1993-94 SESSION COMMITTEE HEARING RECORDS

Committee Name:

Joint Committee For Review of Administrative Rules (JCR-AR)

Sample:

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- *Appointments ... Appt*
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- *Committee Hearings ... CH*
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- **

- *Record of Comm. Proceedings ... RCP*
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Statement on the Scientific Validity of the Wisconsin Department of Natural Resources Proposed Standards for the Maximum Contaminant Level for Radium 226 and Radium 228

Prepared by

Dr. Robert E. Rowland

on behalf of the

Waukesha Water Utility

Waukesha, Wisconsin

March, 1991

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This document was prepared by Dr. Robert E. Rowland. Dr. Rowland holds a Ph.D in Radiation Biology, and has spent almost all of his professional career at the Argonne National Laboratory studying various aspects of the problem of radium in humans. He joined the Laboratory in 1950, became Associate Director of his research division in 1964, Director in 1967, and was appointed Associate Laboratory Director for Biology and Medicine of the Argonne National Laboratory in 1981. He retired in 1983, and has worked as a consultant to the Laboratory and other organizations since that time.

In 1969 the Atomic Energy Commission combined all of its funded research studies on radium in humans into one program, the Center for Human Radiobiology, and placed that program at Argonne under the direction of Dr. Rowland. Although the data referred to in this document are contained in the files of the Center for Human Radiobiology, and many of the published documents referred to were written by the staff of the Center, the opinions expressed in this document are those of Dr. Rowland, and do not necessarily reflect positions of the Center, the Argonne National Laboratory, the Department of Energy, or the U. S. Government.

In 1975 the Environmental Protection Agency (EPA) proposed interim standards for radium in drinking water, and in 1976 published the National Interim Primary Drinking Water Regulations, containing Maximum Contaminant Levels (MCLs) for radium. The MCL for radium was expressed as Ra^{226} plus Ra^{228} equal to 5 pCi per liter. The MCL for gross alpha particle activity (excluding U and Rn) was to be 15 pCi per liter. These levels are still with us today, but much new information has been developed in the meantime which makes these standards unnecessarily stringent.

The data on which radium standards have been set is unique, for it has been developed on human, not laboratory animal, experience. Thus there is no need to introduce modifying factors to translate animal results into predictions of human effects. Unfortunately, there are still unrealistic factors that are being introduced to modify the observed data; these will be pointed out as below.

The files in the Center for Human Radiobiology at the Argonne National Laboratory contain the names of approximately 6000 people who acquired the element radium internally. Many of these people acquired radium when internal radium was prescribed by members of the medical profession, a practice popular in the 1920s and early 1930s. Others

acquired radium as a consequence of buying and drinking water to which high levels of radium had been added. The greatest number, however, acquired radium when they worked as watch-dial painters, applying a radium-containing paint to watch and clock dials so that the hands and numerals would glow in the dark.

Nearly 2500 of these individuals have been carefully studied in the laboratory, both for their radium content and their health status. The ultimate cause of death has been determined for the deceased cases by autopsy or at least by means of a death certificate. It is known that two distinct malignancies have been induced by high levels of radium, bone sarcomas and carcinomas originating in the mastoid air cells or paranasal sinuses. These latter malignancies have been called "head carcinomas" for brevity. Dose response relationships have been derived and published (1, 2, 3) for each of these malignancies.

It should be pointed out that the term "dose" used here refers to a parameter that can be used to quantify the effects of radium. Conventionally, the energy deposited per unit volume of tissue is used for dose, expressed as "rads". In bone, the total energy deposited in the skeletal tissues is usually evaluated and expressed as an average skeletal dose. When applied to radium in humans, the number of rads deposited in the entire skeleton made little sense, for most of the alpha energy from radium and daughters was deposited in bone mineral, and only a small and unknown portion of the energy was deposited in cells where changes could be induced that might result in a neoplasm. When the average skeletal dose, expressed in rads, is used as a measure of risk, calculations show leukemia to be the most likely consequence of internally deposited radium. Since leukemia is now recognized by all to be a malignancy that is not induced by radium, there is general agreement that average skeletal dose is not a meaningful "dose" parameter to be used when evaluating the risk from radium. Had it not been for the human experience with radium, we would be setting MCLs for radium in drinking water to prevent the induction of leukemia in the exposed populations.

