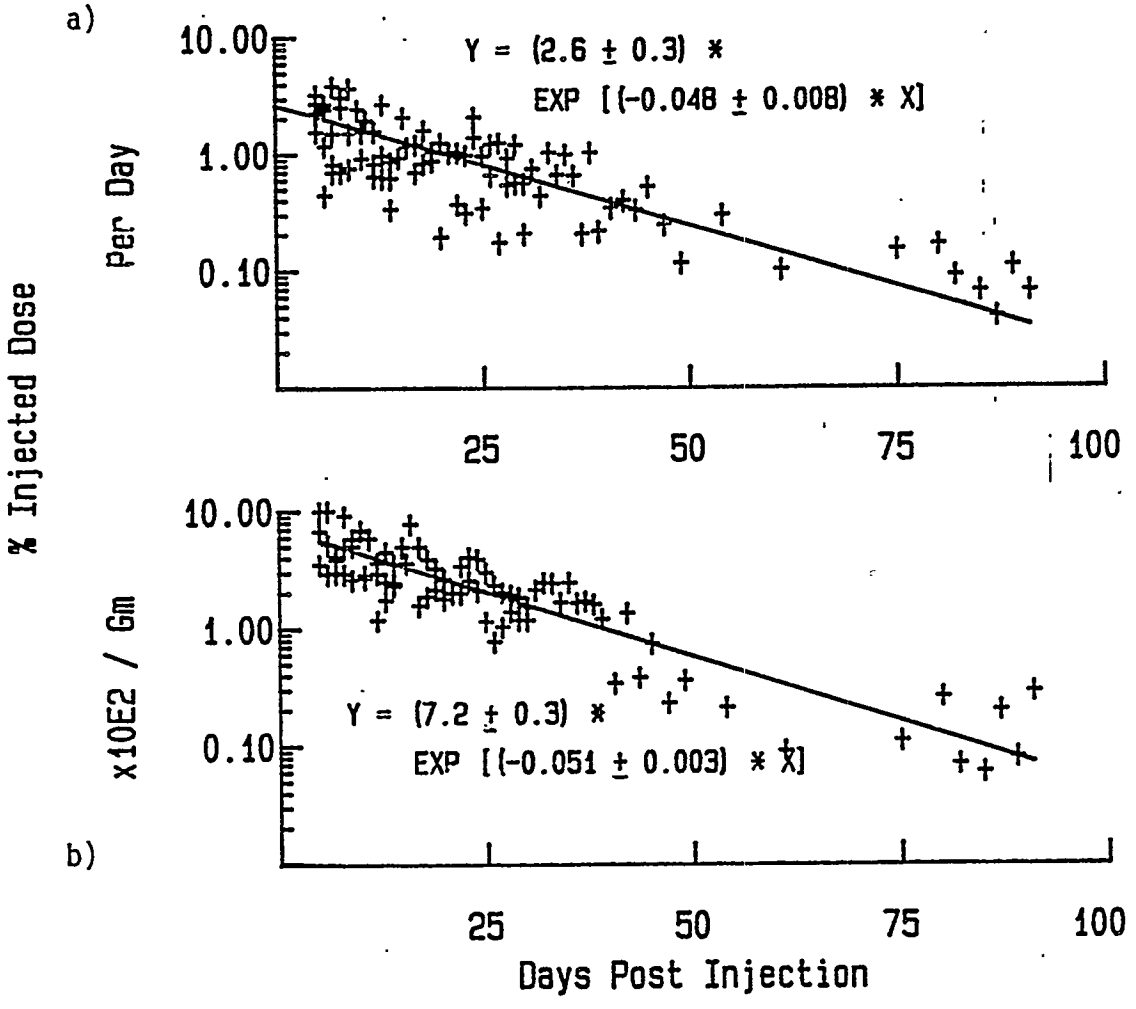


Figure 4.5 Tamarin Blood ^{210}Po Retention

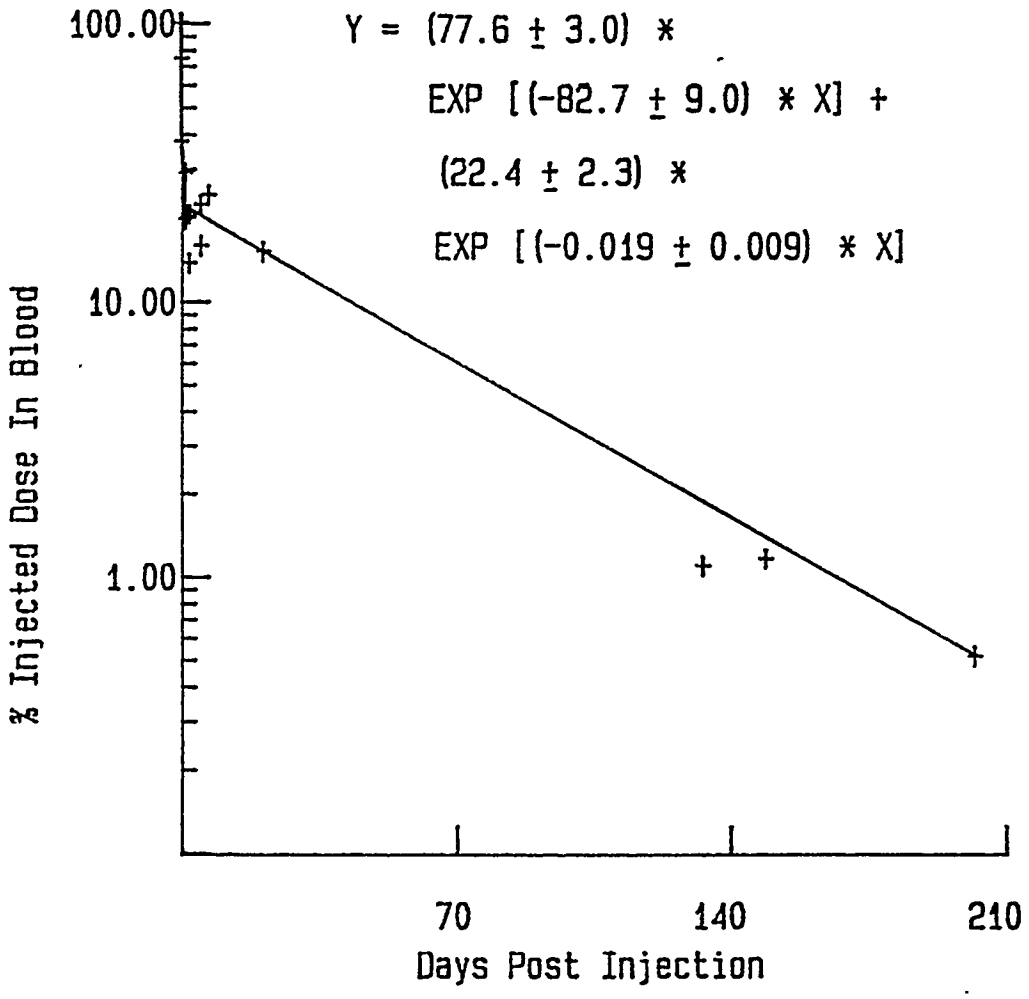


Figure 4.6 Baboon B156, B1060 and B1046 ^{210}Po Whole Blood Retention

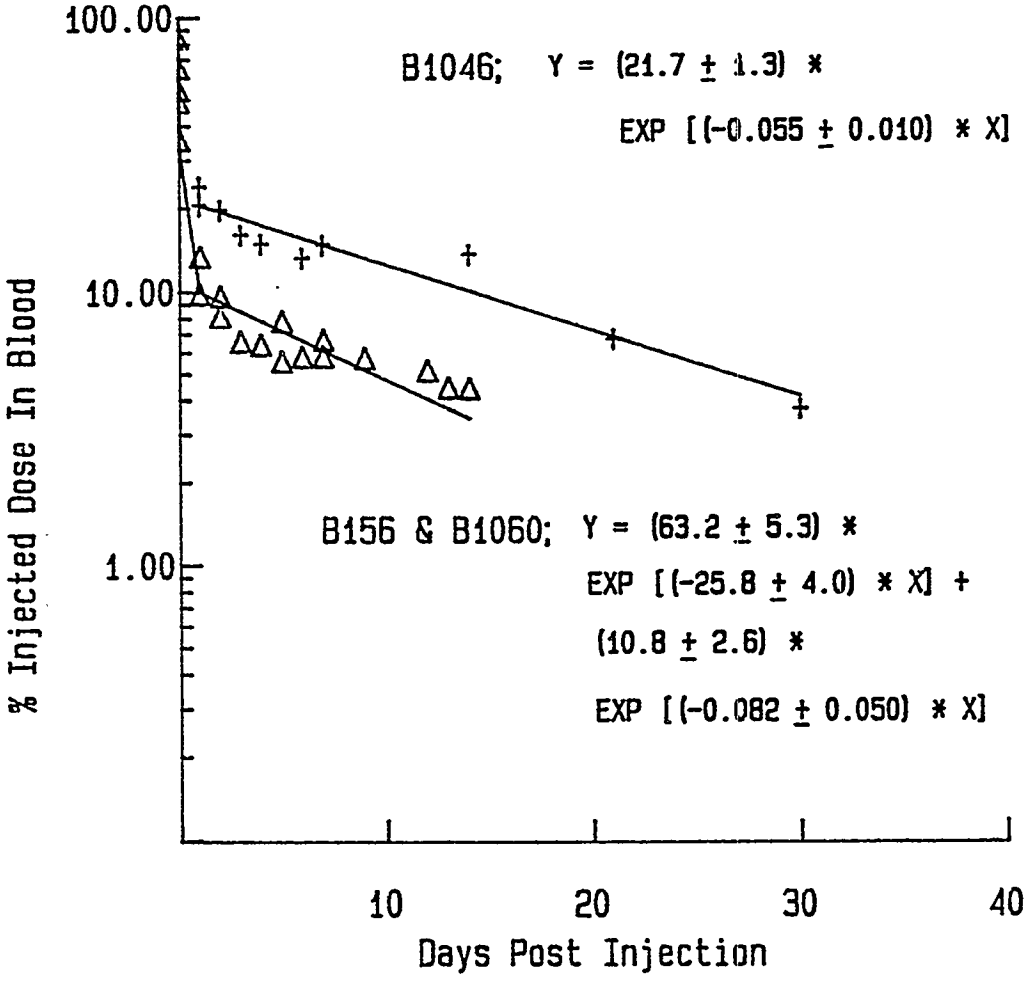


Figure 4.7 Baboon B806 ^{210}Po Blood Retention

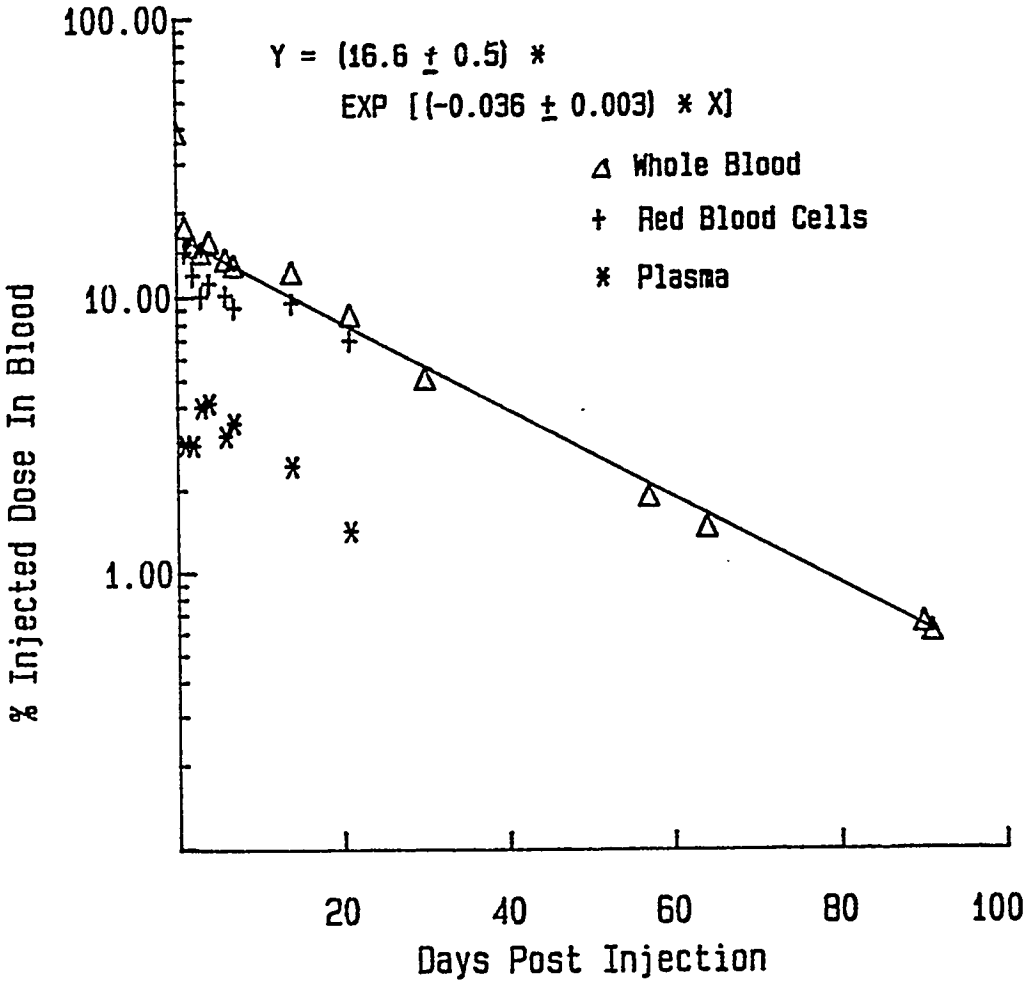


Fig. 4.8 Polonium-210 Retention in the Liver and Kidney Following Serial Sacrifice of Five Adult Female Baboons

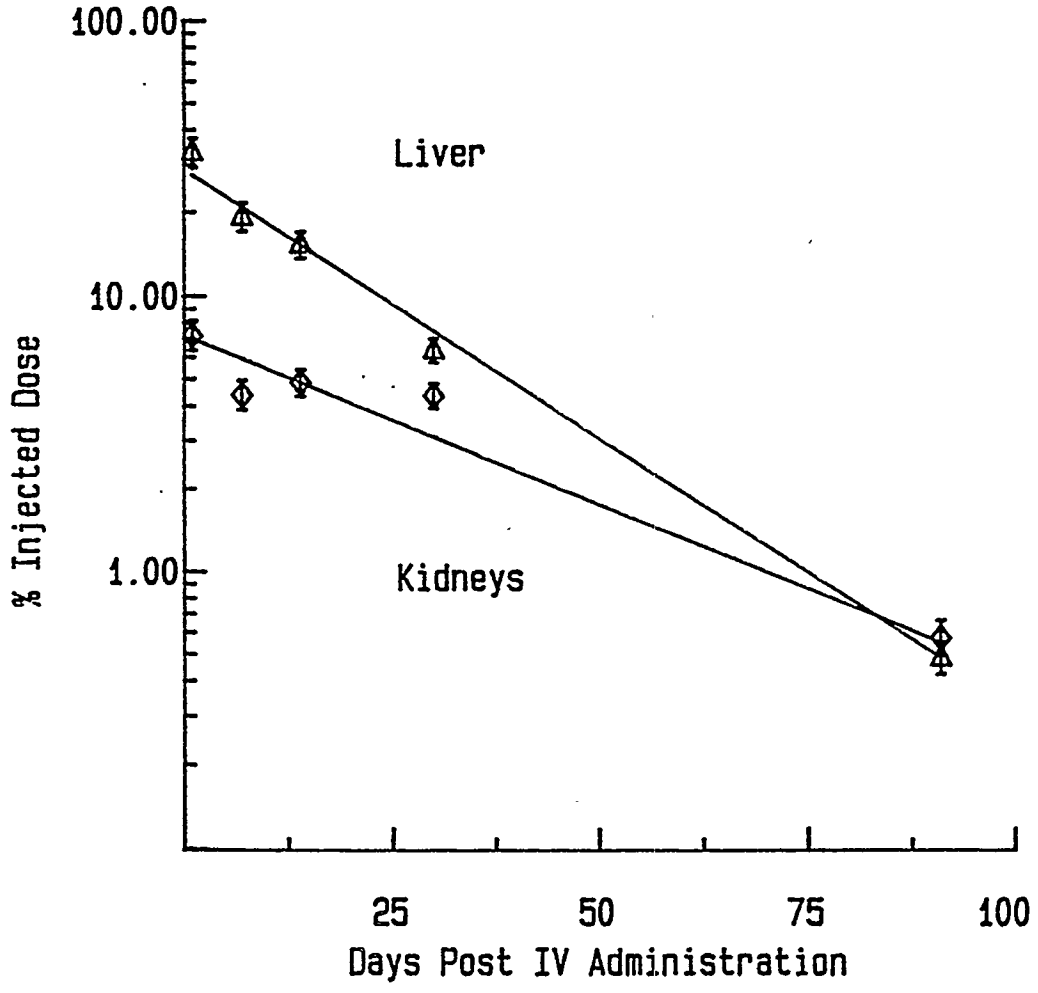


Fig. 4.9 Polonium-210 Retention in the Spleen, Adrenal Gland, and Pancreas Following Serial Sacrifice of Five Adult Female Baboons

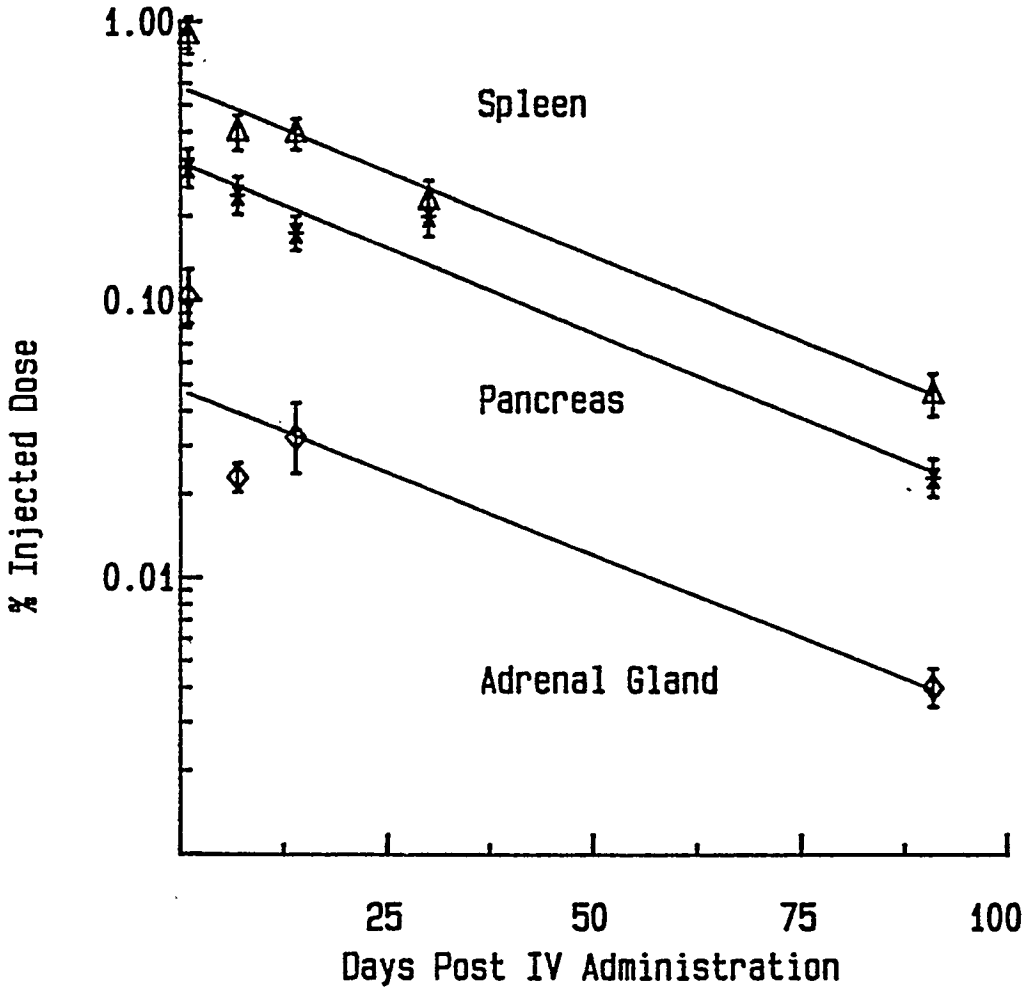


Fig. 4.10 Polonium-210 Retention in the Thyroid and Ovaries Following Serial Sacrifice of Five Adult Female Baboons

