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# HEALTH CONSIDERATIONS FOR WORKERS EXPOSED TO PLUTONIUM

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The story about radiobiological studies in search of the information needed to protect people working with plutonium (Pu) during and after World War II is an exciting bit of occupational health history. Discovered in trace quantities by G.T. Seaborg and colleagues in February 1941, this man-made transuranium metal was being handled in kilogram quantities in 1945 by wartime workers who were developing the atomic bomb. Only a year earlier, Seaborg himself suggested, in January 1944, that due to its alpha radiation and long life, "The physiological hazards of working with plutonium and its compounds may be very great."[16] Until then, not enough Pu had been made to see or to worry about. Seaborg suggested that a highest priority program be initiated to study this problem as soon as possible. Consequently, a portion of the first small batch of Pu produced was immediately made available for radiobiological studies in early February 1944. The results of the first experiments of Pu in rodents by J.G. Hamilton (University of California, Berkeley) were mentioned in the monthly report of the Metallurgical Laboratory (University of Chicago) for February 1944.[2] A special symposium on the Pu biological research project was held at the annual meeting of the Radiological Society of North America in 1946.[10]

It is interesting to observe that today the discussions, public concerns, and legal battles over health risks presented by Pu are not only vigorous but also accelerating. Most of the time it seems difficult, if not impossible, to bring the technical results from extensive research efforts to bear on these questions.

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Our knowledge of the biochemistry, pathophysiology, dosimetry, and radiobiology of Pu has increased enormously during the intervening 45+ years since the first experiments. For the first time in the history of science and industry, extensive epidemiologic studies are being conducted on the majority of all people in this country who have worked with a material since its introduction and before anyone has had any known acute or chronic illness from exposure to it.

## PLUTONIUM STUDIES IN ANIMALS

Experimental studies in rodents and dogs during 1944–1945 searched for the levels of Pu that could cause acute, lethal, and subacute effects.[27] These studies also looked at the uptake pathways and distribution in the body, effects in organs, and excretion mechanisms. Contrary to some common perceptions, Pu was found to be less "toxic" on an acute $LD_{50}$ basis than the "supertoxic" chemicals (e.g., botulinus toxin, diphtheria toxin, curare, strychnine).[26] (The early radiobiology literature uses "acute toxicity" as a term to compare $LD_{50}$ values of radionuclides or chemicals. Use of this terminology is unfortunate, because it confuses chemical toxicity with acute radiation effects for radionuclides like Pu. The radiological hazard of Pu far exceeds any known chemical hazard of heavy metals.) The main routes to internal deposition in animals were found to be absorption from contaminated wounds or by inhalation of respirable particles. Absorption through the gastrointestinal tract was noted to be very low (for humans it is now considered to be $10^{-3}$–$10^{-5}$ depending on the chemical form[14]). Essentially no absorption was observed after contamination on intact skin.

Major research efforts were also expended, especially in the post-World War II years, on the comparative hazards of various radionuclides. It was soon apparent from experiments in rodents that Pu was about 15 times more acutely "toxic" than radium-226 ($^{226}Ra$) for acute (lethal) effects based on the radioactivity injected per unit body weight. Such studies played an important role in setting the first protective guidelines for worker protection.

Research interest turned immediately to a concern for late health effects, especially cancer, that may result from Pu deposition in the body. For example, a 1946 report by Brues et al.[6] reported on cancers, including osteogenic sarcoma, that were found in rodents exposed to Pu. The results of that study were also published in the proceedings of the 1946 Pu Symposium.[17]

Animal studies on the late effects of Pu have gone on at U.S. universities, national laboratories, and other research laboratories around the world for nearly five decades. No summary does justice to the details of this mass of technical work, but fortunately there are several superb books that put much of the information in easy reach for the reader. Hodge et al.[11] produced a reference that is still valuable even though it was published almost 20 years ago. Stannard, in his nearly 2,000-page history of radiobiology,[28] has brought together in one book the major results of research on all the internal emitters. This monumental work covers the period of World War II through the end of the 1970s. Thompson[29] summarizes four decades of investigation of the effects of ionizing radiation in dogs, including the effects of internal deposition of Pu and other radionuclides. The bibliography lists over 1,100 citations.