It has been found that the most meaningful and useful measure of risk from radium is the total quantity of radium that entered the systemic circulation, i. e., the blood stream. When radium is given as an intravenous injection the quantity injected is the systemic intake. Very few cases received documented radium injections; most radium cases that have been studied received radium orally. For these cases what is actually measured in the laboratory is the total quantity of radium in the body at the time of measurement. Radium deposits in bone; it acts within the body as an analog

for calcium. Thus, since adult bone is lost from the body very slowly, radium, once deposited, leaves the human body very slowly, and a significant radium burden can be easily measured three quarters of a century after acquisition.

In 1931 a group of patients at the Elgin State Hospital in Illinois was given radium chloride intravenously for the treatment of their mental illness (4). The quantity of radium given each patient was recorded and the radium remaining in the body was measured at two different times and published in the referenced document. These patients were found to be still in the mental hospital in the early 1950s, and their radium content measured several times during the next few years. From an analysis of these measurements Norris and his co-workers published (5) a formula for the retention of radium as a function of time that has become known as the Norris retention function. From this equation, if the time of acquisition is known, a body content measurement at a later date may be used to determine the quantity of radium that entered the systemic circulation when the radium was acquired. This worked well, but if one were interested in knowing the total quantity of radium that had been ingested, by a dial painter or by one who drank radium water, it was of little value, for it was not then known how much radium, acquired by mouth, was absorbed into the circulating blood.

A critical and significant study of the relative gut absorption of radium was undertaken at the Massachusetts Institute of Technology. It addressed the problem of the absorption of radium following oral uptake, particularly for the dial painters. The study measured the uptake in aged volunteers, of the short-lived radium isotope Ra^{224} (halflife 3.5 days), prepared in the form of a mock dial paint. It showed that the absorption of radium from dial paint was of the order of 20% of the quantity ingested. This study (6) made it possible to determine from a radium body content measurement the total oral intake for a person who had painted radium dial watches or who had consumed water to which radium had been added. It is from this study that the accepted value of 0.2 is taken for the ratio of absorbed radium to ingested radium. However, there is reason to believe that the ratio may often be less than this; some of these reservations were expressed in the referenced document.

The analysis of the relationship between radium intake and the induction of radium-induced malignancies, mentioned above (1, 2, 3), depended upon the systemic intake calculated with the Norris retention function. The Elgin patients, upon whom it was based, received very large injections of pure Ra^{226}. These ranged from a low of 70 to a maximum of

450 μCi. Eight of these 31 patients ultimately developed radium-induced malignancies. It has only been in recent years that the validity of the of the Norris retention equation has been questioned.

In 1973 a Task Group of the International Commission on Radiological Protection (ICRP) formulated a new retention equation for radium in humans. This was published as an ICPR Report (7), and is known as ICRP 20. Subsequently, a revision of this retention equation has been published (8) which substantially improves its fit to the human data. Neither of these improved retention functions have been used to calculate initial systemic intakes for the radium cases.

It is known that very high doses of radium, large enough to have a high probability of inducing a malignancy, could cause necrosis of bone. Lower doses were observed to cause blockage of some of the very small blood vessels within bone; such blockage would prevent the loss of radium from these necrotic regions. It wasn't surprising then that in the mid-1980s reports appeared that showed that the loss of radium from the body depended upon the level of radium within the body (9, 10). These studies showed that individuals whose radium levels were lower than the Elgin cases lost radium at a higher rate than predicted by the Norris function.

The consequences of these findings have not been fully absorbed by the radiobiological community. They imply that when a individual containing a low level of radium is measured, the systemic intake, calculated by means of the Norris function, is actually significantly lower than the true systemic intake, because that individual's radium was eliminated from the body faster than predicted by the Norris function. This, in turn, indicates that the low dose cases used in the analysis of risk versus intake (1, 2, 3) actually had intake levels greater than they were credited with in those analyses.

Keane et al. (10) pointed out that the Norris retention function predicts that the average rate of radium loss from the body over the period from 30 to 60 years after intake was 1.2% per year. Both the ICRP 20 function (7) and the Schlenker et al. (8) modification predict an average rate of loss of 2.8% per year over this period. Keane et al. (10) found that individuals with systemic intakes of the order of 4 μCi lost their radium at a rate of 4% per year over the same period. They went on to point out that the Norris function under estimates the initial systemic intake for these cases by almost a factor of three.