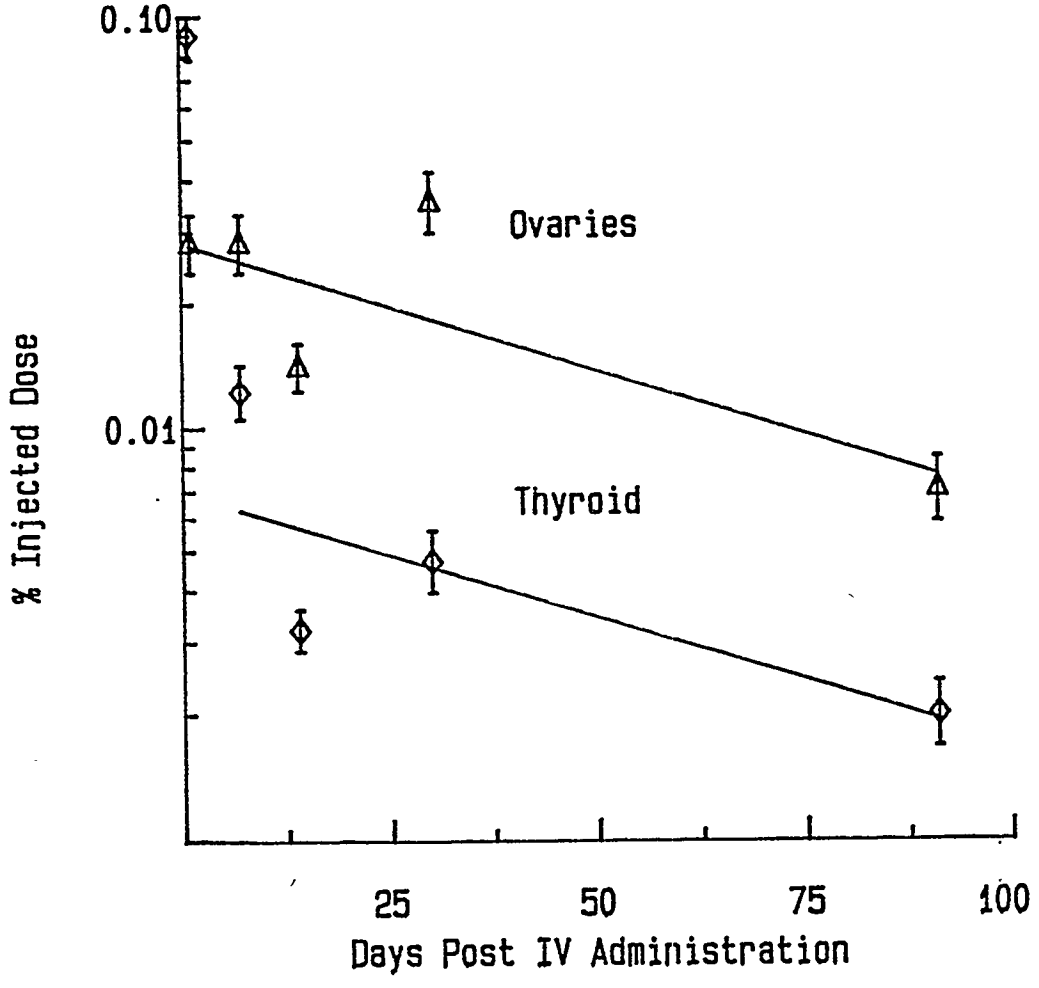


Fig. 4.11 Polonium-210 Retention in the Lungs and Skeleton Following Serial Sacrifice of Five Adult Female Baboons

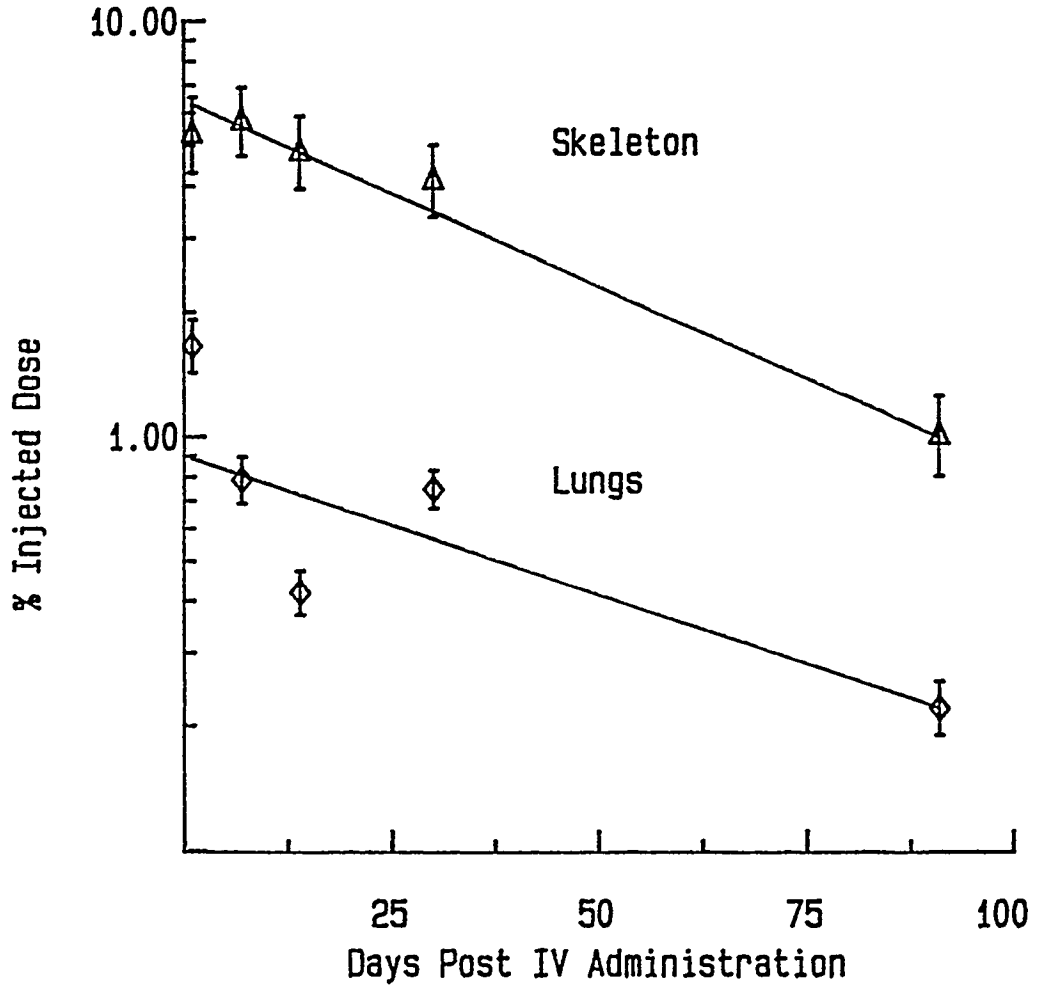
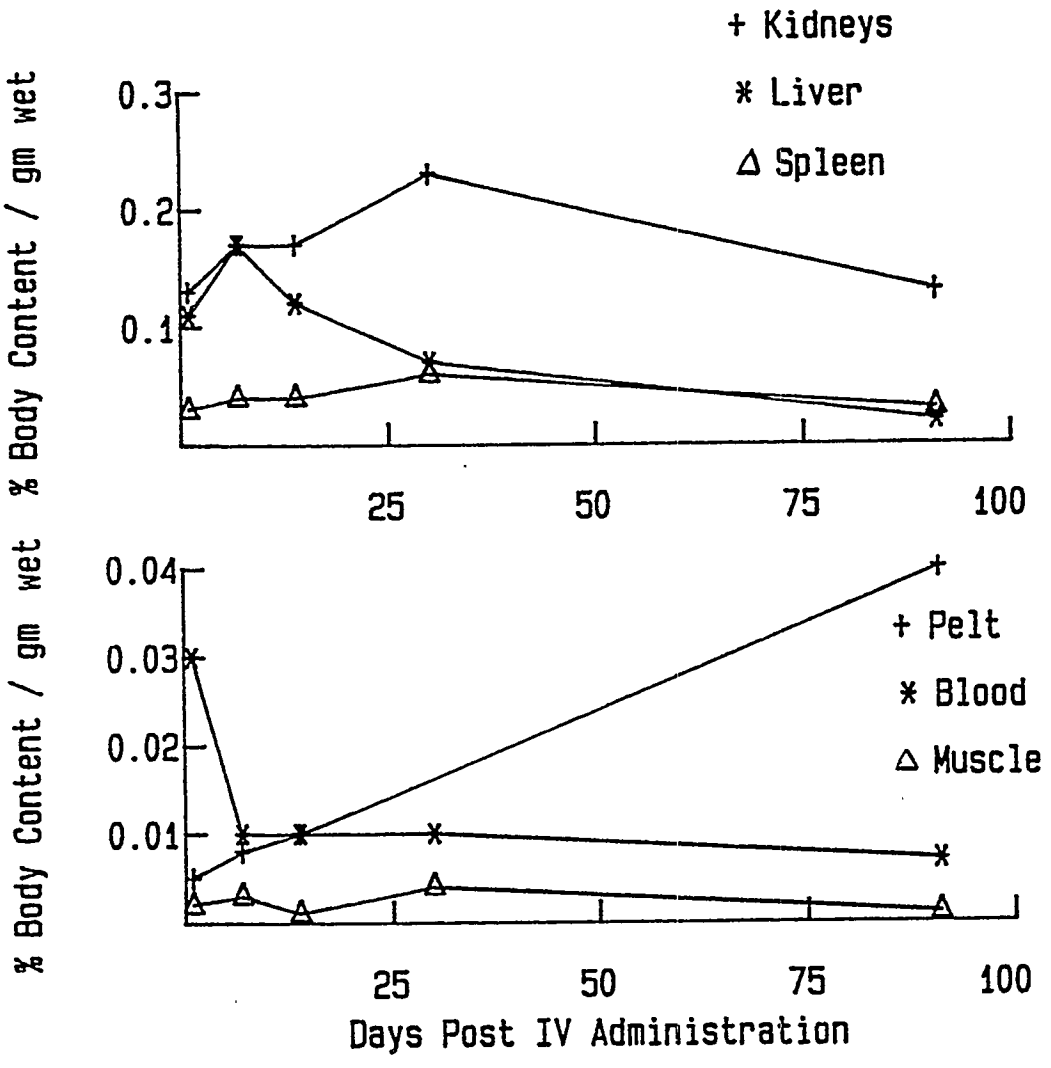


Fig. 4.12 Relative Concentration of ^{210}Po In Several Tissues Following Serial Sacrifice of Five Adult Female Baboons



5 Mound Laboratory Po Urinalysis Monitoring

Early work done at the Dayton, Ohio facility of the Dayton Project showed that Po is excreted in measurable quantities via the urine and feces (Silverman 1944). As part of the health physics program at Dayton and later continued at the Mound Laboratory, workers submitted urine samples at intervals averaging one time per week. The Po concentration of the samples was determined radiochemically and compared to an established tolerance limit which was set at 8 and later 12 counts per minute per 50 mL of urine (Spoerl 1950; Meyer 1956). Workers whose urine Po levels were confirmed to be in excess of the limit were removed from potentially contaminated work areas. The worker returned to his normal job activities when his urine Po level dropped beneath the tolerance limit. Polonium was processed at Mound until the 1970s.

The procedure used at Mound to monitor Po exposure was as follows (Steinberg 1946; Spoerl 1950; Meyer 1956): Weekly spot urine specimens were submitted at the plant in a "clean room" on the morning of the first day of the work week. Samples were collected in Sealright paper cartons and assayed within a few hours of sample collection. After thorough shaking, a 50 mL aliquot was acidified to 1*N* with 10 mL of 6*N* HCl in a waxed paper cup. A Cu disc (2.54 cm diameter, 16 gauge thickness) was suspended in the urine on a glass hook through a 0.24 cm diameter hole bored near the edge of the Cu. A glass paddle stirred the solution for 2 hours at 150-700 rpm. The disc was then removed, rinsed with water and air dried prior to counting in parallel plate alpha particle counters. Both sides of the disc were counted for 20 minutes each. The sum of the counts on both sides is a measure of the total Po deposited on the disc.

In 1964, the procedure was altered slightly to increase the sensitivity of the assay (Sheehan 1964b). The volume of the sample analyzed was changed from 50 mL to 100

mL and the geometry of the plating cell was changed such that only one surface of the Cu disc was used for plating Po. These changes resulted in more statistically valid results while retaining the 20 minute counting time.

There has been little change in the procedure for analyzing ^{210}Po in urine over the past several decades (Fink 1950; Spoerl 1950; Meyer 1956; Hursh 1958; Sheehan 1964). The current procedure most typically utilized is described in the EML Procedures Manual (EML 1983) and is almost identical to the procedure described above, the main difference being the use of Ni planchettes rather than Cu ones for ^{210}Po deposition.

Spontaneous deposition of ^{210}Po on Cu, Ni, and Ag has been reported in the literature (Fink 1950; Helmkamp et al. 1979). Researchers have drawn inconsistent conclusions concerning the metal conducive to the most efficient ^{210}Po recovery. For example, Bale et al. (1975) noted that Ag had been the metal of choice for most investigators, and that Cu resulted in lower recoveries than either Ag or Ni. In contrast, a comparison of the ^{210}Po recovery on Cu vs. Ag discs when deposited out of urine showed that Cu extracted a significantly greater amount of activity than did Ag (Spoerl 1950). Loose Ni filings removed ^{210}Po from large volumes (approximately 1 L) of acidified urine solutions with the same efficiency as Ag filings, and ^{210}Po deposition onto Cu and Ag foils were comparable (Fink 1950). A technique requiring ^{210}Po deposition on a relatively small metal disc for autoradiographic analysis of environmental samples utilized Ni rather than Ag since the former are inexpensive enough to discard after one use (Taylor et al. 1964).

The recovery of ^{210}Po deposited directly out of urine onto Cu was studied extensively (Spoerl 1950). Blank urine samples (i.e., urine samples from unexposed persons) were spiked with known amounts of ^{210}Po and plated under standard conditions

(1*N* HCl for 2 hours). The recoveries measured were normally distributed, with a mean recovery of 86.1 ± 11.9% for urine with ^{210}Po levels at count rates of less than 200 counts per minute per 50 mL sample.

The mean 86.1% recovery to quantitate the actual ^{210}Po content of a urine sample implies that tracer Po added to a blank urine sample deposits onto a suitable metal disc with the same efficiency as metabolized Po (i.e., Po which has first been filtered out of the blood by the kidneys and is possibly bound to protein or other metabolic product before being excreted). This assumption was tested by comparing the published historical method of analyzing ^{210}Po in urine (referred to here as the unashed/untraced method) with the procedure utilized in this research, which incorporates the addition of ^{208}Po tracer and the complete chemical digestion of the urine sample by HNO_3 prior to deposition of Po onto a Ni disc (referred to here as the ashed/traced method).

5.1 Duplication of the Mound Laboratory Procedure

Table 5.1 identifies the differences between the historical unashed/untraced procedures, the reconstructed historical method utilized in this research, and the EML methodology previously described (EML 1983). A picture of the plating apparatus used at NYUMC appears in Fig. 5.1. After the Cu disc was dried, both sides were counted separately in a conventional gas flow proportional counter.

In the initial part of the study, the recovery of Po added to blank aqueous solutions and raw urine from unexposed humans and non-human primates was determined. This was an attempt to validate the recovery values measured by Spoerl and reported by Meyer (Spoerl 1950; Meyer 1956). Average plating recoveries for the unashed/untraced procedure are given in Table 5.2. At three concentrations of Po activity in human urine ranging from 0.06-0.66 Bq/mL (3.3-33 Bq total), a mean recovery of 80.4 ± 3.4% was

determined. Recovery of ^{208}Po from two baboon urine samples spiked with approximately 0.38 Bq/mL (19 Bq total) was 84.5 ± 1.6%. Recovery of ^{208}Po which had been added to 1*N* HCl (1.3 Bq/ml, 65 Bq total) was not significantly different from the spiked urine recoveries, with the average of three measurements equal to 83.4 ± 1.6%. Combining the urine and acid solution recovery data yield an average recovery of 81.7 ± 3.2%, a value similar to the 86.1 ± 11.9% value determined at Mound Laboratory (Spoerl 1950; Meyer 1956). It is interesting to note that the recoveries measured did not decrease when the count rate exceeded 200 cpm (approximately 400 dpm) in a 50 mL sample, as reported by Spoerl (1950). A possible explanation for this difference is that the alpha proportional counters used in the 1940s would often "lock up" (i.e., exceed the number changing capacity of the mechanical meters thereby causing them to become nonfunctional) when counting relatively high activity samples.

5.1.1 Ashed vs. Unashed Urine

Methods

Urine samples collected from four of the baboons and three of the tamarins injected with approximately 18.5 Bq (0.5 uCi)/kg of non-colloidal ^{210}Po citrate were obtained to compare the unashed/untraced and ashed/traced ^{210}Po analysis methods. Although the majority of the samples were collected during the first month post injection, ten baboon samples were collected beyond 50 days post injection. Duplicate 50 mL aliquots were prepared from each sample. The average recovery of 81.7% was used to calculate the ^{210}Po activity in the aliquot processed by the unashed/untraced procedure.

The ashed/traced procedure used for the analysis of environmental samples requires a four hour Po deposition period in a plating cell placed in an 80°C water bath. Tests showed that the water bath was not necessary for quantitative deposition of Po.

Duplicate aliquots from eight baboon urine samples were analyzed with both the original EML method and the modified NYUMC method, which eliminated the water bath heating of the plating cells during spontaneous deposition. Samples processed by the original EML method with the water bath were plated for two hours. Samples processed at room temperature with the NYUMC method (Appendix A) were plated for periods of either two or three hours to determine whether the longer period was necessary. The results of these studies are presented in Table 5.3.

Recovery was greatest when the water bath was used, resulting in a mean value of 77.5 $\pm$ 3.5% for the eight samples. The average recovery determined for room temperature plating was 62.8 $\pm$ 11.7% for the two hour plating period and 72.5 $\pm$ 11.0% for the three hour period. These recovery values were sufficiently high to enable subsequent deposition of Po to be conducted without the use of a water bath.

Results of Comparison

The mean ^{208}Po radiochemical recoveries for 67 ashed/traced baboon urine samples and 17 ashed/traced tamarin urine samples were 83 $\pm$ 18% and 81 $\pm$ 16%, respectively. However, there were a few recovery values as low as 40-50%. Using a tracer to directly determine the recovery for each sample is preferable to the use of an average recovery because it provides greater accuracy and minimizes the uncertainty in the result.

As shown in Fig. 5.2, the ashed/traced analysis method results in recovery of more ^{210}Po from the baboon urine than does the historical unashed/untraced procedure. Therefore, human monitoring data resulting from an historical unashed/untraced method may significantly underestimate the quantity of Po in urine. The ratio of the ashed/traced values to the unashed/untraced values is shown as a function of time in Fig. 5.3. The following temporal relationship, or "correction function," described the change in the ratio starting with data on the second day post injection:

$$CF(t) = 10.47 \cdot EXP[-0.0086 \cdot t] \qquad \text{Eq. 5.1}$$

where,

CF(t) = Ratio of the % Injected dose in urine per day [ashed method/unashed method]

t = days post injection

Polonium-210 urinalysis results and excretion functions determined for the baboon from both the ashed/traced and unashed/untraced methods are presented in Fig. 5.2. Urinary excretion is best described by single compartment exponential kinetics. The magnitude of urinary ^{210}Po excretion is much greater and the kinetics somewhat more rapid (biological half-time of 14.8 ± 0.4 days vs. 19.2 ± 1.1 days) when data from the ashed/traced method (upper curve in Fig. 5.2) are utilized in metabolic modeling compared to data from the unashed/untraced method (lower curve in Fig. 5.2).

Recoveries of ^{210}Po from tamarin urine were also greater when the ashed/traced method was used, although not to the same degree as was observed in the baboon urines. Unlike the baboon data, the ratio of the ashed/traced values to the unashed/untraced values for the tamarin data was relatively constant after the second day post injection, with a mean ratio of 3.5 ± 0.8 (Fig. 5.4).

Results of the urinary ^{210}Po excretion obtained with the unashed/untraced methodology in the non-human primate were compared to the data obtained after the clinical administration of ^{210}Po to human subjects reported by Fink (1950) discussed in Section 2.2.4. The ^{210}Po contents of the human urine samples were determined via a procedure similar to the unashed/untraced procedure used at Mound. The urinary excretion curves determined by least squares regression to the daily ^{210}Po urinary data for three of the patients (patient #2 died only six days following the administration of Po) are shown in Fig. 5.5, along with the non-human primate urine data generated with the unashed/un-

traced procedure. The estimates of urinary ^{210}Po excretion in both species of non-human primates are similar to humans whose urinary ^{210}Po had been analyzed by the same method.

5.1.2 Dosimetric And Other Implications

Differences in ^{210}Po content between duplicate aliquots of urine prepared from the same sample and processed separately with the ashed/traced and unashed/untraced procedures, respectively, reflect differences in the recovery of metabolized ^{210}Po based on whether the sample was wet ashed prior to spontaneous deposition. Given its tendency for binding to globin and plasma proteins in the blood (Campbell and Talley 1954; Thomas 1955; Thomas 1964), Po atoms will most likely be bound to proteins in the urine. It can be hypothesized that deposition of metabolized ^{210}Po out of raw urine is not as efficient a process as it is for the nuclide in an uncombined state (i.e., following wet ashing of urine containing metabolized ^{210}Po). When urine is chemically processed (i.e., wet ashed), the matrix is destroyed and the availability of the Po for spontaneous deposition is presumably maximized.