Pu was identified as a bone seeker in initial radiobiological studies.[27] Hamilton[10] was the first to recognize that Pu deposits on bone surfaces. In this respect, it differs from radium, which deposits more uniformly throughout bone. Liver is the other organ in which higher concentrations of injected Pu are

consistently found. Exposure by inhalation of relatively insoluble particles of Pu, e.g., $^{239}PuO_2$, results in retention of a significant proportion (50–90%) of the particles in the lung and associated lymph nodes for years. The portion of particulate Pu that becomes soluble in body fluids is distributed by the systemic circulatory system primarily to bone (50%) and liver (30%).[14]

It is thus not surprising that animal experiments showed excess cancers primarily in bone, lung (after inhalation exposures only), and liver.[28,29] Bone tumors in dogs were most frequently osteogenic sarcomas arising in trabecular bone. Types of liver tumors, in descending frequency, were bile duct adenomas, bile duct carcinomas, various sarcomas, and, infrequently, hepatic cell tumors. Liver tumors usually occurred late in the dog's life and were a less common cause of death than were bone tumors. Lung tumors occurred principally after inhalation of insoluble Pu particles, e.g., high-fired $^{239}PuO_2$. The more soluble Pu chemical forms, e.g., $^{239}Pu(NO_3)_4$ or $^{238}PuO_2$, resulted in bone tumors more often than in lung tumors.

About 3–7% of Pu deposited in human bone is located in the bone marrow,[21] which raises a question about the risk of inducing leukemias or myeloproliferative disorders. These diseases are not a significant finding in the dog studies[29]; however, high doses of Pu result in considerable damage to hematopoiesis and bone marrow function in mouse experiments.[31] Some radiobiologists consider the leukemogenic risk from plutonium to be significant[30]; however, animal data do not support this viewpoint strongly.

## HISTORY OF PROTECTIVE GUIDELINES

Use of health protective standards in Pu work evolved rapidly during World War II as a result of both early recognition of the hazard and the immediate radiobiological studies. Initially, provisional and tentative standards were used at the several facilities using Pu in the Manhattan Project.[16] By March 1945, officials responsible for the health and safety of workers in the project judged that a maximum allowable Pu body burden would be 1 $\mu$g (0.06 $\mu$Ci or 2,200 Bq). Air and water tolerance concentrations were also derived for workers and the general population.

### Standard Based on Radium Data

The allowable Pu body burden was based on a comparison of energy deposition from Pu and 0.1 $\mu$Ci of radium with a safety factor of 5 or 10 as a precaution against the difference in distribution between radium and Pu in bone.[15] The value of 0.1 $\mu$Ci of radium was recommended by the National Bureau of Standards (Handbook 27) in 1941 as the maximum permissible internal deposit. The clinical study of 3 persons exposed to $^{226}Ra$ and $^{228}Ra$ on which this recommendation was based, plus 27 other cases, was fully described by Aub et al.[3]

In 1949, a meeting of knowledgeable scientists from the United States, the United Kingdom, and Canada took place at Chalk River, Ontario, Canada, to review the Pu biological data. Judgments on the risk of Pu were still based primarily on the toxicity ratio of plutonium to radium. These deliberations led to the establishment of 0.04 $\mu$Ci (1,480 Bq) as the maximum permissible amount of $^{239}Pu$ fixed in the body.[16] This guideline was used for protection of workers until the early 1980s, when gradual implementation of new radiation protection concepts using calculated organ doses began.

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### Standard Based on Dosimetry

In 1977, the International Commission on Radiological Protection (ICRP) produced Publication 26,[12] in which it described a new radiation protection concept. In it, the maximum occupational dose guideline is based on a calculated effective dose equivalent by the use of organ doses and weighting factors. The overall guideline for occupational exposure is not to exceed an effective whole-body dose equivalent of 50 mSv (5 rem) annually from all types of occupational radiation exposure, internal and external.