What is the significance of these new findings? They indicate that all of the systemic intake values for the low dose cases - cases that fall below the levels where malignancies have been seen - are in error; they are too low. When an appropriate dose-related retention function is found they will all be recalculated., and new dose-response functions derived. Due to the upward shift in the systemic intake values for the low dose cases new dose response functions will show an even steeper relationship between dose and tumor rate.

The dose response function derived in reference (2) for bone sarcomas is a steep function. The dose response function found was of the form

$$\text{Incidence} = (C + \beta D^2)e^{-\gamma D},$$

where $\beta = (7.0 \pm 0.6) \times 10^{-8}$

and $\gamma = (1.1 \pm 0.1) \times 10^{-3}$

and $C = 0.7 \times 10^{-5}$ bone sarcomas per year.

Incidence is in units of sarcomas per person year.

This dose squared exponential is a short form of a general equation used in radiobiology, usually written Incidence = $(C + \alpha D + \beta D^2)e^{-\gamma D}$, but in this case the coefficient of the linear term, α, was found to be equal to zero. The dose-squared term indicates that for each 10-fold decrease in systemic intake the bone sarcoma rate drops by a factor of 100. The actual data shows such a sudden decrease in tumor rate that some have suggested that a threshold exists, below which tumors will not be induced. I doubt this; a continuous relation between systemic intake and the probability of tumor induction probably is a more appropriate description of the process. In this data set the bone sarcoma incidence dropped so quickly that it was not possible to fit a linear function to the data.

What effect would an increase in the assigned values of systemic intake have on the low dose cases used in this analysis? It means that all cases currently thought to have initial systemic intakes below, say 25 µCi, probably have intakes three times higher than assigned. Cases as high as 50 µCi may actually have intakes near 100 µCi. Thus more than 1200 low dose cases (among whom no bone sarcomas were observed) in the analysis of reference (2) actually have higher intake values than were used in the derivation of the dose response function. This increase in intake values will make the steep dose response curve observed and now described by the dose-squared function above even steeper, and will make it even more unlikely that any linear function could be valid. This point is very important, for after accepting all the human data assembled, the EPA insists on

calculating the risk at very low doses with an artificial linear dose response function. The relationship between systemic intake and bone sarcoma incidence, however, is definitely not linear.

With the currently available dose response functions we now examine the process of quantifying the risk of drinking water containing radium at the proposed MCL of 20 pCi per liter. Risk from the ingestion of drinking water containing radium is derived by taking the MCL, in pCi per liter, multiplying it by a consumption factor of 2 liters per day, and then multiplying by the number of days this water is consumed, usually 70 years. This provides for a 75 year lifetime; with a latent period of five years the last five years of consumption will not induce any sarcomas. The consumption factor is recognized to be overly large; most individuals probably consume less than one liter per day, but factors of two are not worth quibbling about. If we take, as a example, the suggested MCL of 20 pCi per liter and the suggested consumption of 2 liters per day, we calculate the seventy year consumption to be 1.02 μCi. One fifth of this will be the calculated systemic intake, 0.204 μCi. The dose response function above yields, for such an intake, the natural rate, 0.7×10^{-5}, plus 2.8×10^{-9} radium-induced sarcomas per person each year after 70 years of intake. It is evident that the natural rate is more than a thousand times greater than the rate induced by the radium in the water.

When we take instead a linear dose response function as used by the EPA, and follow the method used by Mays et al. (3), we use

$$\text{Incidence} = C + 1 \times 10^{-5}D.$$

Mays et al. (3) found the risk at the end of life, averaged it over the lifetime (zero risk in the first year) then multiply by 70 years. For 20 pCi per liter and 2 liters per day, the intake after 70 years is again 0.204 μCi. The radium risk after age 75 is then $10^{-5} \times 0.204$ or 2×10^{-6} bone sarcomas per person each year. The lifetime risk is the average of zero and 2×10^{-6} or 1×10^{-6} bone sarcomas per person each year.

Thus one has obtained two estimates of the risk to be expected from 20 pCi of Ra^{226} per liter of drinking water. The risk calculated with the dose response function that was derived from and accurately describes the data used (but which we now know needs revising) yields a risk of 2.8×10^{-9} bone sarcomas per person each year. The second, obtained from a linear expression that did not fit the data, but was acceptable to the EPA because it was linear, predicts 1×10^{-6} bone sarcomas per person each year. The factor between the two results, approximately 3,000, may be considered to

be the safety factor introduced by the dependence on linearity. Similar results will be obtained for the other radium isotope, Ra^{228}.