The difference in the ratio of deposition efficiency between the two radiochemical procedures for the two species of non-human primates can be explained by the fact that no difference was seen when the samples were not ashed but a noticeable difference was observed when the samples were ashed.

A similar experiment reported in the literature was performed to compare deposition efficiency between ashed and unashed rat urine following intravenous administration of a ^{210}Po chloride solution (Black 1956). As with the non-human primates in the current study, more ^{210}Po was recovered in samples which were wet ashed prior to plating. However, the magnitude of the differences between the two procedures was

much less than that observed with either the baboon or the tamarin. The activity deposited from the unashed aliquot of a rat urine sample had 83% of the activity deposited from the ashed aliquot of the same sample. Nevertheless, while the author was attempting to answer the same question as in the present investigation, i.e., whether metabolized Po was complexed with constituents in the urine causing a reduction in plating efficiency, the only urine samples assayed were collected "several weeks" post injection. Based on the time dependence of the correction function fit to the baboon urine data, it is possible that the rat urine sample chosen for the radiochemical comparison was not sufficient to accurately characterize the magnitude and/or temporal nature of the plating efficiency differences. It should also be noted that the ^{210}Po in the rat urine was plated out of a 0.5 *N* HCl acid solution while the non-human primate urines used in the current study were plated out of a 1 *N* HCl acid solution.

The difference between sample results processed by the ashed/traced and unashed/untraced methods was not nearly as great as expected when baboon urine collected on the first day post injection was analyzed. The average ratio of the ashed/traced to unashed/untraced data was only 2.4 compared to values ranging from 6-10 for all post day-one samples. These results could be explained by a greater percentage of the ^{210}Po being available for deposition from the unashed aliquots taken from the day-one urine samples than from subsequent samples. It appears that the mechanism responsible for restricting ^{210}Po deposition from a direct plating procedure in urine does not fully manifest itself during the first 24 hours post exposure, but is established within a 24 to 48 hour period following intravenous introduction of ^{210}Po. The availability of proteins to complex with Po is probably insufficient immediately following uptake so that more "unbound" Po is excreted on day-one. Thereafter, Po in

the transfer compartment and that recycled from other organs and soft tissue has had adequate time to bind with available proteins, making wet ashing of urine necessary for efficient extraction of Po during spontaneous deposition.

The reduced availability for spontaneous deposition of metabolized ^{210}Po was observed to a lesser degree in tamarin urine. The ratio of the ashed/traced to unashed/untraced data from samples collected during the first two days post exposure ranged from 1.1-2.0, compared to the mean factor of 3.5 for all other samples.

A similar phenomenon has been seen in human urine (Sedlet and Robinson 1971). Only a small fraction of the metabolized Po present in urine could be deposited directly from the raw urine of seven individuals who had inhaled neutron-irradiated ^{209}Bi. A similar result has also been observed in the blood of rats, i.e., a direct assay method gives a significantly lower Po recovery than after a chemical digestion pretreatment method (Davis 1950b).

It can be concluded, therefore, that evaluation of body burden based on ^{210}Po urinary excretion may be underestimated if it was plated directly out of unashed urine.

Effect of Recovery on the Urinary Excretion Fraction

The urinary excretion fraction relates urinary excretion to total excretion and thus to systemic body burden. The existing metabolic models for Po include a urinary excretion fraction of 0.1 (ICRP 1968; Jackson and Dolphin 1966). More recently, Bernard (1979) estimated a fecal-to-urine excretion ratio of 9 for systemic Po following intravenous injection, corresponding to a urinary excretion fraction of 0.1. However, when urinary ^{210}Po content was determined via the ashed/traced method in two species of non-human primates, a considerably greater percentage of the administered dose was detected. These

studies (discussed in the previous section) resulted in estimated urinary ^{210}Po excretion fractions of 0.38 $\pm$ 0.04 and 0.20 $\pm$ 0.01 for the baboon and the tamarin, respectively. The fecal-to-urine Po ratio was 1.5 for the baboon and 3.5 for the tamarin.

Re-evaluation of ^{210}Po excretion data presented by Fink (1950) suggests that a 0.1 urinary excretion fraction for humans may be too low. Of the four individuals receiving intravenous administration of ^{210}Po chloride, sufficient data exist to permit an estimation of total ^{210}Po excretion for one patient. Urinary and fecal ^{210}Po excretion parameters were determined for patient #3 by performing a least squares regression on the provided ^{210}Po excretion data. The resultant ^{210}Po excretion curves appear as single exponential models in Fig. 5.6. Based on integration of the urinary and fecal excretion functions, estimates of 54% and 5% of the administered dose were excreted via the feces and urine (out to infinity), respectively. The data, as found in the literature, fail to account for approximately 40% of the administered dose, which could be explained if the correction function describing the ratio of the ashed/traced to unashed/untraced deposition efficiencies for baboon urine is applied. Doing so increases the total urinary ^{210}Po output to an estimated 35% and accounts for the majority of the previously undetected percentage of the administered dose (Fig. 5.7).

Breuer and Clemente (1979) developed a mathematical model to describe the metabolic behavior of Po based on the ^{210}Pb and ^{210}Po intake, excretion, and body burden data reported for the general Italian population. While they were most interested in predicting lung exposure to radon progeny from urinary excretion of the two nuclides, the authors calculated that for any systemic input of Po, the urinary excretion fraction is equal to 0.36, a value in good agreement with the 0.38 $\pm$ 0.04 measured in the baboon.

5.1.3 Summary

The historically important technique of analyzing ^{210}Po in urine has been investigated. The recovery value used as part of the routine health monitoring program at Mound Laboratory was based on the incorrect assumption that metabolized Po is plated by spontaneous deposition with the same efficiency as tracer Po added to blank urine samples. Duplicate aliquots of urine samples collected from non-human primates were analyzed by an ashed/traced method and an unashed/untraced method similar to that used routinely in the past at Mound. The ^{210}Po deposition recovery was significantly lower when the nuclide was analyzed with the unashed/untraced method than after preparation by the ashed/traced technique.

5.2 Systemic Dosimetry Model for Po

5.2.1 ICRP And Other Models

A prospective current metabolic model for Po is described by the ICRP (1979). The model references the human excretion data summarized by Jackson and Dolphin (1966) and the animal data reported by Fink (1950) and Smith et al. (1961). Whole body retention is described by the following function:

$$R(t) = EXP\ [(-\ln(2) / 50) \cdot t] \qquad \text{Eq. 5.2}$$

where,
t = days post injection.

Organ partition coefficients of 0.1 are assumed for the liver, kidney, and spleen and 0.7 for all other tissues combined. Polonium is retained in all tissues with a biological half-time of 50 days.

The metabolic model presented by Bernard (1979) is similar to that of the ICRP. Citing the human clinical data of Fink (1950) and the metabolic studies conducted at the University of Rochester (summarized in Section 2 of this report), Bernard described a model whereby Po deposits preferentially in the tissues of the reticuloendothelial system (RES). Consistent with the ICRP model, the partition coefficients to liver, kidney, and spleen are each 0.1. Distribution is uniform throughout all other tissues at a concentration 10 times less than in the RES tissues. Exceptions are muscle, bone, and testes with one-tenth the average tissue Po concentration. Retention of Po in the tissues is described by two phase kinetics, with the majority of the radionuclide clearing with a 50 day biological half-time. The uptake from the GI tract to the blood (f_1 value) is 0.1, and as stated in the previous section, the fecal-to-urine excretion ratio is equal to 9.

The characterization of Po distribution and excretion in the published metabolic models have both similarities and differences with that observed in the non-human primates of this study. The tissue concentration pattern described by Bernard was, for the most part, demonstrated in the baboon, with the primary exception being the lower ^{210}Po concentration in the baboon spleen. However, retention and excretion half-times were consistently more rapid in the baboon. In addition, a major difference was found in the fecal-to-urine excretion ratio, which was found to be equal to 1.5 and 3.5 for the two species of non-human primates.

5.2.2 The NYUMC Model

Evaluation of Po urinalysis data for individual members of the "former Mound Laboratory employee group" indicate that the time sequence of exposure to the radionuclide varied extensively as would be expected in an industrial situation. (Appendix E consists of a number of sample plots of worker urinary Po excretion.) No

consistent Po excretion pattern was apparent among the workforce. Observed Po urinary excretion as well as the excretion rate kinetics were different from worker to worker, more indicative of the dynamics associated with monitoring workers than actual Po biokinetics.

The variability of Po excretion patterns observed among the Mound workforce is not considered unusual, in light of the many metallurgical and chemical processes then in effect which contributed varying amounts of Po aerosols to which the workers were exposed. Since the vast majority of the exposures were estimated to occur via the inhalation pathway (Garner 1986), the urinary Po excretion was influenced not only by the rate of Po clearance from blood to urine, but also by the rate of Po absorption into the bloodstream from both the lung and the gastrointestinal tract (following ingestion as a result of lung clearance via the mucociliary escalator).

A model has been developed to estimate the systemic radiological dose equivalent to members of the Mound Po workforce based on their past Po urinalysis data. The model utilizes the Po metabolic parameters determined here in studies with the adult female baboon. The tamarin urinary excretion data was not combined with the baboon data due to the species differences observed; covariant analysis of the data sets indicated significant differences between the two. The existing body of literature establishing physiologic and metabolic similarities between the baboon and human was an additional contributing factor in the exclusive selection of the baboon data for the model.

The model works equally well on any pattern of urinary Po excretion; it is applicable to both acute and chronic exposure conditions. Mathematically, the model is based on the single exponential baboon urinary excretion function (13.7 day effective half-time) and single exponential baboon tissue retention functions. Dose equivalent is calculated from the following equation (Eq. 5.3):

$$H_j = K * SEE * \sum_{i=1}^{n} I_i * \int_0^{\infty} \frac{F_u(t)}{f_u} * f_j \int_0^{50} F_j(t)$$

where:

H_j = dose equivalent to tissue j (mSv)
SEE = specific effective energy for tissue j (MeV/disintegration-kg)
I_i = amount of ^{210}Po in urine resulting from ith intake after adjusting with radiochemistry based CF (cpm/mL)
t = time (days)
f_u = urinary excretion fraction for systemic Po
f_j = partition coefficient for tissue j
F_u = urinary excretion function
F_j = retention function for tissue j
K = conversion factors:
1,400 ± 530 mL/day
Mound Lab Radiochemical yield = 0.86 ± 0.12
86,400 disintegrations/day-Bq
0.5 cpm/dpm
1.6 E-13 J/MeV
1 Bq/60 dpm
1 kg-Gy/J
20 Sv/Gy; 1000 mSv/Sv
ICRP 26 organ specific weighting factors

It should be noted that the model estimates dose equivalent values on a gross organ basis. The actual microdosimetric distribution within any specific tissue (e.g., based on cell type or function) may differ from the gross organ estimate. However as pointed out in Section 2.2.2, autoradiographic studies on the cat and rat have shown that the distribution of nonaggregated Po is the same in several tissues irrespective of the route of administration, dosage level, and physicochemical form.

A Fortran program named Omdos has been written to convert an individual's records from the Mound Laboratory urinary Po data base into a format accessible for dosimetry calculations. The output file from Omdos is used in the Fortran program Dose, which estimates the systemic dose equivalent from the Po bioassay data. The user is asked for a worker case number. Sample dates are converted initially to Julian days and

then to Arabic numerals, with day 0 assigned to the first sample. A column labelled "days post first sample" is written to a new file along with the sample Po count rate, expressed as counts per minute per mL urine.

There are a number of data entries resident on the Mound data base that need to be rejected as described in internal Mound memorandum. These are indicated by entries of "." in the sample description column of the data base. The inclusion of these in the data sets would adversely affect the testing of the data for outliers, which is described below. Therefore at the outset, Omdos rewrites the data set excluding the aforementioned entries. For other sample data, the symbol "*" appears in the description column indicating that a change in sample volume from 50 to 100 mL may be warranted depending on the date of sample collection. These changes are also made by Omdos.

Historical records indicate that some urine samples analyzed at Mound were externally contaminated. Visual inspection of some data show an occasional sample with Po levels two to three orders of magnitude greater than follow-up samples taken later in the same day or during the ensuing days. A significant intake is reflected by a proportional increase in urine Po content. But for a sample Po count rate to be truly reflective of an intake, the ensuing sample must have a predictable Po level based on expected excretion rates of Po. For example, biological considerations dictate that an accurate urinary Po measurement simply cannot be on the order of 1000 cpm/mL on day 1 and 0-1 cpm/mL on day 3.

Omdos takes the first value and predicts urinary Po excretion from that point in time based on the urinary biokinetics for non-human primates determined in this research. Likewise, the uncertainty associated with each predicted point is known from the regression statistics; consequently, the range of a predicted value can be described within a confidence interval. Similarly, for each value, an error term (based on counting

statistics) and distribution about the mean can be calculated. A Students t-test made using the second measured excretion value and the associated predicted value is performed to determine two factors.[6] The first is whether or not the intake represented by the first value is real or should be eliminated as a false positive? And secondly, does the second value represent an additional intake, or does it reflect predicted clearance resulting from the most recent intake? In Omdos, the former question is addressed. The maximum estimate of the 95% confidence interval describing the second value is compared to the minimum predicted estimate of the 95% confidence interval at that time. Failure of the t-test where t is negative (i.e., the measured value is less than the predicted value) is the criterion for deleting the potential intake point from the data set as a "high side" outlier. Omdos continues to check all data points for outliers.

It was decided not to incorporate an analagous procedure in the algorithm to eliminate "low side" outliers. Integrating the urinary excretion function beginning with a data point identified as a statistically significant intake will not be affected by any such subsequent outliers. If an inaccurate low data point is used in a t-test to eliminate a potential intake point, the quantitative effect on the dosimetry calculation will be minimal because the increased Po output in urine would have been measured in the next sample submitted by the worker. "High" level samples were usually followed up within a few days; often, a duplicate, same day sample was submitted. In addition, due to the reduction in Po plating efficiency resulting from deposition out of freshly voided unashed urine, it is possible that some samples will not record more than a few counts during the 20 minute count time utilized at Mound Laboratory.

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6 After a relatively high urine ^{210}Po measurement, duplicate samples were often collected and analyzed on the same day. When the second data point on the data base was taken from the same day as the first data point, Omdos advances to the next data point for use in the t-test.

Finally, Omdos checks the remaining data set for multiple same-day entries. Where these occur, the mean count rate is calculated and written to the output data file.

Program Dose uses the data file prepared by Omdos. In the first section of the algorithm, a search of the data file is made to determine all data which can be statistically shown to represent systemic uptake of Po. As was done in the outlier testing in Omdos, a predicted curve (and associated error based on the t-distribution) is generated from the first intake point[7] based on the urinary excretion function for Po that was determined in the baboon.

The minimum of the 95% confidence interval describing all subsequent data (error bands for the measured data are based on counting statistics) are compared to the corresponding maximum predicted value based on the 95% confidence interval resulting from the initial intake event. This is synonymous with a t-test. The procedure continues until failure of the t-test occurs where t is positive (i.e., the data point, or measured value is greater than the predicted value), signifying that the data point tested represents the occurrence of an additional Po intake. Biologically, the systemic input of Po may represent either Po passing across the lung epithelium, through the wall of the small intestine, or an additional occupational exposure.

In the next section of the program, Dose applies the "correction function" which describes the ashed/traced to unashed/untraced spontaneous deposition recovery ratio to the intake points (Eq. 5.1). The first intake point is multiplied by a correction factor of 10.0 (CF(t), where t=5 days post exposure). Application of the CF begin with days post

7 To start the procedure, the first positive data point is assumed to represent the first intake.

exposure equal to 5 because urine samples were usually submitted on Monday morning at Mound. The bioassay measurement thus reflected potential intakes which had occurred from 3 to 7 days earlier.

The CF is then applied to all remaining intake points. The days post exposure for a new intake is set equal to 5 if the Po excreted at that time is entirely due to the new intake. However, the Po being excreted at that point in time may be influenced by one or more previous intakes, depending on that individuals's exposure history. Therefore, prior to application of the CF, the intake point is segmented into portions based on the predicted Po excretion from prior intakes. For example, if:

$3x$ = the amount of Po in urine resulting from a statistically significant intake
$1x$ = the predicted amount of Po excretion based on the previous intake
t_1 = the time of the previous intake (days post first sample)
t_2 = the time of the new intake (days post first sample)

then:

$3x-x = 2x$ = the portion of the measurement attributable to the new intake.

The CF is applied to give the new adjusted intake point as follows:

Portion magnitude	Source	Time post intake	CF
2x	new intake	5 days	10.0
x	previous intake	t_2-t_1	CF(t); $t=t_2-t_1$

Therefore, the adjusted intake point = [2x * 10.0] + [x * CF(t)].

By integrating the urinary excretion function, the quantity Q, or time integral of internal contamination (ICRP 1968), can be calculated (Eq. 5.4):

$$Q = \sum_{j=1}^{n} \int_{0}^{\infty} I_j * \exp(-\lambda_u * t)$$

where,

I_j = adjusted amount of ^{210}Po in urine resulting from the jth intake
t = time (days)
λ_u = effective clearance rate of Po from urine (day^{-1})

Dose performs this calculation by applying the baboon urinary excretion function for systemic Po to the adjusted intake data. The contribution to Q due to each intake is summed to determine the total Q for the entire series of measurements.

The program calculates organ specific dose equivalents by multiplying Q by the proper constants, metabolic parameters, conversion factors, and weighting factors as recommended in ICRP 26 (1977). The individual dose equivalents are summed to determine the total systemic dose equivalent. The ICRP dosimetric methodology assigns weighting factors to the gonads, skeleton, bone marrow, lungs, and thyroid. The liver, kidney, spleen, adrenal gland, and pancreas are the five remaining organs with the greatest Po concentrations and are therefore assigned a weighting factor of 0.06.

The metabolic parameters utilized are the organ partition coefficients and effective retention half-times determined in the adult female baboon (Table 4.5).[8] Some of the parameters have been summarized along with previously published parameters in Table 5.4. The model is applied, however, to a data base corresponding mostly to males. A study of sex differences in the metabolism of Po in rats supported the supposition that the use of metabolic parameters determined in the female might reasonably be applied to the

8 The retention half-times in Table 4.5 reflect biological processes only. These have been adjusted so that the dosimetry algorithm uses the effective half-times.

male of the species (Stannard and Angell 1956). That is both excretion and tissue retention rates were not significantly dependent on sex, although the partition coefficients for the kidney and spleen were slightly higher for females. If this difference is also a fact for primates, then use of the partition coefficient determined in the female would be dosimetrically conservative.

The assumption that the ^{210}Po partition coefficient and retention time for ovaries is the same as for testes was found to be inaccurate in rats (Stannard and Angell 1956). Initial Po concentration in the ovaries was much greater than that in the testes. However, the loss of Po from the testes occurred at a slower rate such that Po concentration in the two gonadal tissues was equal at approximately 90 days post intravenous administration. Since the total radiation dose to the ovaries exceeded that to the testes, use of the metabolic parameters determined for the female gonads results in conservative dose estimates (as is the case for the kidney and spleen) when applied to males.

Throughout the entire algorithm, standard statistical error propagation techniques are followed whenever variables are multiplied, divided, added or subtracted. For example:

$$(A \pm a) * (B \pm b) = A*B \pm (A*B)*[(a/A)^2 + (b/B)^2]^{1/2}$$

$$(A \pm a) / (B \pm b) = A/B \pm (A/B)*[(a/A)^2 + (b/B)^2]^{1/2}$$

$$(A \pm a) + (B \pm b) = A+B \pm [a^2 + b^2]^{1/2}$$

$$(A \pm a) - (B \pm b) = A-B \pm [a^2 + b^2]^{1/2}$$

Sources of error with their approximate range and the basis for their estimation, are given in Table 5.5.

The algorithm was checked for accuracy as it was developed. During program execution, key variables (e.g., intake point values, quantity of systemic Po, etc.) were

written to the terminal screen as they were calculated. Hand calculations made prior to program execution were compared with these variables as a means of assuring that the algorithm was in fact processing the data correctly.

The source codes for Omdos, Dose, and Mndose, the dBase III+ batch file which accesses Omdos and Dose, are listed in Appendix F along with instructions for their use. Sample dosimetry output tables appear in Appendix G.

5.2.3 Model Validation

The dosimetry model is constructed in part by applying the biokinetics which describe excretion of Po in the urine of non-human primates. The metabolic parameters utilized were determined following intravenous administration of Po whereas the occupational exposure of workers occurred primarily due to inhalation exposure. A biokinetic parameter used in the model (i.e., half-time of Po in urine following intravenous injection) is a measure of a different physiological phenomenon than is the half-time following regression of an excretion model to a set of worker bioassay data. After intravenous administration to the baboon, the entire intake is deposited in the bloodstream (i.e., within the systemic compartment). But following ^{210}Po inhalation exposure of a worker, the systemic deposition is controlled by the retention of the radionuclide in an external organ (e.g., the lung). Therefore, the biokinetics for Po in urine predicted by the model should not be the same as the half-time resulting from a regression performed directly on the health monitoring data.