Between 1979 and 1988, a series of reports known collectively as ICRP Publication 30 contained the derived annual limits of intakes (ALI) of radionuclides for the protection of workers. The current revision of ALIs for plutonium was published in 1988 (ICRP 30)[13] and is based on current understanding of the behavior of Pu in the body as given in ICRP Publication 48 (ICRP 48).[14]

Although the conceptual basis for limiting exposure to Pu has changed drastically, from a practical standpoint, the limit on internal deposition is not so greatly changed. The ICRP protection concept requires calculations of organ doses. For Pu, these doses are uncertain, because the internal distribution of Pu varies greatly from one case to the next and the microdistribution of dose within organs is poorly understood. Therefore, the effective dose equivalent for Pu is normally calculated using standard models as recommended in ICRP Publication 30. One of the advantages of the ICRP dose concept is the ability to add internal and external radiation doses for radiation protection purposes.

Over the past decade, the ICRP concept has gradually found its way into national regulatory standards. This revised worker protection guidance was placed into effect for U.S. Department of Energy facilities at the beginning of 1989. The Nuclear Regulatory Commission has developed similar regulatory guidance, which is planned for implementation in the near future.

New ICRP recommendations were published in the spring of 1991.[15] The occupational radiation exposure guideline limit will be reduced to 20 mSv (2 rem) per year (external plus internal radiation doses). This limit may be averaged over 5 years, but there is a further provision that the dose should not exceed 50 mSv (5 rem) in any single year.

## PLUTONIUM STUDIES IN MAN

The above synopsis of radiobiological studies on the biological hazards of Pu and the brief history of protective guidelines point up that the start of such efforts occurred almost simultaneously with the earliest handling of this material. It was not the witness of ill health or disease among Pu workers that triggered the studies, as is common in the history of occupational medicine. There is no series of case studies to demonstrate the risk of Pu exposure.

Protection from Pu exposure was a major concern of those responsible for protecting the health of workers at Pu facilities. The protective guidelines that regulated Pu exposures in this industry were based on a limit judged to be as safe as the limits for other types of ionizing radiation. Admittedly, protection methods and equipment have improved greatly through the years, but the concern and the effort to control and eliminate exposure were present from the beginning.

The above activities, if based on good risk estimates and effective implementation, should influence the expectation of findings in epidemiologic studies of Pu-exposed workers. Under controlled working conditions, risk from small exposures within the guidelines will be difficult, if not impossible, to detect by epidemiologic

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methods. Accidental exposures to air releases of Pu particles or to contaminated wounds did occur, but the numbers of workers exposed in excess of the guideline limits are surprisingly small.

Interestingly, the first long-term medical surveillance of Pu workers was started only a few years after the first exposures. The study consisted of the workers who had helped to build the first atomic bomb at Los Alamos, New Mexico, during World War II. Wright Langham and Louis Hempelmann had responsibility for the health and safety of those who did this work at Los Alamos in 1944–1945. In 1951, Langham and Hempelmann traced and located 26 workers who were judged to have had the highest Pu exposures. Most of them had left Los Alamos immediately after the war. The objective of the study was simple. Were the workers still healthy or not? Medical examinations were obtained on all. No health problems attributable to Pu exposure were found. It was the start of a small but important study that is continuing 40 years later. Perhaps the most important outcome of this study was the recognition in the mid-1970s that epidemiologic studies needed to be extended to a large segment of Pu workers in the U.S. nuclear industry.

Epidemiologists at Los Alamos National Laboratory have been collecting and analyzing data on the long-term health experience of Pu workers. Table 1 lists the number of workers employed from the onset of operations until 1978–1979 for the facilities under study: Los Alamos National Laboratory and Zia Co., Los Alamos, New Mexico; the Rocky Flats plant near Denver, Colorado; and Mound facility near Dayton, Ohio. Data have been collected on all workers at these locations, whether or not involved in Pu operations, and include more than 54,000 workers. These workers include a majority (over 80%) of all persons involved in Pu work in the United States. Vital status of the persons in these cohorts is currently known with about 95% completeness to the end of 1983. In the future, data on a smaller number of Pu workers at the Hanford Site, Oak Ridge National Laboratory and Savannah River facilities will also be obtained from other ongoing epidemiology studies to be used in pooled data analyses.

Table 2 lists the number of white males in these cohorts who have been exposed to radiation from external radiation doses and internal Pu depositions. Arbitrary levels of > 1 rem external and > 74 Bq (2 nCi) Pu deposition are used to define an exposed worker. By this definition, about 20% of the cohort have been exposed to external radiation and about 5.6% to internal Pu deposition. White males are listed, because they compose the largest number of workers involved in exposure at these plants. A much smaller proportion of females in the work force were exposed during the period of these studies.