The other malignancy induced by radium, the so-called head carcinomas, has been found to be induced only by Ra^{226}, so this isotope is the only one that need be considered for the induction of these malignancies. Referring to reference (1), at the time it was written (1978) there had been observed 38 bone sarcomas but only 17 head carcinomas among the 759 women employed as dial painters who provided the data (now known to need revision) for the dose response function that was used to determine the risk of the induction of head carcinomas . Actually, four functions were found to fit the data for the head carcinomas with a probability greater than p = 5 %. These were the forms that fit:

$$\text{Incidence} = C + \alpha D$$
$$\text{Incidence} = (C + \alpha D)e^{-\gamma D}$$
$$\text{Incidence} = (C + \beta D^2)e^{-\gamma D}$$
$$\text{Incidence} = (C + \alpha D + \beta D^2)e^{-\gamma D}.$$

One reason so many forms fit the data was the fact that there were so few head carcinomas to work with. Statistically speaking, there were too few degrees of freedom (due to the small number of carcinomas) to provide leverage to distinguish between these forms. Therefore, the conservative approach has been to use the linear function. This was the approach used by Mays et al. (3). That publication thus predicted that drinking water containing 5 pCi per liter and consuming one liter per day would result in the induction, by the radium in the water, of 9 bone sarcomas and 12 head carcinomas over a 75 year lifetime. Note that it predicted more head carcinomas than bone sarcomas.

The relative frequency of the two radium-induced malignancies does provide a key to the validity of the predictive dose response functions used. As of 1990 the files of the Center for Human Radiobiology contained data on 2460 measured radium cases. In this population there were 64 bone sarcomas and 32 head carcinomas. From some 4000 additional cases, not studied because of death or because we were unable to make them part of the studies, there are 21 more bone sarcoma and 5 addition head carcinoma cases. Thus the total number of verified malignancies assumed to be induced by radium is 122; of these 85 were bone sarcomas and 37 were head carcinomas. Thus we should expect any prediction of radium-induced malignancies to contain more bone sarcomas than head carcinomas. If it fails to, there is good reason to suspect its validity.

Had the dose-squared exponential function derived in the 1978 publication (1), which had a p-value of 11 %, and form

$$\text{Incidence} = (C + 1.4 \times 10^{-7} D^2) e^{-2.1 \times 10^{-3} D},$$

been used, the intake calculated above would yield an incidence of 5.8×10^{-9} radium-induced head carcinomas per person each year after 70 years of intake. This is almost as low as the bone sarcoma risk calculated above, and would indicate that both of these radium-induced malignancies will appear at rates far below the natural levels as a consequence of drinking water containing 20 pCi per liter of radium.

The analysis outlined above assumes that we may consider the risk from the absorption of radium over a lifetime to be the same as if that radium were acquired over a relatively short period, as was the case for all of the high level radium cases from whom the risk estimates were derived. This is probably a poor assumption, for a given quantity of radium acquired over a short time is undoubtedly more hazardous than the same quantity acquired in daily increments over a lifetime. A short acquisition time produces a high body content, which slowly decreases over a lifetime. The daily acquisition over a lifetime never results in a high body content, for the radium is continually lost from the body, and the highest body content is but a small fraction of the total amount acquired.

For the case considered above, 20 pCi of radium per liter and 2 liters consumed per day, the systemic intake was 0.204 µCi after 70 years. The risk estimates treat this as the original body content, and derive a risk for the years of life to follow. But the maximum body content achieved from this daily intake has been estimated (7) to be of the order of 22 times the daily intake, or about 880 pCi. This is only 0.4% of the calculated systemic intake.

The true risk from the consumption of water containing radium at levels as low as 20 pCi per liter will never be known. At the present time systemic intakes, acquired over a short period in early life, of the order of 40 to 50 µCi, have induced malignancies 50 to 60 years after the exposure to radium. Lower levels have not induced malignancies. The steep dose-response curve observed and the inability to obtain populations large enough to demonstrate effects at these levels, preclude an experimental solution to the problem. It is important to realize that communities throughout the midwest have been drinking water with elevated radium levels for many years, but no elevation in the incidence of bone cancer has been seen in

these areas. Indeed, a study designed to detect such an effect from local death records found a higher bone cancer rate in Chicago, which obtains its water from Lake Michigan, at 0.03 pCi per liter, than in the surrounding suburbs, where the radium levels ranges from 5 to 15 pCi per liter (11).