While an intake resulting in an elevated urine Po count rate may be of an acute nature, the absorption of Po into the systemic compartment is invariably a temporal

process. For this reason, the occupational exposure episodes are more accurately classified as "chronic" systemic exposures resulting from one or more acute intakes which had occurred during the previous work week.

When a urinary Po sample count exceeded the pre-set tolerance limit of 8 or 12 cpm per 50 mL of urine, the standard procedure at Mound Laboratory called for the individual to be moved to a relatively "Po free" location. Another single void sample was usually assayed to confirm the presence of an elevated urinary Po content. An accelerated schedule of urinalyses continued until excretion of the radionuclide dropped to an acceptable level.

From the Mound Po bioassay data base a subset of approximately 200 cases was initially identified consisting of individuals with urinary Po levels which clearly exceeded the tolerance limit. However, after removing outliers and examining the clearance pattern for Po in urine, the number of episodes in which the worker was moved to avoid further possible exposure was reduced to 54.

A test of the model must first consider the movement of Po through the compartments shown in Fig. 5.8. First, the absorption of Po from the pulmonary region into the bloodstream is calculated as a function of time through use of the ICRP 30 lung and gastrointestinal retention models (Figs. 5.9 and 5.10). Direct absorption occurs from lung compartments a, c, e, and i (through h). Retained Po clears from compartments b, d, d (through f), and d (through g) into the stomach, through which a fraction (the f_1 value) gains entrance into the bloodstream via absorption through the small intestine. The contribution of Po from each compartment into the blood and from the blood to urine is shown in Table 5.6.

The f_1 value for Po is given in ICRP 30 as 0.1. However, f_1 values reported in the literature indicate that a value of 0.05 may be more accurate. Studies in the rat (Silberstein et al. 1950a; Stannard 1954; Stannard and Angell 1956; Spoerl and Anthony 1956; Stannard 1964a) consistently determined that the f_1 value ranged from 0.03-0.05. The f_1 of a human subject who had ingested Po may have reached 0.1, but the estimate was largely conjectural and may have been considerably less, according to the authors (Silberstein et al. 1950b). Based on the conclusions of these studies, the value chosen for use in the model validation calculations was 0.05.

Having established the temporal input of Po from the lung and GI tract into the systemic compartment based on ICRP 30 models, the baboon model describing the rate of urinary excretion of systemic Po is applied. The entire biokinetic model (i.e., including lung and gi tract Po clearance into blood and into urine) predicts that Po is excreted into the urine with a 28.0 day half-time. The average half-time detemined via least squares regression analyses for the 54 occupational exposure episodes is 38.1 $\pm$ 15.9 days. These data reflect the kinetics expected for a Class W substance clearing from the lungs (ICRP 1979). However, the most accurate description of this parameter must also incorporate the CF described in Section 5.1.1. Application of the CF to the human data reduces the average effective half-time of Po in the urine to 25.9 $\pm$ 10.8 days, a value in excellent agreement with the 28.0 days predicted by the model.

TABLE 5.1 UNASHED/UNTRACED PROCEDURE COMPARISON FOR PO DEPOSITION

Procedure:	Meyer 1956	NYUMC[1] 1989	EML[2] 1983
Sample:	weekly spot specimen	daily 24 h sample	unspecified
Solution	1*N* HCl	1*N* HCl	1*N* HCl
Plating:	50 mL wax paper cup room temperature 16-gauge Cu 2.54 cm diameter 2 h plate time water rinse	50 g plastic cup room temperature 8-gauge Cu 2.54 cm diameter 3 h plate time ethanol rinse	100 mL 250 mL beaker in 55°C water bath 0.64 mm Ni 2.22 cm diameter 2.5 h plate time water rinse
Deposition Recovery:	86 ± 12% (limit tested: approx. 6.7 Bq)	82 ± 3% (limit tested: 70 Bq)	70%

[1] NYUMC=New York University Medical Center
[2] EML=Department of Energy Environmental Measurements Laboratory

TABLE 5.2 SUMMARY OF UNMETABOLIZED PO RECOVERIES

Sample Type	^{208}Po Tracer (Bq mL^{-1})	# of Cu Plates	Mean Percent Recovery ± sd	Recovery Range low high
Human urine	0.06±0.00	4	78.6±3.3	75.4 82.8
Human urine	0.27±0.00	2	80.6±2.2	79.0 82.1
Human urine	0.66±0.01	2	84.1±0.9	83.4 84.7
Baboon urine	0.38±0.01	2	84.5±1.6	83.3 85.7
mean recovery		10	81.2±3.5	
Acid solution	1.30±0.04	3	83.4±1.6	81.5 84.4
All samples		13	81.7±3.2	
Spoerl 1950			86.1±11.9	

TABLE 5.3 THE EFFECT OF A WATER BATH ON PO RECOVERY*

Deposition Condition	Plate Time (hours)	N	Recovery (% ± sd)
Water Bath	2	8	77.5 ± 3.5
Room Temp.	2	4	62.8 ± 11.7
Room Temp.	3	4	72.5 ± 11.0

*(Comparison of Po deposition recovery results from urine samples plated in an 80°C water bath and at room temperature).

TABLE 5.4 METABOLIC PARAMETERS FOR SYSTEMIC PO

	Model			
Parameter	NYUMC 1989	ICRP 1979	Bernard 1979	Breuer and Clemente 1979
Biological Retention	15-50 days[1]	50 days	50 days	50 days; 400 days
Absorbed Fraction (f_1)	--	0.1	0.1	0.25
Urinary Excretion Fraction (f_u)	0.38	0.1	0.1	0.36
Partition Coef.:				
Liver	0.29	0.1	0.1	--
Kidney	0.07	0.1	0.1	--
Spleen	0.006	0.1	0.1	--

[1]Range of retention times for individual organs

TABLE 5.5 SOURCES OF ERROR IN PROGRAM DOSE

Source of Error	Relative Range (%)	Basis for Propagation
Urine ^{210}Po measurement	1-50	counting statistics
CF regression	25-40	regression error about least squares line
Baboon urinary excretion curve	5-15	regression error about least squares line
Reference man:		
daily urine output	38	ICRP 23 and Snedecor (1956)
organ weights	6-33	ICRP 23 and Snedecor (1956)
Metabolic parameters:		
a) organ partition coef.	3-56	parameter errors from least
b) clearance half-times	4-63	squares regressions performed on
c) urinary excretion fraction	11	baboon data

TABLE 5.6 ICRP 30 LUNG COMPARTMENT CONTRIBUTIONS TO SYSTEMIC UPTAKE OF PO AND SUBSEQUENT URINARY EXCRETION FOLLOWING AN ACUTE INHALATORY INTAKE[1]

Compartment	Fraction of Intake (Q)
Lung->Blood	
a	0.03
c	0.04
e	$0.0375 \cdot (1-\exp(-0.0189 \cdot t^{*}))$
i through h	$0.0125 \cdot (1-\exp(-0.0189 \cdot t))^{2}$
Lung->GI	
b	$0.27 \cdot (1-\exp(-1.7379 \cdot t))$
d	$0.04 \cdot (1-\exp(-3.4707 \cdot t))$
d through f	$0.10 \cdot (1-\exp(-0.6981 \cdot t)) \cdot (1-\exp(-3.4707 \cdot t))$
d through g	$0.10 \cdot (1-\exp(-0.6981 \cdot t)) \cdot (1-\exp(-3.4707 \cdot t))$
GI->Blood**	$\sum_{i=1}^{4} GI * (1-\exp[-24 * t]) * f_1 * (1-\exp[-0.3161 * t])$
Urine+	$(Q_{Pulm} + Q_{GI}) \cdot (1-\exp(-0.0495 \cdot t))$

[1] Polonium assumed to be 100% Class W; rates include radioactive decay; transfer rates between compartments taken from ICRP 30 models

* days

** $f_1 = 0.05$

\+ effective urinary Po excretion rate = 0.0495 $days^{-1}$

Fig. 5.1 Apparatus utilized for the NYUMC unashed/untraced method of spontaneous deposition of Po.

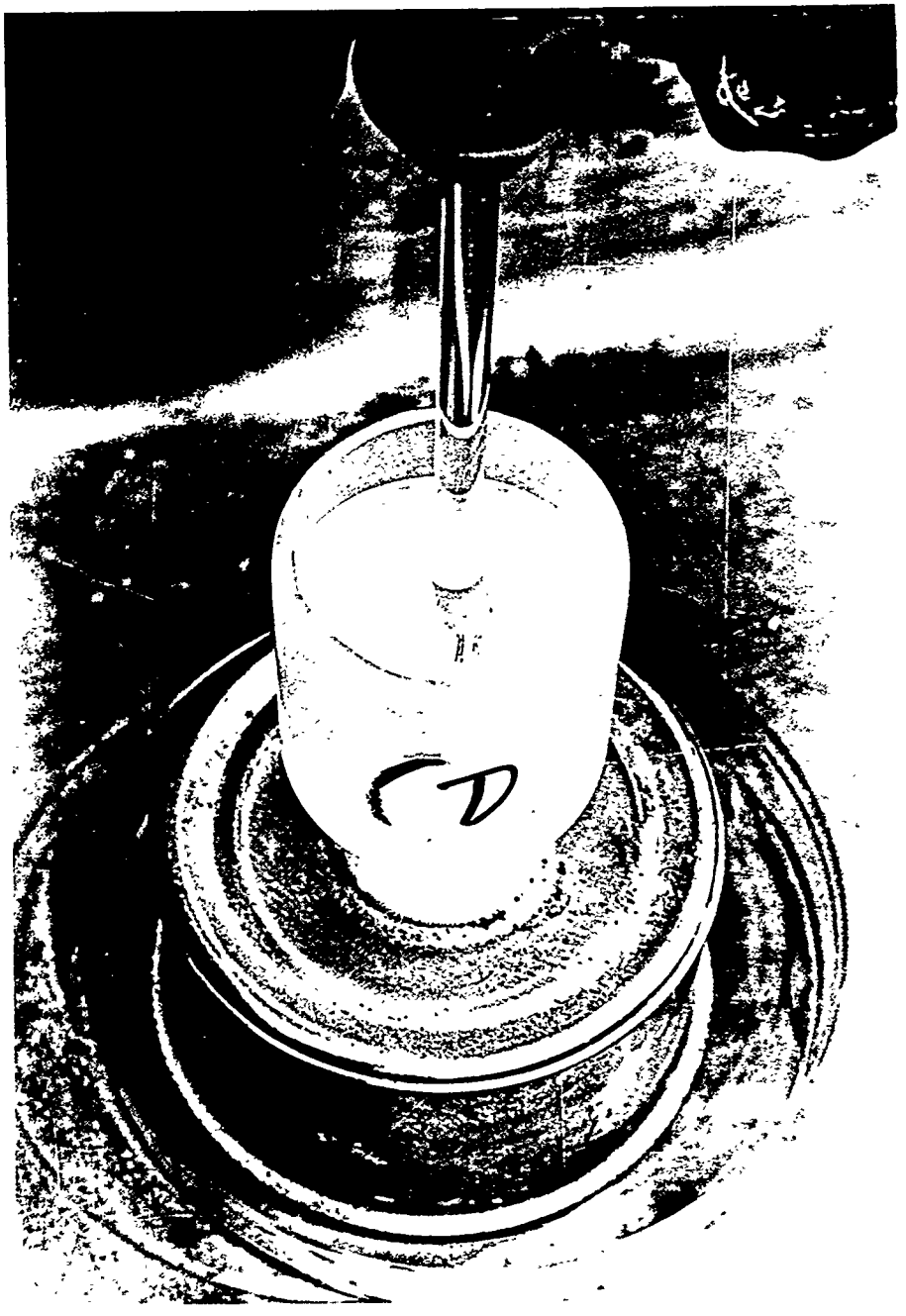
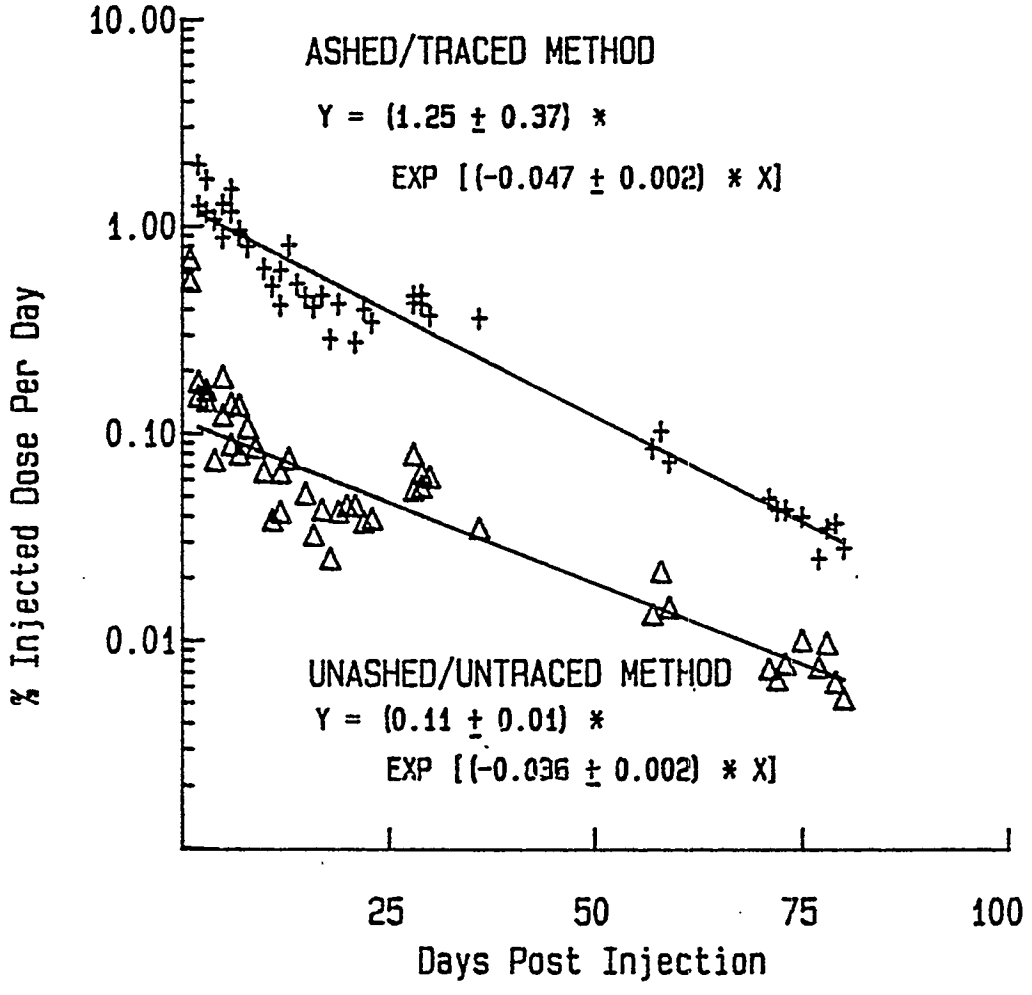


Fig. 5.2 Urinary ^{210}Po excretion determined from split samples using two radiochemical procedures following intravenous administration of ^{210}Po citrate in the adult female baboon.



all data points have relative standard deviation < 10%

Fig. 5.3 Temporal relationship resulting from the linear regression of the natural log of the ratio of ashed/traced to unashed/untraced baboon urine ^{210}Po data on days post injection (day one samples not included in the regression).

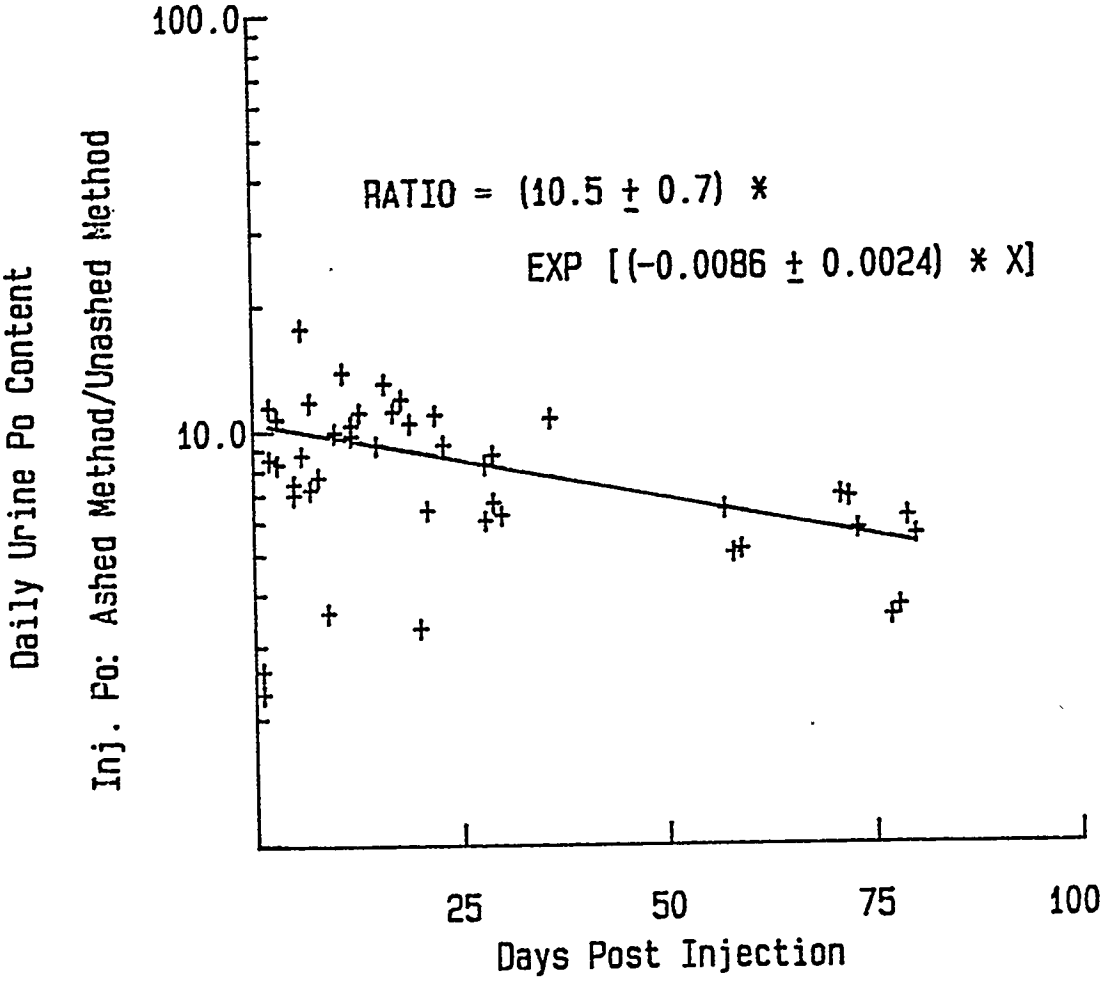


Fig. 5.4 Ratio of ashed/traced to unashed/untraced tamarin urine ^{210}Po data. Samples collected after the second day post injection had an average value of 3.5 ± 0.8.

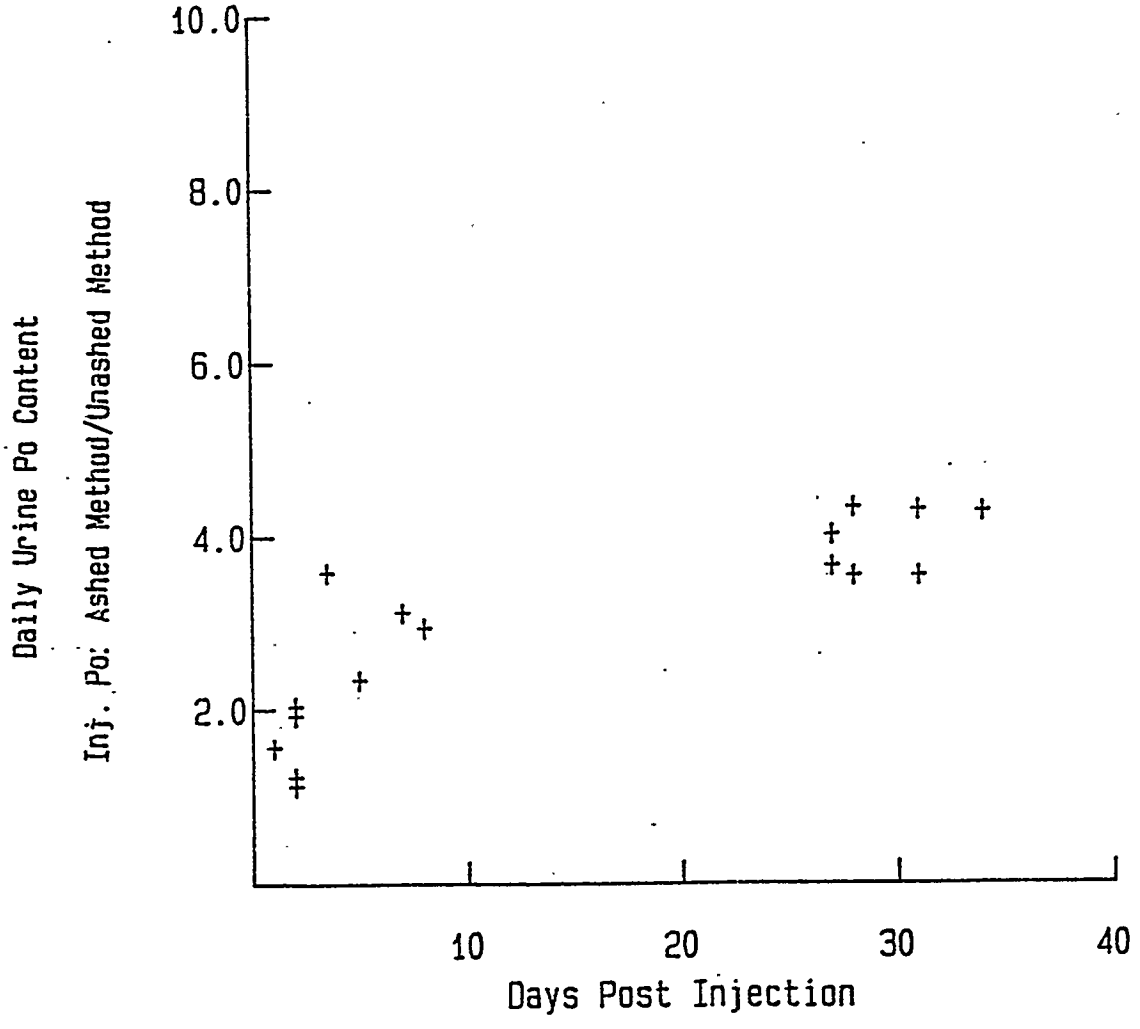


Fig. 5.5 Urinary ^{210}Po excretion curves regressed to data presented by Fink (1950) for three humans compared to the unashed/untraced data from both species of non-human primates. The human data were also generated with an unashed/untraced procedure.