To monitor workers for potential Pu intake, scheduled periodic urine samples are measured for Pu excretion. This general method has been used since 1944 and has proved to be the most sensitive biological indicator available. Persons with

***TABLE 1.*** Cohorts Included in the Study of Health Effects from Plutonium*

| Facility | Work Period | Cohort Size |
|---|---|---|
| Los Alamos Lab | 1943–78 | 23,200 |
| Los Alamos Zia | 1946–78 | 14,700 |
| Mound | 1943–79 | 6,900 |
| Rocky Flats | 1951–79 | 9,500 |

* Plutonium workers from Hanford, Oak Ridge, and Savannah River will be included in pooled analyses.

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*TABLE 2.* Radiation-exposed White Males in Cohorts to Study Effects from Plutonium

| Facility | Total | External > 1 Rem | Internal Pu > 2 nCi |
|---|---|---|---|
| Los Alamos Lab | 16,114 | 2,300 | 276 |
| Los Alamos Zia | 13,465 | 487 | 126 |
| Mound | 4,847 | 1,364 | 280 |
| Rocky Flats | 7,162 | 3,354 | 1,125 |
| Total | 41,588 | 7,505 | 1,807 |

significant exposures to Pu will excrete it in urine throughout their lifetime. Thus, urinalysis for Pu as a long-term exposure measure is unique for its monitoring capability compared with measurement of most occupational hazards.

Direct in vivo measurement of Pu in the lungs, using special low-energy radiation detectors, has also been available for about two decades. The minimum detectable activity by chest counts is higher (poorer) than by urine excretion methods, except for detection of insoluble Pu particles deposited in the lungs. Other important measurement techniques to detect possible exposures to workers in the workplace are constant air measurements made in the workplace and monitoring for skin and wound contamination.

The monitoring and detecting of worker exposure to Pu have been good, according to results from postmortem tissue measurements for Pu. The precision of internal Pu estimation by urine excretion measurements has improved through the years but is still limited by lack of knowledge of the chemical forms of Pu particles inhaled, particle sizes inhaled, and variations in individual Pu urine excretion rates. Thus, identification of the exposed individuals in the cohorts is believed to be very good; however, the precision of internal deposition estimation may vary by a factor of three or four, and occasionally more.

About one-quarter of the persons working at these facilities have been monitored at least once by means of a urine sample. These samples are requested selectively from workers whose work area or history indicates Pu exposure is possible. Samples are usually submitted on a regular schedule. A rather remarkable number in Table 3 is that only 50 persons (0.0036 of those monitored) are estimated to exceed 1,480 Bq (40 nCi) Pu deposition, which was the lifetime maximum permissible body burden protective guideline used during most of this period.

*TABLE 3.* Numbers of Plutonium-monitored and Plutonium-exposed Persons in the National Plutonium Workers Study

| Cohort | Persons Monitored | Latest Estimate (nCi) | | | |
|---|---|---|---|---|---|
| | | < 2 | 2–10 | 11–40 | 40+ |
| Los Alamos Lab | 4,428 | 4,119 | 237 | 59 | 13 |
| Los Alamos Zia | 3,044 | 2,913 | 18 | 12 | 1 |
| Mound* | 1,402 | 1,122 | 96 | 63 | 21 |
| Rocky Flats† | 4,872 | 3,747 | 1,042 | 67 | 15 |
| Total | 13,746 | 11,901 | 1,594 | 201 | 50 |

* Numbers are currently under revision.
† Includes only males.

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Three papers on the results of mortality studies of the Rocky Flats cohort have been published at different stages of data collection.[35,39,40] A study of mortality among females employed by Los Alamos National Laboratory has been completed.[37] These studies are the only ones that are currently available for the worker cohorts at these Pu handling facilities. Analyses are being conducted now on Los Alamos Laboratory and Zia Co. cohort data, but results are not yet available. Several special studies of Los Alamos workers, however, add importantly to the body of information.[1,32,34,36]

Beral et al.[4] have reported their study of 22,552 workers employed by the Atomic Weapons Establishment in England between 1951 and 1982. There were 3,742 workers within this cohort who were monitored for possible internal exposure to Pu. No Pu dose information was given or used in the analyses.