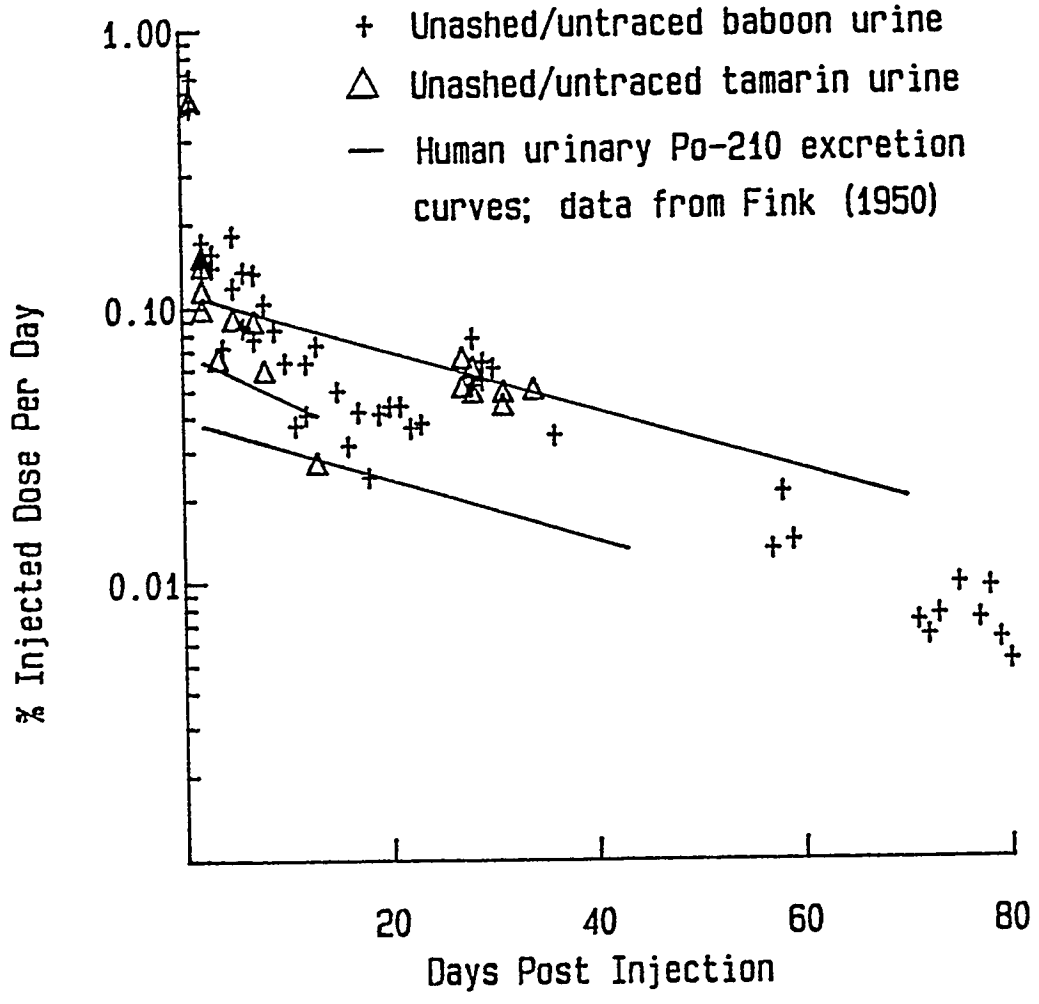


Fig. 5.6 Fitted curves, data, and excretion functions for a human injected with ^{210}Po chloride (data from Fink 1950). Integration of the functions show that 54% and 5% of the administered dose are excreted via the fecal and urinary routes out to infinity, respectively.

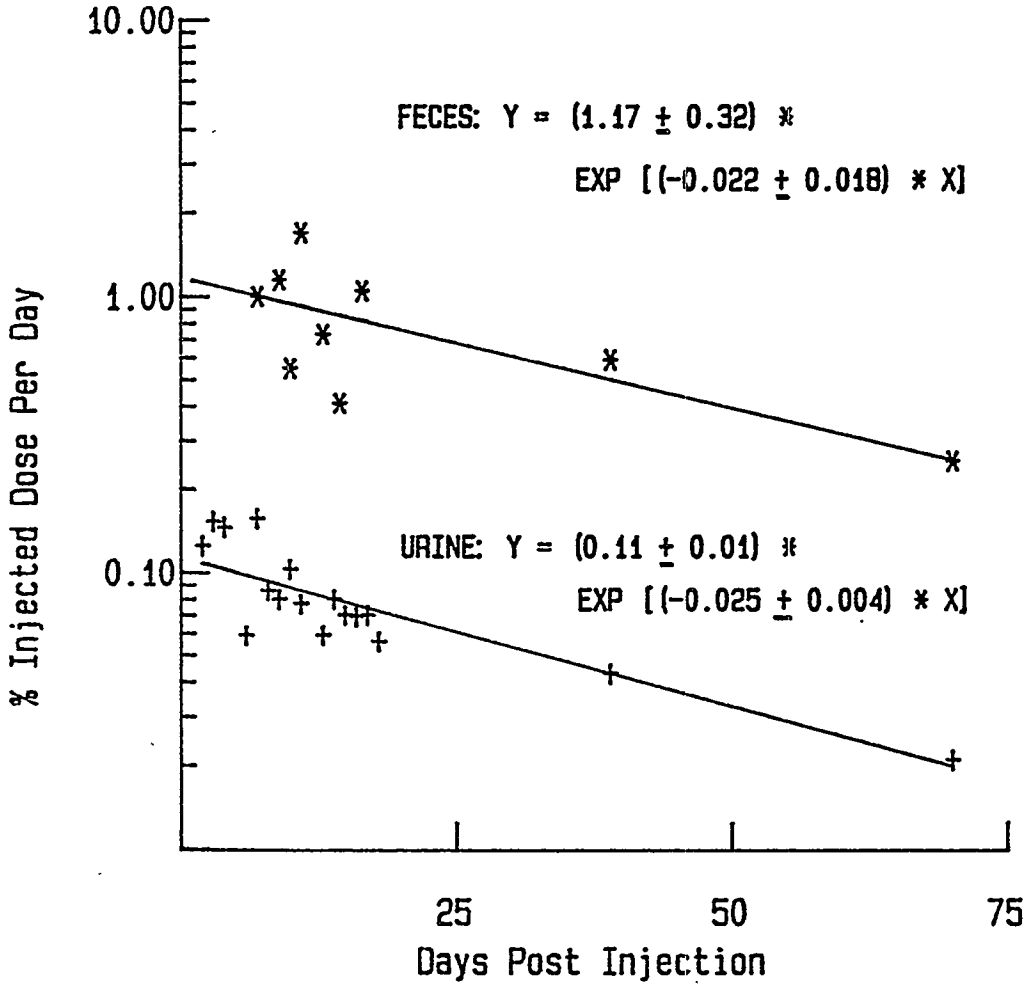


Fig. 5.7 Adjusted urinary excretion of ^{210}Po for a human injected with ^{210}Po chloride. The urinary Po data has been adjusted to account for the ratio of ashed/traced to unashed/untraced deposition efficiencies observed in baboon urine. The total ^{210}Po urinary output increases from 5% based on the original data (lower curve) to 35% of the administered dose.

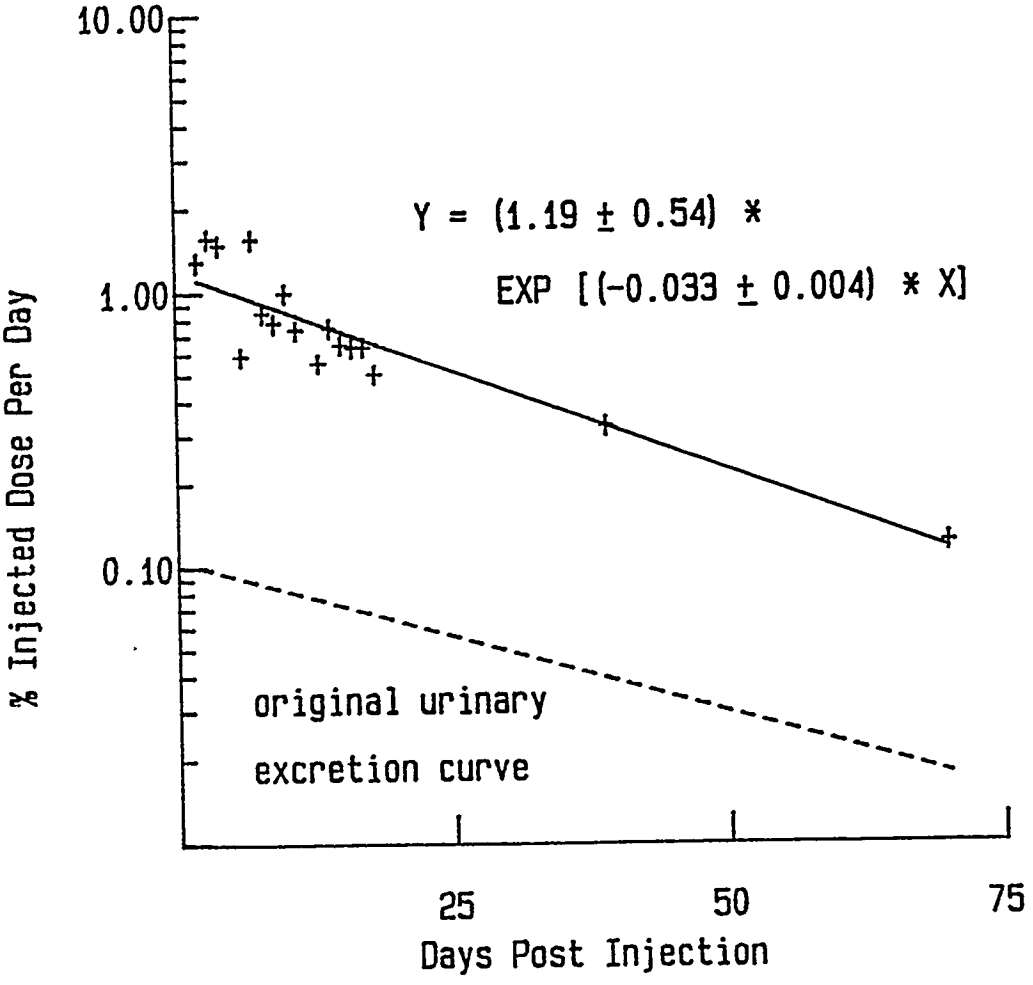


Fig. 5.8 Schematic of material transfer following deposition in the lung

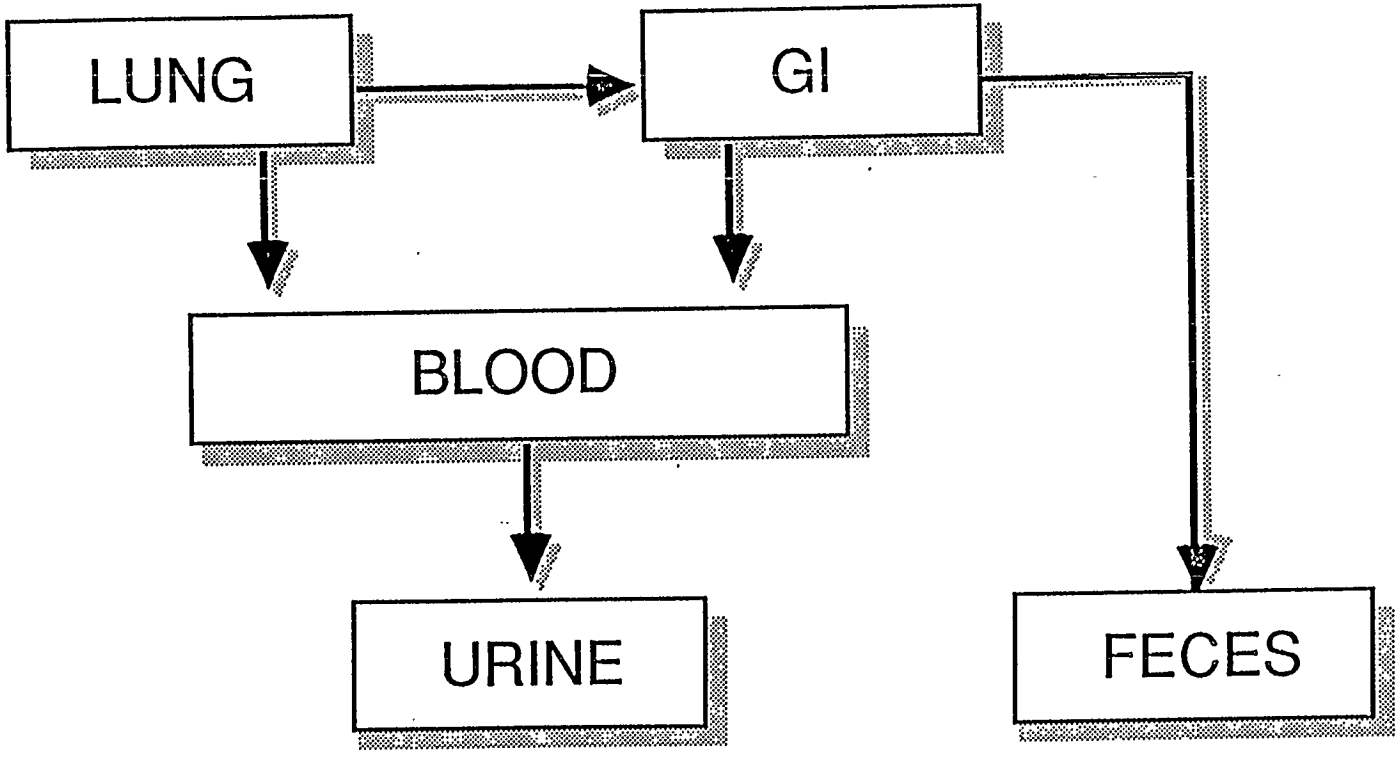


Fig. 5.9 The ICRP 30 Lung Model

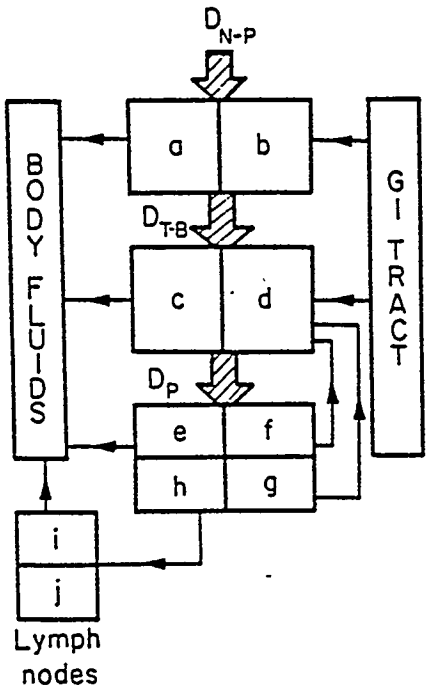
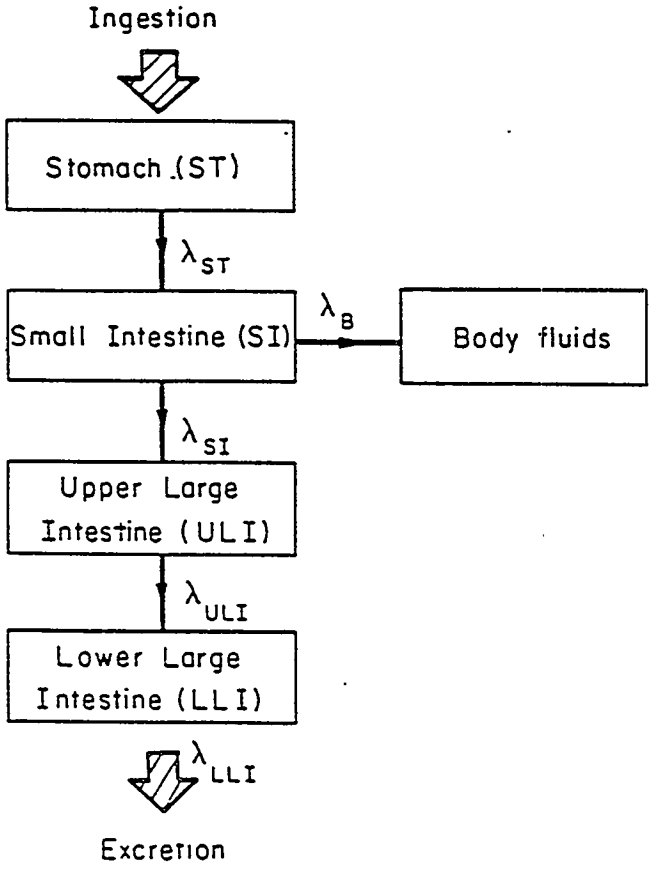


Fig. 5.10 The ICRP 30 GI Model



6 Summary of Significant Findings

The characterization of Po metabolism in non-human primates revealed the following:

- The radiochemical deposition efficiency of metabolized ^{210}Po is significantly lower when spontaneously deposited from fresh (unashed) urine compared to urine which has been wet ashed in HNO_3.
- The Po excretion rate is more rapid than the rates in the literature for non-primate species and in the ICRP 30 metabolic model.
- The urinary excretion fraction for Po is greater than the 0.1 value in the ICRP 30 metabolic model, with measured values of approximately 0.2 and 0.4 in the tamarin and baboon, respectively.
- Polonium distributes throughout the soft tissues. However, organ partition coefficients were not equal for the liver, kidney, and spleen as would be predicted by the ICRP 30 metabolic model.
- Considerably less ^{210}Po than expected deposits initially in the spleen. This distribution is most likely the result of using an injection solution free of aggregates.
- The ^{210}Po content of residual blood contributes significantly to the *in vitro* organ Po measurement of some organs (especially spleen and lung) under certain circumstances.

Evaluation of human urine Po data collected during the Manhattan Project led to the following:

- Re-evaluation of data collected following the clinical administration of ^{210}Po to humans by Fink (1950) suggest that the failure to wet ash urine prior to spontaneous deposition assay caused a decrease in the deposition efficiency of a similar magnitude as that measured in baboons as part of this research. Adjusting the human data to account for the quantitative effect of wet ashing urine on deposition efficiency results in good agreement between the urinary excretion parameters derived from the human and baboon data.
- A model has been developed to retrospectively estimate organ specific systemic radiological dose equivalent values to workers at Mound Laboratory based on their past Po urinalysis data. The model incorporates statistical testing to determine data reflective of significant Po intakes. Metabolic parameters determined in the baboon are utilized in the dosimetry calculations.
- Inclusion of lung retention parameters to the model (using an existing lung model or preferably new data based on ^{210}Po inhalation exposure of non-human primates) could be easily accomplished. This would enable estimation of the effective dose equivalent.

7 APPENDICES

APPENDIX A. Radiochemical Procedures For Determination of ^{210}Po In Bioassay Samples

BIOASSAY PROCEDURE FOR PO IN URINE

50 - ml representative aliquot from 24 hr. urine sample

↓

Spike with Po - 208 tracer

↓

Wet Ash with concen. HNO3

↓

Dissolve ashed sample in 100 - ml of 1N HCL

↓

Transfer 10 - ml aliquot to nickel plating cell

↓

Add 1 - ml sat. ascorbic acid solution

↓

Adjust to 20 - ml with 1N HCL

↓

Stir for 3 hrs at room temp.