## MORTALITY OF PLUTONIUM WORKERS

Mortality data on all causes of death and all cancer deaths for both all-worker cohorts and special Pu-exposed groups at facilities under study by the Los Alamos group are summarized in Table 4. Standardized mortality ratios (SMR) for all causes of death in the cohorts (unexposed and exposed workers) were all significantly less than 100. A ratio below 100 means the mortality rate of the study cohort is less than that of the comparison group (U.S. general population in these studies). Significantly low SMRs or standardized incidence ratios (SIRs) are usually attributed to a large healthy worker effect, which is frequently observed in studies of employed populations if no large health impact from the occupation is present.

*TABLE 4.* Standardized Mortality/Incidence/Rate Ratios for Worker Cohorts from Pu Handling Facilities and for Pu-exposed Worker Groups

| Study | Sex[a] | All Causes | All Cancers | Ref |
|---|---|---|---|---|
| | | Standardized Mortality Ratios[b] | | |
| Cohort mortality | | | | |
| Los Alamos | WF | 76 (69,84)[c] | 78 (65,92) | 37 |
| Mound | WM | 89 (83,95)[d] | 91 (78,107) | 38 |
| Rocky Flats | WM | 62 (57,68)[d] | 71 (59,84) | 39 |
| Pu-exposed worker mortality | | | | |
| Los Alamos (N = 26) | WM | 41 (11,104)[c] | 45 (1,252) | 33 |
| Los Alamos (N = 224) | WM | 76 (69,84)[c] | 78 (65,92) | 36 |
| | | Rate Ratios[e] | | |
| Los Alamos (N = 26) | WM | .69 (.25,1.90)[c] | .82 (.11,6.10) | 33 |
| Rocky Flats | WM | 1.14 (.91,1.43)[f] | 1.01 (.62,1.66) | 39 |
| Cohort Incidence | | Standardized Incidence Ratios[g] | | |
| Los Alamos (1969-79) | WM | | 60 (46,78)[c] | 1 |
| | WF | | 121 (83,171)[c] | 1 |

[a] WF = white female; WM = white male.
[b] Based on U.S. general population mortality unless otherwise indicated.
[c] 95% confidence intervals.
[d] 90% confidence intervals.
[e] Rate ratio for Pu-exposed workers relative to contemporary unexposed Los Alamos workers.
[f] Rate ratio for Pu-exposed workers relative to unexposed Rocky Flats workers using a 2-year cancer induction time.
[g] Relative to New Mexico Tumor Registry cancer incidence data.

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The second section of Table 4 consists of data on the mortality of Pu-exposed workers at Los Alamos and Rocky Flats. Again, there is no evidence of significant excess of deaths from all causes or all cancers. Two of the studies used rate ratios to compare mortality rates of Pu-exposed workers with those of unexposed workers at the same facility. If the mortality rates of exposed and unexposed workers are equal, the rate ratio is 1.0. If the mortality rate of the exposed exceeds the unexposed, the rate ratio is above 1.0. This technique has an advantage over using an external comparison with state or national rates, because the employment standards for the exposed and unexposed persons are the same. This procedure effectively eliminates the healthy worker effect. Readers should note that the rate ratio from the Rocky Flats Pu-exposed-worker data for all causes of death is 1.14 (90% CI = 0.91,1.43). If 5-year and 10-year cancer induction times are used, the standardized rate ratios for all causes of death become significantly elevated, at 1.33 (CI = 1.05,1.68) and 1.39 (CI = 1.04,1.87), respectively.[39] Persons exposed to external radiation (> 1 rem) in Rocky Flats did not exhibit elevated rate ratios as the Pu-exposed workers did. Interpretation of this interesting observation would be strengthened if the finding is confirmed in other, future cohort studies.

The Beral et al. study[4] of 3,742 British workers monitored for possible Pu exposure found an SMR of 82 for all causes of death except malignant neoplasms and 81 for all malignant neoplasms. The rate ratios relative to other workers with radiation records were 1.11 and 1.10, respectively, and were not statistically significant.

## CANCER IN PLUTONIUM WORKERS

The following sections discuss specific cancers of special interest to the study of Pu hazards, with emphasis on the findings to date in human epidemiology. It anticipated that the induction times for Pu-induced cancers are likely to be very ng, probably in excess of 30 years. Epidemiologic research studies are continuing .d will record such events as they unfold.

### Bone Cancer

Plutonium was identified as a bone seeker in the first biological experiments in animals. Bone cancers, mostly osteogenic sarcomas, are a prominent finding in dogs with internal systemic deposition of Pu.[29] These tumors almost always originate in trabecular bone. The lowest radiation dose suspected of inducing bone sarcoma in animals may be of interest. In beagle experiments, 1 in a group of 20 dogs injected with low doses of $^{239}$Pu died of a bone sarcoma. The average skeletal dose for this dog was estimated to be 0.02 Gy (2 rad).[19,20]

None of the worker cohort overall studies have revealed significantly elevated SMRs from bone cancer. There are no bone cancer deaths present in the Pu-exposed (defined as > 74 Bq [> 2 nCi] deposition) workers in the Rocky Flats study.[39]

One of the 26 Manhattan Project Pu workers exposed at Los Alamos developed symptoms from an osteogenic sarcoma of the sacrum in late 1988 and died of the disease in 1990.[33] It appears that this is the first case in which a bone sarcoma has been observed in a person exposed to Pu. The worker was a Pu chemical operator in 1945-1946, and Pu exposure was mostly by inhalation, but the worker had had one contaminated wound treated by excision. The activity in the excised tissue was relatively low, being reported as 1,640 counts per minute. The estimate of $^{239}$Pu deposition at the end of this worker's life, using urine excretion measurements, is 560 Bq (15 nCi)

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The incidence of bone cancer in humans is ordinarily low. In a group of 26 adult males over a 40+-year period, the likelihood is only about 1% that a bone cancer would occur.

The origin of this tumor in the sacrum is also noteworthy. This anatomical location is an unusual site for a bone sarcoma. In humans, only about 15% of naturally occurring bone sarcomas have their primary site in the axial skeleton (head, vertebrae, sacrum/pelvis, ribs, and sternum).[25] It is noteworthy that in dogs exposed to Pu, 19 of 24 bone tumors (79%) were located in the axial skeleton.[7,23] In another series, 24 of 31 bone tumors (77%) originated in the axial skeleton in Pu-injected dogs.[5] It should be noted that distribution of bone tumors in dogs may differ from that in humans. For example, after $^{226}$Ra injection of adult dogs, 11 of 26 bone tumors (44%) occurred in the axial skeleton,[5] whereas among humans the anatomical distribution of bone tumors in radium-exposed persons is not significantly different from natural bone tumor distribution, i.e., about 15% of tumors occur in the axial skeleton.[25]

The latent period from time of exposure (1945) until clinical appearance of this human bone tumor (1988) was 43 years. In dogs, the mean survival period after time of exposure is about 13 years in both control and low-exposure groups. Whether such difference in survival after exposure and length of irradiation time is an important factor in the Pu risk to man is unknown. This study of the 26 Manhattan Project Pu workers has the longest period of follow-up of all plutonium worker studies to date. The bone tumor finding points up the need for lengthy follow-up of persons exposed to internal alpha emitters with long effective half-lives.

The cumulative dose to the bone surface in this case is estimated to be 0.44 Gy (44 rad) through the end of 1986, 2 years prior to the appearance of the tumor. Marshall et al.[18] calculated a relative distribution factor (RDF) for bone doses of $^{239}$Pu versus $^{226}$Ra of about 28 for a surface source of Pu and 0.96 for a volume source. Dividing the 0.44 Gy surface bone dose by an RDF of 28 gives an average skeletal (volume) dose of 0.016 Gy. This estimate is comparable to the 0.02 Gy average skeletal dose in a beagle that developed a bone tumor. It should be recognized that this tentative bone dose is subject to large potential error. The estimated radiation dose in this worker was below current radiation protection guidelines.

## Lung Cancer

SMRs for the cohorts studied thus far in Pu handling facilities show no increases in lung cancer compared with the U.S. general population. For example, Rocky Flat's SMR of 64 (90% CI = 46,87)[19] is significantly low. The SMR for lung cancer in females employed at Los Alamos National Laboratory[37] from 1943 to 1981 was 94. A study of cancer incidence among Los Alamos employees from 1969 to 1978 used the incident cancer rates for the state of New Mexico for comparison.[1] The SIR for lung cancer was 0.25 for males; no lung cancer was recorded for females. These low incidence ratios are thought to be related to a lesser cigarette smoking history among this population. An SMR of 80 for lung cancer was observed for the Pu-monitored workers in the British study.[4] A rate ratio of 1.66 for the latter group relative to other radiation workers was not statistically significant.