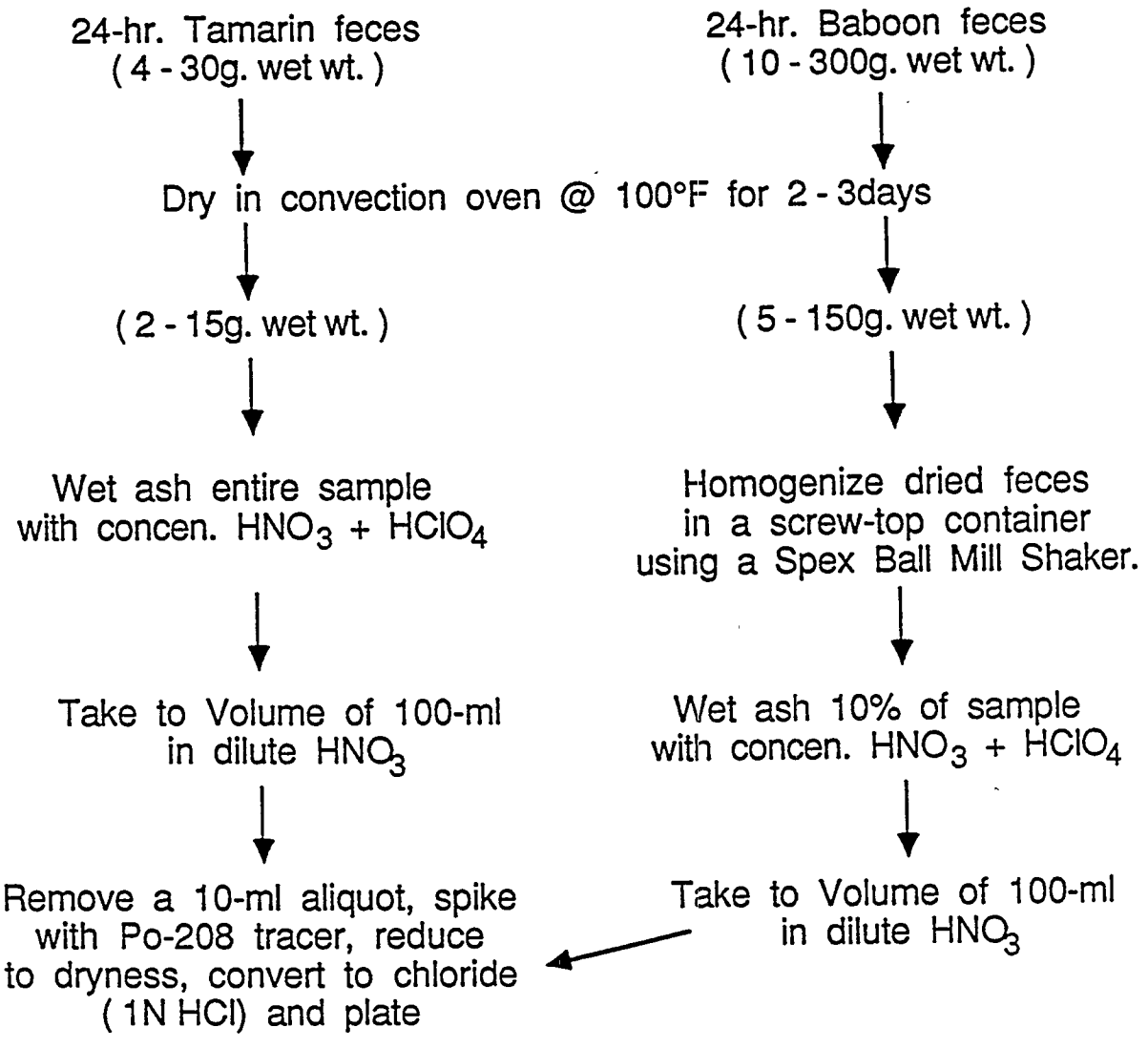
↓

Remove disc and rinse with ethanol

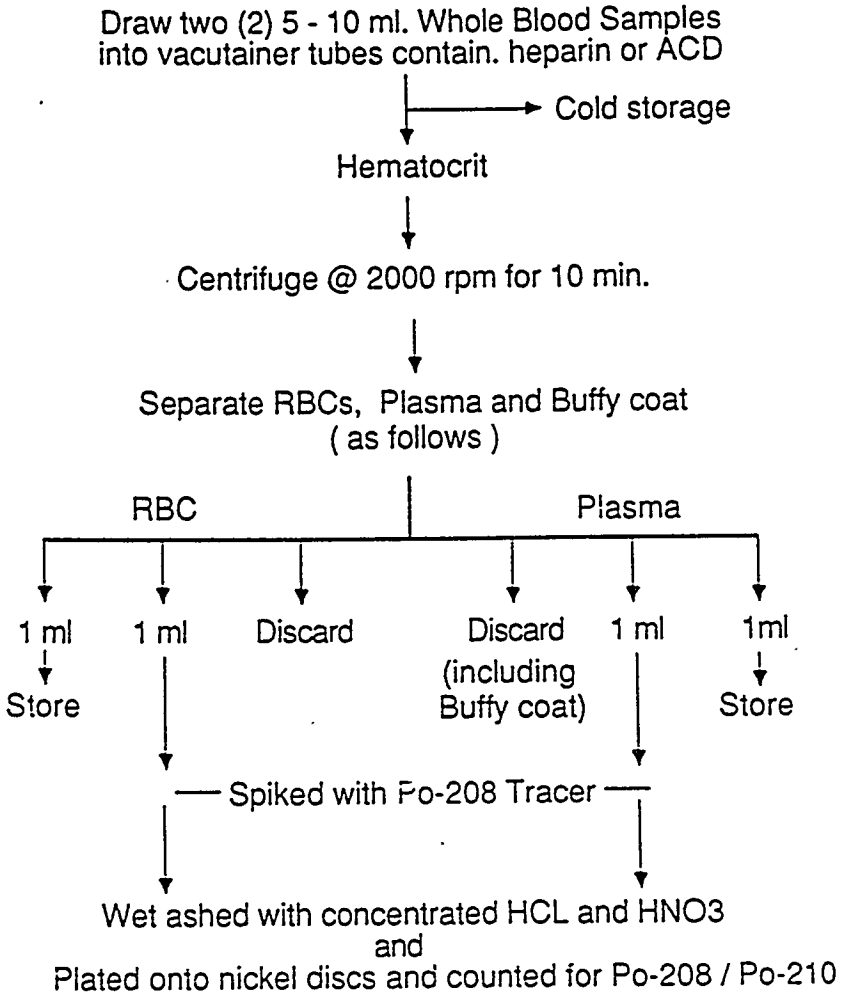
↓

Count disc on an alpha spectrometer to resolve Po - 208 and Po - 210

BIOASSAY PROCEDURE FOR PO IN FECES



BIOASSAY PROCEDURE FOR PO IN BLOOD



APPENDIX B. Preparation of ^{51}Cr-labeled Erythrocytes*

1. Draw a 5 mL whole blood sample into a vacutainer containing 0.75 mL of acid citrate dextrose (ACD) solution.
2. Centrifuge @ 2000 rpm for 5 minutes @ 4°C.
3. Remove serum and buffy coat.
4. Wash RBCs three times with physiologic saline (PS), 0.9% NaCl.
5. Add dropwise 0.37-0.74 kBq (10-20 uCi) of sterile sodium ^{51}Cr per mL RBC with mixing.
6. Incubate mixture with mixing for 30 minutes @ 37°C.
7. Wash ^{51}Cr-RBC with PS.
8. Resuspend in 5-10 mL culture medium (90% RPMI-1640, 10% Bovine Serum, 1% Penn/Strep.)
9. Refrigerate overnight @ 4°C.
10. Centrifuge @ 2000 rpm for 5 minutes @ 4°C.
11. Remove medium and wash ^{51}Cr-RBC with PS.
12. Resuspend ^{51}Cr-RBC in approximately 10 mL PS.
13. Inject (iv) cells.
14. Allow labeled RBC solution to circulate *in vivo* for 5-10 minutes prior to sacrifice by exsanguination.

*Modified from Frank et al. (1979)

APPENDIX C. Preparation of ^{210}Po Citrate Solution for Intravenous Administration to Non-human Primates

(1) Withdraw ~0.5 cc of ^{210}Po stock soln. (2 *N* HCL) into a 1 cc tuberculin syringe.

(2) Transfer Po solution into a pre-weighed 30 mL polypropylene bottle and obtain the solution weight.

(3) Add ~9.5 mL of 0.1 *M* Na citrate solution slowly with mixing (in 0.1 mL aliquots).

(4) Re-weigh bottle to determine the amount of citrate added.

(5) Wait 15-20 minutes to complete reaction.

(6) Draw off an aliquot. Calibrate solution and test pH with short-range indicator paper (solution pH 4-5).

(7) Draw up solution into a 35 cc syringe with a Leur-lock neck.

(8) Attach a 0.22 uM Swinex (Millipore) filter and collect filtered solution in a pre-weighed 30 mL PP bottle. Weigh.

(9) Test pH (4-5) with short-range paper and calibrate an aliquot of the solution.

(10) Compare solution activity concentrations before and after filtration to determine filterability.

Final administration solution is 100% ultrafilterable (0.22 uM) with pH 4-5 and 0.1 *M* Na citrate.

APPENDIX D. Po Excretion Data In Non-human Primates

TAMARIN

Tamarin #	Days Post Administration	% Injected Dose Excreted In Urine d^{-1}*	% Injected Dose Excreted x 10E3 mL^{-1} d^{-1}*
T500	1	.643	6.298
T500	2	.231	2.179
T500	3	.253	2.014
T500	4	.330	2.161
T500	5	.233	2.031
T500	6	.341	2.376
T500	7	.252	2.437
T500	8	.299	1.709
T500	9	.229	1.363
T500	10	.345	3.317
T500	11	.318	1.861
T500	12	.248	5.188
T500	13	.334	1.776
T500	14	.261	1.602
T500	15	.320	1.698
T500	16	.270	7.337
T500	17	.305	1.836
T500	18	.219	3.411
T500	19	.242	2.840
T500	20	.381	2.389
T500	21	.301	2.339
T500	22	.226	1.894
T500	23	.202	1.872
T500	24	.292	2.086
T500	25	.181	1.759
T500	26	.237	2.114
T500	27	.202	2.174
T500	28	.209	2.105
T500	29	.216	2.703
T500	30	.202	1.443
T500	31	.186	1.513
T500	32	.147	1.574
T500	33	.151	2.658
T500	34	.211	2.116
T500	35	.213	2.669
T500	36	.194	1.952
T500	37	.146	1.597
T500	38	.202	2.428
T500	39	.183	1.889
T500	40	.194	1.948
T500	41	.134	1.971
T500	42	.152	1.867
T500	43	.142	2.152

Tamarin #	Days Post Administration	% Injected Dose Excreted In Urine d^{-1}*	% Injected Dose Excreted x 10E3 mL^{-1} d^{-1}*
T500	44	.113	2.112
T500	45	.138	2.396
T500	46	.189	3.500
T500	47	.118	3.226
T500	48	.105	5.438
T504	1	.585	1.364
T504	2	.188	7.529
T504	3	.409	5.013
T504	4	.427	8.099
T504	5	.314	4.443
T504	6	.454	3.783
T504	7	.256	4.263
T504	8	.377	3.721
T504	9	.246	5.417
T504	10	.359	3.586
T504	11	.453	3.485
T504	12	.325	4.198
T504	13	.321	3.273
T504	14	.301	2.846
T504	15	.425	3.261
T504	16	.771	3.664
T504	17	.369	7.442
T504	18	.288	2.445
T504	19	.281	3.307
T504	20	.650	3.226
T504	21	.254	6.660
T504	22	.258	4.387
T504	23	.235	3.603
T504	24	.332	3.028
T504	25	.313	3.656
T504	26	.294	3.340
T504	27	.235	2.637
T504	28	.210	2.450
T504	29	.201	2.349
T504	30	.296	3.083
T504	31	.171	2.418
T504	32	.212	2.140
T504	33	.113	4.501
T504	34	.269	5.000
T504	35	.276	4.891
T504	36	.205	3.489
T504	37	.194	3.015
T504	38	.185	2.853
T504	39	.089	1.784
T504	40	.145	2.673

Tamarin #	Days Post Administration	% Injected Dose Excreted In Urine d^{-1}*	% Injected Dose Excreted x 10E3 mL^{-1} d^{-1}*
T504	41	.189	3.326
T504	42	.202	3.533
T504	43	.121	2.894
T504	44	.137	3.591
T504	45	.103	4.492
T504	46	.178	3.270
T504	47	.177	3.812
T504	48	.177	3.882
T504	49	.245	3.734
T504	50	.216	2.526
T504	51	.189	2.441
T504	52	.124	3.005
T504	53.5	.144	2.952
T504	55	.125	1.502
T504	56	.125	4.480
T504	57	.113	5.081
T504	58	.190	6.141
T504	59	.205	3.800
T504	60	.177	3.417
T504	61	.101	2.818
T504	62	.084	2.886
T504	63	.098	2.044
T504	64	.113	2.284
T504	65	.129	3.038
T504	66	.126	2.959
T504	67	.105	1.883
T504	68	.043	2.126
T504	69	.088	3.945
T504	70	.136	3.667
T504	71	.108	2.523
T504	72	.069	1.545
T504	73	.082	1.700
T504	74	.071	1.592
T504	75	.010	1.277
T504	76	.142	.2513
T504	77	.075	3.568
T504	78	.101	2.095
T504	79	.099	1.836
T504	80	.092	2.152
T504	81	.086	1.190
T504	82	.065	1.286
T504	83	.080	1.952
T504	84	.078	1.790
T504	85	.063	1.320
T504	86	.088	1.755

Tamarin #	Days Post Administration	% Injected Dose Excreted In Urine d^{-1}*	% Injected Dose Excreted x 10E3 mL^{-1} d^{-1}*
T504	87	.056	1.397
T504	88	.066	1.343
T504	89	.064	1.260
T504	90	.036	1.538
T504	195	.014	1.129
T504	196	.018	0.256
T504	197	.018	0.265
T504	198	.014	0.511
T504	203	.021	0.253
T500	1	.849	0.358
T500	2	.169	10.489
T500	3.5	.229	1.727
T500	5	.209	1.737
T500	6	.134	2.024
T500	7	.154	1.834
T500	8	.171	2.000
T500	10	.140	1.682
T500	12	.212	0.661
T500	13	.047	4.680
T500	14	.132	0.502
T500	15	.117	1.322
T508	1	.743	1.046
T508	2	.166	17.043
T508	3.5	.229	1.630
T508	5	.211	4.845
T508	6	.196	4.933
T508	7	.272	5.921
T508	8	.151	2.939
T508	10	.158	3.990
T508	12	.115	1.048
T508	13	.142	2.838
T508	14	.151	3.160
T508	15	.103	3.030

*relative errors range from 2-10%

Tamarin #	Days Post Administration	% Injected Dose Excreted In Feces d^{-1}*	% Injected Dose Excreted x 10E2 g^{-1} d^{-1}*
T504	1	0.568	14.190
T504	2	0.667	10.588
T504	3	1.031	12.886
T504	4	0.543	3.332
T504	5	0.535	3.996
T504	6	1.011	5.053
T504	7	0.599	4.684
T504	8	0.745	9.315
T504	9	0.680	2.178
T504	10	1.015	5.835
T504	11	1.227	8.293
T504	12	0.620	5.001
T504	13	0.675	4.625
T504	14	0.624	4.520
T504	15	0.589	3.982
T504	16	0.699	6.359
T504	17	1.034	6.155
T504	18	0.702	10.972
T504	19	0.412	3.298
T504	20	0.092	0.694
T504	21	1.124	10.310
T504	22	0.969	14.460
T504	23	0.908	7.264
T504	24	0.834	8.421
T504	25	1.046	7.068
T504	26	1.005	5.911
T504	27	0.836	6.014
T504	28	0.583	4.860
T504	29	0.833	15.427
T504	30	1.035	5.783
T504	31	1.105	9.867
T504	33	0.686	5.968
T504	34	0.638	3.799
T504	35	1.305	9.959
T504	36	1.014	6.001
T504	37	0.603	5.687
T504	38	0.706	4.413
T504	39	0.387	5.687
T504	40	0.599	6.888
T504	41	0.756	7.136
T504	42	0.735	7.899
T504	43	0.747	6.789
T504	44	0.531	7.702
T504	45	0.367	11.484

Tamarin #	Days Post Administration	% Injected Dose Excreted In Feces d^{-1}*	% Injected Dose Excreted x 10E2 g^{-1} d^{-1}*
T504	46	0.723	5.199
T504	47	0.992	7.940
T504	48	0.870	6.848
T504	49	0.828	5.749
T504	50	0.592	3.697
T504	51	0.301	1.749
T504	53.5	0.538	2.626
T504	55	0.602	3.837
T504	56	0.557	6.050
T504	57	0.677	7.443
T504	58	1.043	6.062
T504	59	0.643	3.652
T504	60	0.465	2.434
T504	61	0.403	3.124
T504	62	0.390	6.502
T504	63	0.383	4.073
T504	64	0.678	5.427
T504	65	0.337	2.408
T504	66	0.350	3.094
T504	67	0.488	4.878
T504	68	0.201	5.033
T504	69	0.511	14.195
T504	70	0.532	3.095
T504	71	0.520	1.683
T504	72	0.644	6.779
T504	73	0.648	2.064
T504	74	0.519	2.610
T504	75	0.075	3.752
T504	76	0.525	4.011
T504	77	0.410	7.454
T504	78	0.392	2.990
T504	79	0.404	2.022
T504	80	0.281	0.954
T504	81	0.319	1.151
T504	82	0.177	1.024
T504	83	0.207	1.627
T504	84	0.254	1.590
T504	85	0.237	1.625
T504	86	0.256	1.550
T504	87	0.221	2.141
T504	88	0.209	1.367
T504	89	0.177	1.290
T504	90	0.214	13.398

Tamarin #	Days Post Administration	% Injected Dose Excreted In Feces d^{-1}*	% Injected Dose Excreted x 10E2 g^{-1} d^{-1}*
T504	195	0.035	0.291
T504	196	0.047	0.243
T504	197	0.054	0.349
T504	198	0.049	0.718
T504	203	0.062	1.034
T500	1	0.898	
T500	2	0.740	
T500	3.5	0.494	
T500	5	0.851	
T500	6	0.379	
T500	7	0.357	
T500	8	0.525	
T500	10	0.311	
T500	12	0.041	
T500	13	0.311	
T500	14	0.523	
T500	15	0.391	
T508	1	1.223	
T508	2	0.559	
T508	3.5	0.640	
T508	5	0.909	
T508	6	0.314	
T508	7	0.353	
T508	8	0.718	
T508	10	0.444	
T508	12	0.466	
T508	13	0.407	
T508	14	0.418	
T508	15	0.452	

*relative errors range from 2-10%

BABOON

Baboon #	Days Post Administration	% Injected Dose Excreted In Urine d^{-1}*	% Injected Dose Excreted x 10E3 mL^{-1} d^{-1}*
B1054	1	0.918	3.586
B156	1	1.212	2.166
B156	2	1.854	3.727
B156	3	2.470	3.750
B156	4	2.705	2.204
B156	5	2.328	3.858
B156	6	1.448	3.281
B156	7	1.315	3.525
B1060	1	1.502	2.641
B1060	2	2.151	2.325
B1060	3	1.832	1.466
B1060	4	1.854	1.107
B1060	5	0.965	1.253
B1060	5	0.957	1.242
B1060	6	1.639	1.361
B1060	7	1.072	1.038
B1060	7	0.911	0.882
B1060	8	1.050	1.890
B1060	9	0.473	1.790
B1060	9	0.509	1.927
B1060	10.5	1.263	0.495
B1060	12	0.690	0.685
B1060	12	0.654	0.648
B1060	13	0.884	1.038
B1060	14	0.638	0.788
B1060	14	0.450	0.555
B1060	15	0.225	5.080
B1046	0.22	0.454	7.423
B1046	1	0.793	2.359
B1046	2	1.227	3.355
B1046	2	1.185	3.241
B1046	3	1.453	3.640
B1046	3	1.625	4.070
B1046	4	1.553	5.711
B1046	4	1.389	5.108
B1046	5	1.521	2.510
B1046	6	1.233	1.752
B1046	7	1.130	1.546
B1046	8	1.132	1.116
B1046	9	1.126	0.890
B1046	10	0.933	0.631
B1046	11	0.936	0.616
B1046	12	0.748	1.036