The study by Wilkinson et al.[39] of workers at the Rocky Flats plant makes a comparison of mortality rate ratios between workers who have Pu depositions of

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74 or more Bq (> 2 nCi) with unexposed workers (< 74 Bq). The ratios of lung cancer rates for exposed and unexposed workers were not significantly different, using cancer induction times of 2, 5, and 10 years. Analysis of the 10-year induction time resulted in the highest rate ratio of 1.4 (90% CI = 0.33,4.65) based on only three lung cancer deaths in the exposed group. No smoking data were available to aid interpretation of the Rocky Flats mortality data.

Another study involved 224 white males with the highest Pu exposures at Los Alamos.[36] This group included all exposed workers with an estimated Pu deposition in excess of 370 Bq (10 nCi) as of 1974. Follow-up was 100% complete through 1980. Only one death from lung cancer occurred over a 33-year follow-up period.[36] The SMR for lung cancer based on U.S. rates was 20 (95% CI = 0,110). A review of lung cancer that occurred in the 82 active smokers in the group did not demonstrate the high Pu risks to smokers, as proposed by Gofman.[9] Using Gofman's risk estimate, an estimated 9–13 excess lung cancers should have occurred in these smokers by 1980, but none was observed.

Clinical follow-up of the 26 Manhattan Project Pu workers[33] shows that lung cancer has been the most frequent malignancy in the group, as would be expected for white males. Three cases in a group of 26 men over a 44-year period is a higher incidence than expected but is still within the limits of expectation. All three men had a long history of cigarette smoking. How much additional risk may have been imposed by inhalation of Pu cannot be discerned from these data.

Cigarette smoking is a severe confounding risk for lung cancer in human cohort studies. Data on smoking have not been available for interpretation of mortality data from the larger cohorts with Pu exposure. Additional studies that include a careful lifetime smoking history on all study subjects are needed to address this important issue. In animal studies, lung cancer was the major finding after inhaling $^{239}PuO_2$ particles. Inhalation is the most common mode of Pu exposure, and $^{239}PuO_2$ is a common chemical form of Pu particles found in the workplace. The early epidemiologic results suggested that Pu occupational guidelines and protective measures have kept the risk from Pu-induced lung cancer low. Additional studies with smoking data are needed to confirm or revise this tenuous interpretation.

## Liver Cancer

Mortality rates for cancers of the liver and gallbladder have not been elevated in any of the cohort studies listed above. The rate ratio for liver cancer among Pu-exposed workers at Rocky Flats compared with unexposed workers at the facility was low. In a study of all workers employed from 1944 through 1978 at the Hanford Site, other than construction workers, one death from liver cancer was observed in the 457 workers with Pu depositions.[8] No conclusion was drawn about the possible association of this cancer with the low 90 Bq (2.4 nCi) Pu deposition in this single case.

## Blood Cell Neoplasms

The descriptive term "blood cell neoplasms" is used here as shorthand terminology to indicate neoplasms of lymphatic and hematopoietic tissues (ICDA 8th Revision, Codes 200-209). The diseases under these codes are lymphosarcoma, reticulum cell sarcoma, Hodgkin's disease, lymphomas, other malignant neoplasms of lymphoid tissue, multiple myeloma, all forms of leukemia, polycythemia vera, and myelofibrosis. This disparate group of diseases stems from a variety of cell

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types with different functions and different distributions within the body. This grouping is convenient to use for epidemiologic analyses when the number of observed cases is too small to evaluate specific diseases. It has frequently been used in studies of radiation health effects to evaluate potential effects on lymphoid and hematopoietic tissues.

Several of these diseases, e.g., leukemias (other than chronic lymphatic leukemia), non-Hodgkin's lymphoma, and multiple myeloma, have had an increased frequency associated with doses of external radiation.[22] Evaluation of data on Pu-exposed workers data is confounded by doses of external radiation, including neutron doses, which are often associated with Pu work. It was noted earlier that the animal experiments that studied Pu risks did not clearly demonstrate risk of leukemia or other blood cell neoplasms.