Baboon #	Days Post Administration	% Injected Dose Excreted In Urine d^{-1}*	% Injected Dose Excreted x 10E3 mL^{-1} d^{-1}*
B1046	13	0.539	1.228
B1046	14	0.837	0.670
B1046	15	0.813	0.831
B1046	16	0.706	0.630
B1046	17	0.771	0.796
B1046	18	0.703	0.528
B1046	19	0.635	0.591
B1046	20	0.540	1.090
B1046	21	0.378	0.507
B1046	22	0.728	0.846
B1046	23	0.579	0.441
B1046	24	0.538	0.521
B1046	25	0.597	0.399
B1046	26	0.724	0.600
B1046	27	0.540	0.305
B1046	28	0.464	0.308
B1046	29	0.419	0.402
B1046	30	0.372	0.489
B806	1	0.933	2.314
B806	2	1.223	3.641
B806	3	1.339	8.968
B806	4	1.224	5.432
B806	5	1.285	6.232
B806	6	1.353	6.208
B806	7	1.167	7.709
B806	8	1.032	10.225
B806	9	1.135	3.8284
B806	10	1.169	4.488
B806	11	0.821	3.261
B806	12	0.802	3.855
B806	13	0.953	2.212
B806	14	1.157	1.375
B806	15	0.678	1.946
B806	16	0.915	4.159
B806	17	0.934	3.014
B806	18	0.971	1.605
B806	19	1.166	3.414
B806	20	0.759	1.075
B806	21	0.596	1.538
B806	28	0.428	1.187
B806	29	0.469	1.269
B806	30	0.489	1.415
B806	31	0.402	0.909
B806	32	0.309	1.130
B806	33	0.497	2.289

Baboon #	Days Post Administration	% Injected Dose Excreted In Urine d^{-1}*	% Injected Dose Excreted x 10E3 mL^{-1} d^{-1}*
B806	34	0.383	1.059
B806	35	0.404	1.993
B806	36	0.363	2.371
B806	37	0.443	2.171
B806	38	0.410	0.905
B806	39	0.263	1.110
B806	40.5	0.275	0.248
B806	42	0.322	0.487
B806	43.5	0.293	0.313
B806	45	0.383	0.605
B806	47	0.483	0.304
B806	49	0.186	0.641
B806	75	0.067	0.036
B806	77	0.080	0.121
B806	78	0.077	0.069
B806	79	0.072	0.081
B806	80	0.072	0.135
B806	82	0.086	0.033
B806	85	0.076	0.031
B806	87	0.042	0.095
B806	89	0.050	0.042
B806	91	0.043	0.147

*relative errors range from 2-10%

Baboon #	Days Post Administration	% Injected Dose Excreted In Feces d^{-1}*	% Injected Dose Excreted x 10E2 g^{-1} d^{-1}*
B1054	1	0.187	0.761
B156	1	0.535	5.351
B156	2	12.000	29.056
B156	3	3.942	26.457
B156	5	3.221	10.192
B156	6	2.651	10.237
B156	7	0.812	4.060
B1060	1	0.115	0.454
B1060	2	4.431	9.467
B1060	3	3.629	16.495
B1060	4	2.489	5.710
B1060	5	2.696	3.506
B1060	6	1.159	2.899
B1060	7	1.486	2.971
B1060	8	0.696	2.914
B1060	9	1.497	2.603
B1060	10.5	0.912	2.835
B1060	12	0.818	2.920
B1060	13	0.960	2.473
B1060	14	0.611	2.315
B1046	1	0.017	0.190
B1046	2	0.105	0.708
B1046	3	0.141	1.487
B1046	4	13.373	13.162
B1046	5	2.232	6.644
B1046	6	0.440	5.179
B1046	7	0.689	3.826
B1046	8	2.488	4.879
B1046	9	3.646	4.994
B1046	10.5	1.540	2.671
B1046	12	0.635	1.176
B1046	13	0.616	1.741
B1046	14	0.333	2.429
B1046	15.5	2.045	3.601
B1046	17	0.687	1.568
B1046	18	0.816	1.858
B1046	19	0.862	2.128
B1046	20	0.190	1.780
B1046	21	2.030	1.992
B1046	23	0.306	2.548
B1046	24	2.038	2.086
B1046	25	0.338	1.139
B1046	26	0.647	0.772
B1046	27	0.171	1.033

Baboon #	Days Post Administration	% Injected Dose Excreted In Feces d^{-1}*	% Injected Dose Excreted x 10E2 g^{-1} d^{-1}*
B1046	28	0.533	1.378
B1046	30	1.104	1.175
B806	1	0.033	0.367
B806	2	2.641	7.356
B806	3	3.529	16.724
B806	4	1.143	13.288
B806	5	1.536	15.361
B806	6	2.401	20.525
B806	7	3.806	13.891
B806	8	3.051	9.027
B806	9	0.748	5.795
B806	10	2.401	6.782
B806	11	1.920	5.818
B806	12	1.553	3.638
B806	13	2.656	4.479
B806	14	0.849	3.537
B806	15	0.919	4.939
B806	16	1.139	7.695
B806	17	1.195	4.918
B806	18	1.580	3.883
B806	19	1.033	2.228
B806	20	1.228	2.613
B806	22	0.366	3.392
B806	23	0.964	4.016
B806	24	1.360	3.864
B806	25	0.949	2.994
B806	26	1.191	2.326
B806	27	1.228	2.006
B806	28	0.908	1.932
B806	29	1.181	1.834
B806	30	0.204	1.523
B806	31	0.734	2.133
B806	32	0.431	2.447
B806	33	1.014	2.419
B806	34	0.654	1.661
B806	35	0.976	2.447
B806	36	0.643	1.639
B806	37	0.204	1.696
B806	38	1.013	1.602
B806	39	0.215	1.197
B806	40.5	0.342	0.674
B806	42	0.396	1.348
B806	43.5	0.327	0.761
B806	45	0.518	0.740

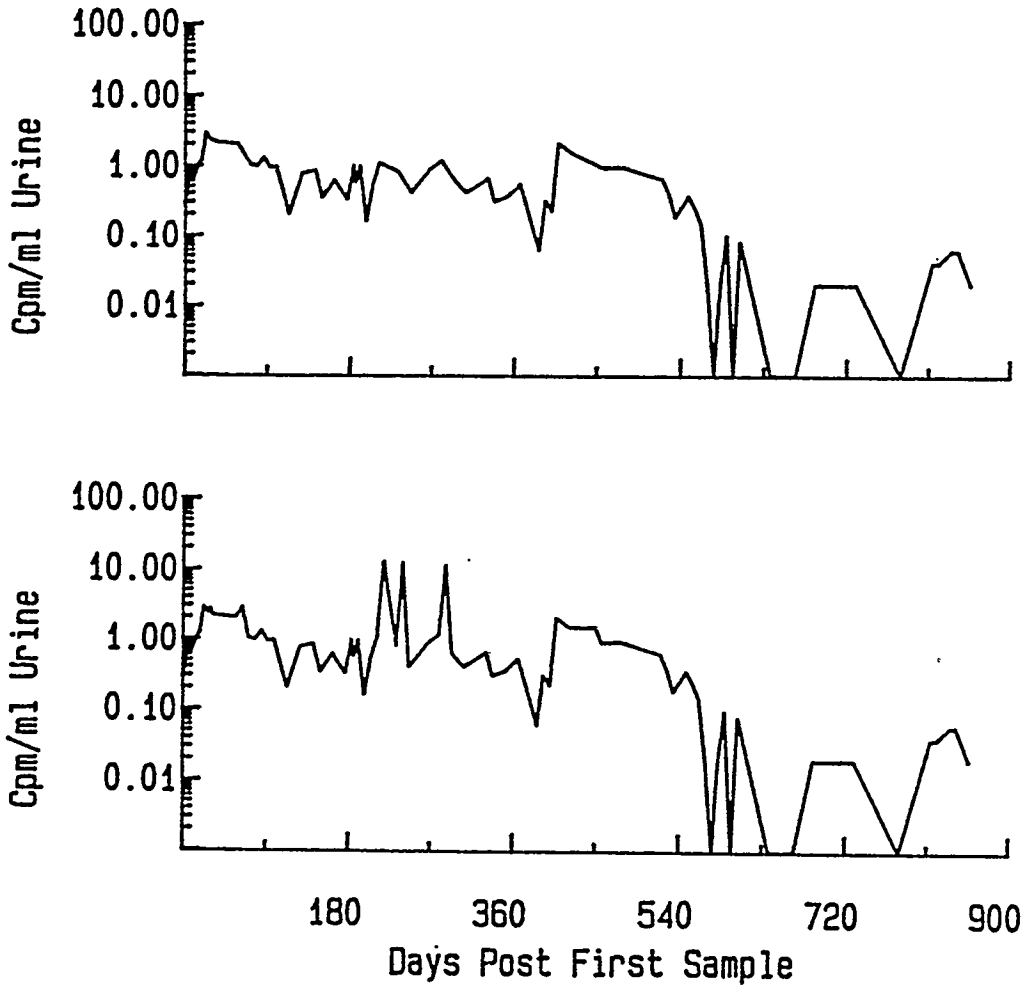
Baboon #	Days Post Administration	% Injected Dose Excreted In Feces d^{-1}*	% Injected Dose Excreted x 10E2 g^{-1} d^{-1}*
B806	47	0.244	0.234
B806	49	0.114	0.360
B806	54	0.296	0.212
B806	61	0.100	0.086
B806	75	0.149	0.108
B806	80	0.164	0.262
B806	82	0.089	0.070
B806	85	0.066	0.056
B806	87	0.040	0.199
B806	89	0.108	0.082
B806	91	0.066	0.291

*relative errors range from 2-10%

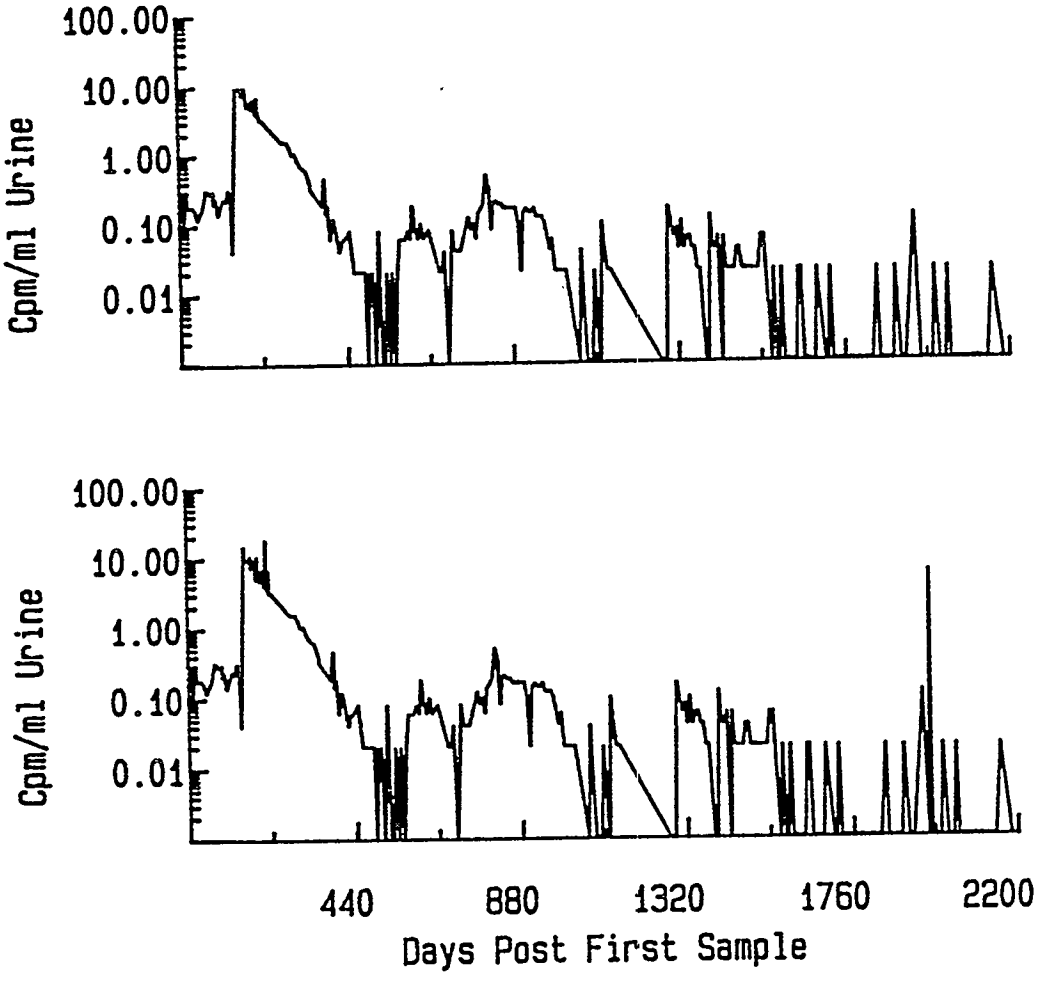
APPENDIX E. Sample Plots of Urinary ^{210}Po Excretion at Mound Laboratory.

Original data plotted on bottom curve. Data following removal of outliers plotted on top curve.

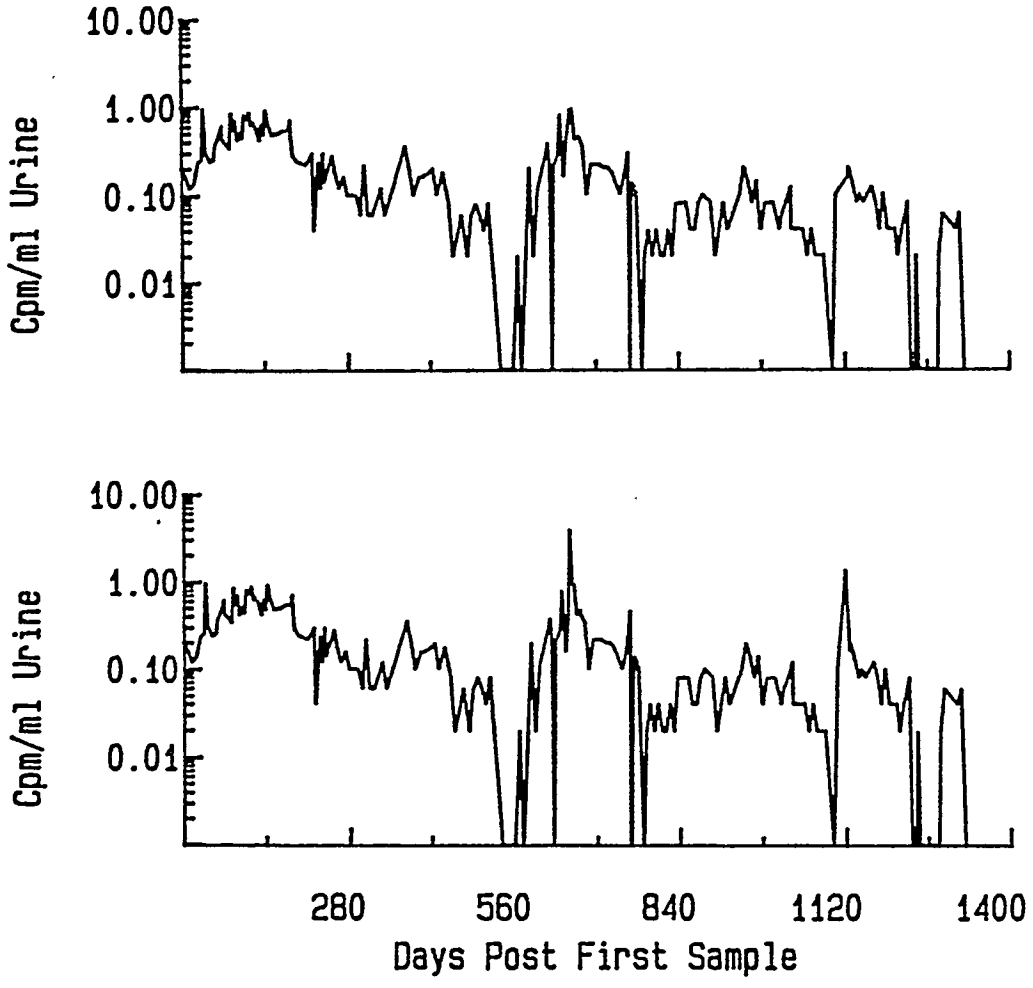
CASE 1424 START DATE: 4/7/1945



CASE 5604 START DATE: 9/29/1947



CASE 6175 START DATE: 11/10/1947



APPENDIX F. Computer Codes Used to Calculate Radiological Dose Based on Urine Bioassay Data and Instructions for Their Use

OMDOS

```
c This program operates on data from the urinary Po-210 data base.
c It is part of the batch program run from within dBase III+ to
c estimate the whole body dose equivalent incurred by Po
c workers on an individual basis.
      program omdos
      character*38 out30,title
      character*3 v(800)
      character*1 qm
      character*3 per,star
      integer vol(800),month(800),day(800),year(800),case(800)
      integer*4 jd(800),dp(800)
      real cpm(800),cpml(800),ecpm(800)
      real forcst(800),eforcst(800)
      real newcpm
      data qm/''''/
      data per,star/' 0','***'/
      data luncon/0/,lundsk/1/,lunprt/2/
      out30='prn'
c
c All records for a specified worker (by ID #) are read in.
c
      open(lundsk,file='a:dp.dat',status='old')
```

```
   i=1
15  read(lundsk,10,end=20)case(i),year(i),month(i),day(i),cpm(i),
 1  v(i)
10  format(i4,i4,i2,i2,f10.1,a3)
    ecpm(i)=sqrt(cpm(i)*20)/20
    i=i+1
    go to 15
c
c The date of sample is adjusted.
c Initially, the Julian day value is computed.  This is
c followed by normalization to the days post first sample.
c
20  do 30 n=1,i-1
    jd(n)=int((year(n)+numdas)*365.25)
 1  +(int(((month(n)+1)-(12*numdas))*30.6001))+day(n)
30  continue
    n1=0
    open(lundsk,file='a:data.dat',status='old')
    rewind(lundsk)
    n=n-1
c
c There are documented memos indicating that some of the records
c on the data base warrant elimination or adjustment.  A period
c in the "comments" column means that the sample was lost or never
c collected.  These data points are eliminated.  A star indicates
```

```
c that the sample volume should be adjusted from 50 to 100 mL if
c the sample was collected beyond a certain date.
c These corrections are done in the following loop.
c
   do 50 k=1,n
   dp(k)=jd(k)-jd(1)
   if(v(k).eq.per)then
    n1=n1+1
    go to 50
     elseif(v(k).eq.star)then
      if(jd(k).lt.717608)then
      v(k)=' 50'
      else
      v(k)='100'
      endif
     endif
   if(k.ge.n-1)then
   go to 31
   endif
c
c In the next portion of the algorithm, the data are tested
c for false positives, which when found are removed from the
c data file. Urinary Po is reflective of the systemic
c Po burden. A datum indicative of a true intake will
c have subsequent data reflecting the elimination of Po
```

```
c at a rate which can be predicted based on studies conducted
c on the elimination of Po in the adult baboon.
c The t-distribution of the mean predicted value of subsequent data
c and the measured data values are compared.
c If the urinary excretion value of the "next" sample is within
c the predicted confidence interval, then the point tested is
c accepted as represented a true intake.
c
c In some cases duplicate samples were run on the same date.
c Where these are found, the duplicate sample is skipped and
c the t-test is conducted on the following sample.
c
      test=cpm(k)/50
      if(test.gt.1)then
      dp(k+1)=jd(k+1)-jd(1)
      dp(k+2)=jd(k+2)-jd(1)
      if(dp(k).eq.dp(k+1))then
      forcst(k)=cpm(k)*exp(-0.0495*(dp(k+2)-dp(k)))
      eforcst(k)=1.99*0.129*sqrt((1/98)+(((dp(k+2)-dp(k)
     1          -23.005)**2)/53861.7)+1)
      else
      forcst(k)=cpm(k)*exp(-0.0495*(dp(k+1)-dp(k)))
      eforcst(k)=1.99*0.129*sqrt((1/98)+(((dp(k+1)-dp(k)
     1          -23.005)**2)/53861.7)+1)
      endif
```

```
   comp=forcst(k)-eforcst(k)
   if(dp(k).eq.dp(k+1))then
    newcpm=cpm(k+2)+(2*ecpm(k+2))
    if(newcpm.lt.comp)then
    n1=n1+1
    go to 50
    endif
   else
    newcpm=cpm(k+1)+(2*ecpm(k+1))
    if(newcpm.lt.comp)then
    n1=n1+1
    go to 50
    endif
   endif
   endif
31  write(lundsk,60)case(k),dp(k),cpm(k),v(k)
60  format(i4,1x,i6,1x,f7.1,1x,a3)
50  continue
   close(lundsk)
   n=n-n1
c
c The cpm/mL are calculated.
c
   open(lundsk,file='a:data.dat',status='old')
   do 70 i=1,n
```

```
   read(lundsk,80)case(i),dp(i),cpm(i),vol(i)
80  format(i4,1x,i6,1x,f7.1,1x,i3)
   cpml(i)=cpm(i)/vol(i)
   if(vol(i).eq.500)then
   cpml(i)=cpml(i)*10
   endif
70  continue
c
c The data are written to file dose.dat.
c Where more than one sample exists on the same date,
c the average is computed.  Only one datum per sample
c date appears on the final data file.
c
   open(lundsk,file='a:dose.dat',status='old')
   ndp=1
   do 140 i=1,n
   if(i.gt.1)then
    if(dp(i).ne.dp(i-1))then
     if(ndp.ne.1)then
     write(lundsk,97)dp(i-1),avg
     ndp=1
     endif
    else
    cpml(i)=cpml(i)+cpml(i-1)
    ndp=ndp+1
```

```
      avg=cpml(i)/ndp
      go to 140
      endif
     endif
     if(i.ne.n)then
      if(dp(i).eq.dp(i+1))then
      go to 140
      endif
     endif
     write(lundsk,97)dp(i),cpml(i)
97   format(i4,1x,f9.3)
140  continue
     close(lundsk)
     end
     function numdas (month)
     dimension month (1500)
     numdas=int(-1*(.7+(1/(month(n)+1))))
     return
     end
```

DOSE

```
c This program calculates the whole body effective dose
c equivalent due to Po-210 based on urinary excretion data.
c The algorithm utilizes the metabolic parameters measured
c in the adult female baboon following intravenous administration
c of Po-210 citrate, references man data (ICRP 23), and the
c weighting factors for determining organ specific dose equivalent
c values published in ICRP 30.
c
c
      program dose
      character*38 xlabel,ylabel
      character*1 qm
      integer case,y,z,dptest
      integer dp(700)
      real cpm(700),cpmpt(700),pred(50,50)
      real ratio(50),forcst(700),eforcst(700)
      real eratio(50),ecpm(700),epred(50,50)
      real intpt(50,2)
      real lambda,input,livede,kidede,lngede
      data qm/''''/
      data xlabel/'Days Post First Sample'/
      data ylabel/'Cpm/mL Urine'/
      nint=1
      scale=1.62
```

```
   xstart=0.
   xorigin=0.
   lambda=0.0495
   elamb=0.0048
   write(*,*) 'Case Number:'
   read(*,200) case
200  format(i4)
   i=1
   open(1,file='a:dose.dat',status='old')
   rewind(1)
c
c Data is read in from a file prepared by program Omdos.
c
210  read(1,220,end=230) dp(i),cpm(i)
220  format(bn,i4,1x,f14.3)
   i=i+1
   goto 210
230  y=0
c
c The first data point is assigned to represent the first
c intake of Po-210.  A forcasted, or predicted, curve is then
c generated along with the associated error band based on the
c urinary Po-210 clearance measured in the baboon.
c
c The error band about the predicted curve is described
```

```
c by the following formula (Draper and Smith 1978):
c y=y(x)+-t*SE(regression)*sqrt(1/n+(((x(i)-x(avg)**2)/s(xx))+1)
c
c Where the count rate of the predicted curve falls below
c 0.1 cpm/mL, the forecasting is cut off and set equal to 0.1.
c
    do 235 m=1,i-1
    if(cpm(m).gt.0)then
    intpt(1,1)=dp(m)
    intpt(1,2)=cpm(m)
    ecpm(1)=sqrt(cpm(m)*20)/20
    goto 236
    endif
235  continue
236  do 240 j=m+1,i-1
    if(j.gt.m+1)then
    if(forcst(j-1).le.0.1)then
     forcst(j-1)=0.1
     forcst(j)=0.1
     eforcst(j)=0.1
     goto 12
    endif
    endif
    forcst(j)=cpm(m)*exp(-lambda*(dp(j)-dp(m)))
    eforcst(j)=1.99*0.129*sqrt((1/98)+(((dp(j)-dp(m)-23.005)**2)
```

```
     1          /53861.7)+1)
240  continue
c
c In the following section, the data points reflecting the
c occurrence of additional Po-210 intakes are identified.
c In iterative fashion, the algorithm proceeds from the
c second datum to the last datum performing a test of the
c means of the expected urinary excretion level (due to the
c most recent prior intake) and the measured urinary excretion
c level.  The t-distribution is utilized for this test.
c
     do 250 k=m+1,i-1
     forcmax=forcst(k)+eforcst(k)
     cpmmin=cpm(k)-(ecpm(k)*2)
     if(cpmmin.gt.forcmax)then
     nint=nint+1
     y=0
      do 252 j=k,i-1
     if(j.gt.k)then
     if(forcst(j-1).le.0.1)then
      forcst(j-1)=0.1
      forcst(j)=0.1
      eforcst(j)=0.1
      goto 252
     endif
```

```
      endif
       forcst(j)=cpm(k)*exp(-lambda*(dp(j)-dp(k)))
       eforcst(j)=1.99*0.129*sqrt((1/98)+(((dp(j)-dp(k)-23.005)**2)
     1          /53861.7)+1)
  252  continue
      intpt(nint,1)=dp(k)
      intpt(nint,2)=cpm(k)
      ecpm(nint)=sqrt(intpt(nint,2)*20)/20
      endif
  250 continue
c
c Significant differences in Po plating efficiency have
c been determined between spontaneous deposition out of raw
c urine (as done in the past) compared to wet ashed urine.
c The following section adjusts the identified intake points
c by application of the ashed/unashed Correction Function.
c The contribution (if any) of all prior intakes on an intake
c are determined and adjusted by multiplication with the
c proper time dependent CF value.
c
c The first intake is multiplied by the CF value at
c 5 days post intake.
c
      ratio5=10.47*exp(-0.0086*5)
      ecft5=2.021*0.193*sqrt((0.0238)+(((5-28)**2)/27198)+1)
```

```
      do 888 j=1,nint
      cpmpt(j)=intpt(j,2)
      if(j.eq.1)then
      ecpm(j)=intpt(j,2)*ratio5*sqrt(((ecpm(j)/cpmpt(j))**2)
     1        +((ecft5/ratio5)**2))
      intpt(j,2)=intpt(j,2)*ratio5
      endif
c
c The urinary elimination of Po after each intake is predicted.
c
      if(j.lt.nint)then
      do 251 m=j+1,nint
      dptest=intpt(m,1)-intpt(j,1)
      if(dptest.lt.250)then
      pred(j,m)=cpmpt(j)*exp(-lambda*(intpt(m,1)-intpt(j,1)))
      epred(j,m)=1.99*0.129*sqrt((1/98)+(((intpt(m,1)-intpt(j,1)
     1          -23.005)**2)/53861.7)+1)
      else
      pred(j,m)=0
      epred(j,m)=0
      endif
251   continue
      endif
      if(j.eq.1)then
      goto 888
```

```
      endif
c
c The CF values are determined for each intake from all prior intakes.
c CF values less than 1 are set equal to one.
c
      jj=j-1
      do 253 n=1,j-1
      if(pred(n,j).gt.0.1)then
      ratio(n)=10.47*exp(-0.0086*(intpt(j,1)-intpt(n,1)))
      eratio(n)=2.021*0.193*sqrt((1/42)+(((intpt(j,1)-intpt(n,1)
     1          -28)**2)/27198)+1)
      else
      pred(n,j)=0
      ratio(n)=1
      endif
       if(ratio(n).lt.1)then
       ratio(n)=1
       endif
253   continue
c
c The magnitude of the intake points are adjusted by
c incorporating the proper CF ratios to the portion
c of each point influenced by prior intakes.
c
      cpmcalc=pred(1,j)*ratio(1)
```

```
      ecalc=0
      if(pred(1,j).gt.0)then
      if(ratio(1).gt.1)then
      ecalc=cpmcalc*sqrt(((epred(1,j))**2)+
     1       ((eratio(1)/ratio(1))**2))
      endif
      endif
       do 254 n=2,j-1
       cpmcalc=cpmcalc+((pred(n,j)-pred(n-1,j))*ratio(n))
      diff=pred(n,j)-pred(n-1,j)
      if(diff.gt.0)then
      errint=sqrt(epred(n,j)**2+epred(n-1,j)**2)
      errint=diff*ratio(n)*sqrt(((errint/diff)**2)+
     1       ((eratio(n)/ratio(n))**2))
      ecalc=sqrt(ecalc**2+errint**2)
      endif
  254 continue
c
c That portion of an intake not resulting from a prior intake
c is multiplied by the CF at 5 days post intake.
c
      den=intpt(j,2)-pred(j-1,j)
      if(epred(j-1,j).gt.0)then
      ecpm(j)=sqrt(ecpm(j)**2+epred(j-1,j)**2)
      ecpm(j)=den*ratio5*sqrt(((ecpm(j)/den)**2)
```

```
     1       +((ecft5/ratio5)**2))
      ecpm(j)=sqrt(ecalc**2+ecpm(j)**2)
      intpt(j,2)=cpmcalc+((intpt(j,2)-pred(j-1,j))*ratio5)
      else
      intpt(j,2)=cpmcalc+((intpt(j,2)-pred(j-1,j))*ratio5)
      ecpm(j)=intpt(j,2)*sqrt(((ecpm(j)/cpmpt(j))**2)
     1       +((ecft5/ratio5)**2))
      endif
888  continue
c
c The dose equivalent is to be calculated from Q, the time
c integral of internal contamination.  Q is determined by
c integrating the urinary excretion function (the baboon
c model is used).  The integrals from each intake are determined
c and summed.
c
      q=intpt(1,2)/lambda
      eq=q*sqrt(((ecpm(1)/intpt(1,2))**2)+((elamb/lambda)**2))
      do 265 j=2,nint
      dptest=intpt(j,1)-intpt(j-1,1)
      if(dptest.lt.250)then
      forcst(j)=intpt(j-1,2)*exp(-lambda*(intpt(j,1)-intpt(j-1,1)))
      eforcst(j)=forcst(j)*sqrt(((ecpm(j-1)/intpt(j-1,2))**2)
     1       +(exp(2*lambda)*(elamb**2)))
      if(forcst(j).lt.0.1)then
```

```
      forcst(j)=0
      eforcst(j)=0
      endif
      else
      forcst(j)=0
      eforcst(j)=0
      endif
      if(intpt(j,2).gt.forcst(j))then
      input=intpt(j,2)-forcst(j)
      einput=sqrt((ecpm(j)**2)+(eforcst(j)**2))
      xq=input/lambda
      exq=xq*sqrt(((einput/input)**2)+((elamb/lambda)**2))
      q=q+xq
      eq=sqrt((eq**2)+(exq**2))
      endif
265   continue
      close(1)
c
c Parameters needed to construct a plot of the data are calculated.
c
      xfinish=dp(i-1)
      xfinish=int((xfinish+100)/100)*100
      xmajor=-(xfinish/5)
      ystart=10.
      do 110 j=1,i-1
```

```
      if(cpm(j).lt.ystart)then
      ystart=cpm(j)
      m=j
      endif
  110 continue
      if(ystart.le.0.1)then
      ystart=0.001
      elseif(ystart.le.1)then
      ystart=0.01
      else
      ystart=0.1
      endif
      ymajor=10.0
      yorigin=ystart
      yfinish=0.
      do 120 j=1,i-1
      if(cpm(j).gt.yfinish)then
      yfinish=cpm(j)
      endif
  120 continue
      j=0
  130 if(yfinish.ge.1)then
      yfinish=yfinish/10.
      j=j+1
      go to 130
```

```
      endif
      yfinish=int(yfinish+1)*(10**j)*10
c
c The variable q has units cpm-day/mL urine.
c By multiplying by the proper constants,
c clearance half-times, and organ partition coefficients,
c the EDE can be calculated for individual organs.
c These constants are:
c 1400 +- 530 ml/day
c 86400 dis/day-Bq
c 5.305 MeV/dis
c 1.6E-13 J/MeV
c 1000mGy/Gy
c dpm/0.5cpm=counter Efficiency
c Bq/60 dpm
c kg-Gy/J
c 1/f(u); f(u)=0.377 +- 0.040 based on NYU baboon study
c 1/Unashed deposition recovery; R=0.861 +- 0.119
c The calculations below utilize ICRP 30 weighting factors
c and a quality factor of 20 to derive EDE in mSv.
c
      cf=1.054342E-2
      ecf=cf*sqrt(((eq/q)**2)+((530/1400)**2)+((0.040/
     1     0.377)**2)+((0.119/0.861)**2))
      erterm=((eq/q)**2)+((ecf/cf)**2)
```

```
      livede=q*0.286*cf*0.06*20/(0.045*1.8)
      eliv=livede*sqrt(erterm+((0.002/0.045)**2)+((0.245/
     1     1.8)**2)+((0.01/0.286)**2))
      kidede=q*0.072*cf*0.06*20/(0.028*0.31)
      ekid=kidede*sqrt(erterm+((0.004/0.028)**2)+((0.02/
     1     0.31)**2)+((0.006/0.072)**2))
      splede=q*0.0058*cf*0.06*20/(0.028*0.18)
      espl=splede*sqrt(erterm+((0.004/0.028)**2)+((0.06/
     1     0.18)**2)+((0.0021/0.0058)**2))
      panede=q*0.0031*cf*0.06*20/(0.1*0.028)
      epan=panede*sqrt(erterm+((0.004/0.028)**2)+((0.02/
     1    0.1)**2)+((0.0004/0.0031)**2))
      adrede=q*0.00048*cf*0.06*20/(0.014*0.027)
      eadr=adrede*sqrt(erterm+((0.008/0.027)**2)+((0.003/
     1     0.014)**2)+((0.00007/0.00048)**2))
      lngede=q*0.009*cf*0.12*20/(0.47*0.0154)
      elng=lngede*sqrt(erterm+((0.0061/0.0154)**2)+((0.11/
     1     0.47)**2)+((0.005/0.009)**2))
c
c The assumption has been made that ovary Po retention
c approximates testis Po retention.
c
      gonede=q*0.00028*cf*0.25*20/(0.035*0.014)
      egon=gonede*sqrt(erterm+((0.006/0.014)**2)+((0.007/
     1     0.035)**2)+((0.002/0.028)**2))
```

```
c Bone surface and red marrow dosimetry done in accordance
c with the ICRP 30 recommendations.
      bsede=q*0.064*cf*0.03*0.25*20/(0.02*0.12)
      ebs=bsede*sqrt(erterm+((0.002/0.02)**2)+((0.03/
     1     0.12)**2)+((0.003/0.064)**2))
      rmede=q*0.032*cf*0.12*0.5*20/(0.02*1.5)
      erm=rmede*sqrt(erterm+((0.002/0.02)**2)+((0.33/
     1     1.5)**2)+((0.0015/0.032)**2))
      thyede=q*0.000069*cf*0.03*20/(0.014*0.02)
      ethy=thyede*sqrt(erterm+((0.009/0.014)**2)+((0.008/
     1     0.02)**2)+((0.0006/0.0069)**2))
      wbede=livede+kidede+splede+panede+adrede+lngede+
     1     gonede+bsede+rmede+thyede
      ewb=sqrt(eliv**2+ekid**2+espl**2+epan**2+eadr**2+
     1    elng**2+egon**2+ebs**2+erm**2+ethy**2)
c
c The results are written to file case.dos on drive a
c
      open(2,file='a:case.dos ',status='new')
      write(2,320)
320   format(' ')
      write(2,330)case
330   format('DOSIMETRY REPORT: CASE # ',i4)
      write(2,320)
      write(2,340)
```

```
340  format('ORGAN',9X,'EFFECTIVE DOSE EQUIVALENT')
     write(2,342)
342  format(20x,'(mSv +- 1sd)')
     write(2,320)
     write(2,350)livede,eliv
350  format('LIVER',12X,F7.0,1X,'+- ',F7.0)
     write(2,360)kidede,ekid
360  format('KIDNEY',11x,f7.0,1x,'+- ',f7.0)
     write(2,370)splede,espl
370  format('SPLEEN',11x,f7.0,1x,'+- ',f7.0)
     write(2,380)panede,epan
380  format('PANCREAS',9x,f7.0,1x,'+- ',f7.0)
     write(2,390)adrede,eadr
390  format('ADRENAL GLAND',4x,f7.0,1x,'+- ',f7.0)
     write(2,400)lngede,elng
400  format('SYSTEMIC LUNG',4x,f7.0,1x,'+- ',f7.0)
     write(2,410)gonede,egon
410  format('GONADS',11x,f7.0,1x,'+- ',f7.0)
     write(2,420)bsede,ebs
420  format('BONE SURFACES',4x,f7.0,1x,'+- ',f7.0)
     write(2,425)rmede,erm
425  format('RED MARROW',7x,f7.0,1x,'+- ',f7.0)
     write(2,430)thyede,ethy
430  format('THYROID',10x,f7.0,1x,'+- ',f7.0)
     write(2,320)
```

```
      write(2,450)wbede,ewb
450   format('WHOLE BODY    ',F9.0,1x,'+- ',f7.0)
      close(2)
c
c A file for plotting the data is written to drive a
c
      open(3,file='a:plot.omn ',status='new')
      write(3,91)qm,case,qm
91    format(a1,18x,'ID# ',i4,a1)
      write(3,92)qm,xlabel,qm
92    format(a1,a38,a1)
      write(3,92)qm,ylabel,qm
      write(3,93)scale
93    format(f4.2)
      write(3,94)xstart,xfinish,xmajor,xorigin
94    format(f2.0,1x,f7.0,1x,f6.0,1x,f2.0)
      write(3,95)ystart,yfinish,ymajor,yorigin
95    format(f6.3,1x,f9.1,1x,f4.1,1x,f6.3)
      i=i-1
      write(3,96)i
96    format(i4)
      do 590 j=1,i
      write(3,600)dp(j),cpm(j)
600   format(i4,1x,f14.3)
590   continue
```

```
      write(3,610)nint
  610 format(i3)
      do 620 j=1,nint
      write(3,630)(intpt(j,m),m=1,2)
  630 format(f5.0,2x,f14.3)
  620 continue
      end
```

MNDOSE

```
clear
input "case number" to cn
set index to d:poli
seek cn
set safety off
copy to a:dp.dat rest fields case,date,cpm,volume for case=cn while case=cn sdf
set safety on
run omdos
run dose
filnam=str(cn,4,0)+".dos"
filnam2=str(cn,4,0)+".omn"
run ren a:case.dos &filnam
run ren a:plot.omn &filnam2
```

INSTRUCTIONS

The urine bioassay data base is put on a hard disk of a PC. The sorted data file is called "pols.dbf." An indexed version of the data file, called "poli.ndx" must also reside on the hard disk. The files dose.exe, omdos.exe, omdos2.exe, mndose.prg, and mndose2.prg are put on the hard disk within the dBase subdirectory. Files "data.dat" and "dose.dat" must appear on a floppy disk in drive a. These are files that will be rewritten during the execution of OMDOSE and DOSE. For the first execution of the job string, the content of data.dat and dose.dat are not important, as long as the files reside on the floppy.

Enter dBase III+ and hit the escape key. This enables the dot prompt. Load the data file by entering "use d:pols" (or c:pols depending on proper drive specification). Enter "do mndose" at the dot prompt to calculate the effective whole body and organ specific systemic dose equivalent values for an individual worker. The user will be asked twice to input a 1-4 digit worker identification number. Enter the number each time and hit the carraige return. When the program is completed, a file with the name "####.dos" (where #### is equal to the worker identification number) will reside on the floppy disk in drive a. A file with the name "####.omn" will also be written to the floppy disk. It can be used to graph the excretion data (without outliers) when utilized with the graphics software package Omniplot. In addition to plotting the time sequence of urinary Po excretion, the intake points used to calculate the time integral of internal contamination (after adjustment with the correction function) are highlighted.

The file "mndose2.prg" is identical to "mndose.prg" with one exception. The mndose2 program uses omdos2.exe instead of omdos.exe. This applies to worker identification numbers 144, 2313, 3552, 4474, 5974, 6628, 8076, and 9835. Some data developed for these individuals warrant volume corrections because of some 24-hour

(rather than spot) sampling. Due to the use of the same coding characters in the original data base for multiple purposes, the portion of the algorithm which makes these corrections could not be included in Omdos.

APPENDIX G. Sample Dosimetry Output Tables

DOSIMETRY REPORT: CASE #1424

ORGAN	WEIGHTED DOSE EQUIVALENT (mSv ± 1sd)
LIVER	85. ± 58.
KIDNEY	188. ± 130.
SPLEEN	26. ± 22.
PANCREAS	25. ± 18.
ADRENAL GLAND	29. ± 22.
SYSTEMIC LUNG	51. ± 57.
GONADS	47. ± 38.
BONE SURFACES	71. ± 52.
RED MARROW	23. ± 16.
THYROID	2. ± 2.
TOTAL SYSTEMIC	548. ± 172.

DOSIMETRY REPORT: CASE #5604

ORGAN	WEIGHTED DOSE EQUIVALENT (mSv ± 1sd)
LIVER	215. ± 159.
KIDNEY	476. ± 357.
SPLEEN	66. ± 59.
PANCREAS	63. ± 49.
ADRENAL GLAND	72. ± 60.
SYSTEMIC LUNG	129. ± 150.
GONADS	119. ± 103.
BONE SURFACES	180. ± 140.
RED MARROW	58. ± 44.
THYROID	6. ± 6.
TOTAL SYSTEMIC	1384. ± 465.

DOSIMETRY REPORT: CASE #6175

ORGAN	WEIGHTED DOSE EQUIVALENT (mSv ± 1sd)
LIVER	37. ± 47.
KIDNEY	81. ± 104.
SPLEEN	11. ± 15.
PANCREAS	11. ± 14.
ADRENAL GLAND	12. ± 16.
SYSTEMIC LUNG	22. ± 34.
GONADS	20. ± 27.
BONE SURFACES	31. ± 40.
RED MARROW	10. ± 13.
THYROID	1. ± 2.
TOTAL SYSTEMIC	236. ± 132.

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