Most Pu worker epidemiologic studies, except for the Rocky Flats worker study, have not shown excess blood cell neoplasms. In the Rocky Flats study,[39] the rate ratio for these diseases indicates the risk is about 5–10 times higher in Pu-exposed workers compared with unexposed Rocky Flats workers using 2-, 5-, and 10-year induction times. These results are summarized in Table 5. No linear dose-response trend was present. The four cases of Pu-exposed workers were of four different types: reticulum cell sarcoma, non-Hodgkin's lymphoma, multiple myeloma, and myeloid leukemia. It is interesting that the rate ratio for blood cell neoplasms in Rocky Flats workers exposed to external radiation is not similarly elevated.

The Pu-monitored workers in the British study[4] had only two deaths from blood cell neoplasms. The SMR and rate ratio were low.

Blood cell neoplasms are an interesting group of diseases for studying ionizing radiation effects in general. It is a group that bears close watching as Pu epidemiology studies unfold.

## Other Cancers

An excess number of brain tumors—benign and malignant combined—in Rocky Flats workers have been reported.[23,40] The increase has varied from about two to three times the expected number in the several analyses. A case-control study of brain tumors in Rocky Flats workers[24] showed no association between these tumors and radiation doses—either internal Pu depositions or external radiation. The reason for the excess brain tumors in this cohort is unknown, but it is clearly not from Pu exposure.

No other types of cancer have been observed to demonstrate a statistically significant increase from the expected numbers in the studies cited. As used here, "statistically significant" means the finding is unlikely to be due to chance either by testing for statistical significance, e.g., p-values, or by interpretation of 90% or 95% confidence intervals.

*TABLE 5.* Rate Ratios (RR) for Lymphopoietic and Hematopoietic Neoplasms Comparing Pu-exposed Rocky Flats Workers with Unexposed Workers*

| Induction Time | Pu Exposed (≥ 2 nCi) | Pu Unexposed (< 2 nCi) | RR | 90% CI |
|---|---|---|---|---|
| 2 years | 4 | 1 | 7.69 | 0.99–72.93 |
| 5 years | 4 | 1 | 9.86 | 1.26–94.03 |
| 10 years | 2 | 3 | 5.22 | 0.57–38.80 |

* From Wilkinson et al., 1987, with permission

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A review of epidemiologic articles of Pu workers was also made to identify additional specific cancers (including combining into major organ groups, e.g., respiratory system or digestive system) that had suggestively higher, although not statistically significant, rates. Two simple criteria were used to screen for other cancers of potential interest. The arbitrary criteria consisted of having at least three cases in the category and an SMR or rate ratio value above 150 or 1.5, respectively.

In the Pu-exposed-worker cohort at Rocky Flats, six cancers of all digestive organs combined gives a rate ratio of 1.68 relative to the unexposed, monitored workers, using an induction time of 5 years. The ratios using 2- and 10-year induction times are 1.31 and 1.46.

The only other cases that met the screening criteria were in a study of Pu-monitored workers by Beral et al.[4] Elevated SMRs or rate ratios were present as a result of four cancers of the esophagus (SMR = 177, rate ratio = 2.09 relative to unexposed workers), six of the prostate (168,1.06), and three of the kidney (240,1.23).

## CONCLUSION

Epidemiologic studies of workers in nuclear facilities have been performed to identify possible health effects due to Pu exposures of workers in the nuclear industry. Generally, the mortality rates from all causes of death and from all cancers combined have not been elevated in Pu workers. An exception to this was observed for the all-causes mortality rate of Pu workers at the Rocky Flats plant, which was significantly elevated compared to the rate among unexposed workers when cancer induction times of 5 years or longer were used. No overall linear dose-response trends were found in that study.

In animals exposed to Pu, an increased number of cancers have been observed in bone, liver/bile ducts, and lung. The most interesting cancer findings, thus far, in the epidemiologic studies of Pu workers have been an elevated rate of blood cell neoplasms (four cases in Pu-exposed workers at Rocky Flats) and one case of osteogenic sarcoma observed in 26 Manhattan Project Pu-exposed workers. Confirmation by other studies is needed. Continued studies are also necessary, because long latent periods, probably over 30 years, are anticipated.

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