I firmly believe that if there is any risk of drinking water containing 20 pCi of Ra^{226} or Ra^{228} it is unmeasurably small; other components of drinking water probably constitute far greater risks than radium at these low levels.

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Radium in Humans: A Review of U.S. Studies, R.E. Rowland. Argonne National Laboratory, Argonne, IL, 1994. 233 pp. Price: $36.50.

The studies of radium in humans are unique in character because exposure to radiation occurred over extended periods of time, rather than acutely as was the case for atomic bomb survivors. We generally think of these studies in terms of internal emitters, but external gamma doses and radon exposure also provide good study data. External gamma doses for radium dial painters were in the range of 0.7-46 cGy/yr. The average radon level was about 51 pCi of radon per liter; about 0.26 pCi of radium per liter existed in dust. Though not often utilized, the studies of radium in humans are of significant value in assessing effects of radiation exposure to humans at low dose rates and in assessing the effects of exposure to radon and naturally occurring radioactive materials (NORM) in humans.

Dr. R.E. Rowland's book, **Radium in Humans, A Review of U.S. Studies**, is an effort "to give an overall picture of what might be called the radium era, that period from the early part of this century, when radium was rapidly exploded as a tool and as a medication, to the present time, when radium is not generally used and the study of its effects has been terminated." The book contains about 135 pages of descriptive text with copious references. The remaining hundred or so pages of the book contains tabular data on 2,403 radium exposed individuals for whom satisfactory measurements on body radium content had been made by the end of 1990. The book contains a fascinating chapter on the early medical uses of systemic intake of radium. Radium once was touted as a "cure all" for many ailments. "Perhaps the best known form of radium available to the public...was radium water. The brand that received the greatest notoriety was *Radithor*." Radithor met its end when Eben MacBurney Byer, a prominent sports figure, and Radithor user, died of necrosis of the jaw, abscess of the brain, secondary edema, and terminal pneumonia. Byer consumed about 5,000 microcuries of radium-spiked water over a period of several years.

The first published record of the adverse effects of radium exposure in humans occurred in 1924 when Dr. Theodor Blum, a dentist, described an unusual mandibular osteomyelitis in a r[illegible] he referred to as *radium jaw*. Other adverse effects were soon noted in populations [illegible] es

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of radium in humans, however, did not begin in earnest until the late 1960s. A total cohort of 6,675 people (4,684 females and 1,991 males) were identified to have known or suspected significant radium intakes through the watch dial painting industry, related industries or medical/health use. Of these 6,675 cases, 2,383 had confirmatory measurements of radium body burdens. There were 85 bone sarcomas in the total cohort (~ 1.3%); 64 were in the measured cohort (~ 2.7%). The risk of bone sarcoma appears to be significantly higher in females (80 total) compared to males (5 total). This apparent large difference in risk due to sex remains unexplained. The first bone sarcoma was seen about 5 years after the first exposure to radium. Frequency fell markedly after 50 years, but one bone sarcoma was identified 63 years after first exposure. This subject had an intake of 100 microcuries, the lowest intake identified with bone sarcoma. The induction of bone sarcoma clearly appears to be a threshold phenomena.

Thirty seven head sarcomas were identified in the total cohort (~ 0.6%); 32 head sarcomas were in the measured cohort (~ 1.3%). Again there appeared to be a greater risk in females as compared to males. In the measured cohort, 27 females and 5 males were identified with head sarcomas.

Other diseases of interest include multiple myeloma, breast cancer, and leukemia. Several studies indicated that there may be an association with multiple myeloma and radium exposure, but Rowland's book suggests no definitive answer regarding multiple myeloma. There also seems to be no clear picture regarding breast cancer. The radium dial painters apparently had more breast cancer deaths than would be expected at some but not all work sites. There is no clear evidence that indicates that the elevation was due to radium acquired internally or due to external gamma ray doses. Leukemia deaths were not elevated in the exposed populations.

I recommend Rowland's book to everyone interested in late radiation injury. I think readers may come away with a new appreciation of late radiation injury. Rowland sums this up beautifully in his preface: "Given the number of people who acquired radium internally, it is remarkable how few suffered significant damage. To be sure, those who eventually developed radium-induced malignancies suffered severely. Those who acquired very large internal quantities of radium, as did many of the early dial painters, also suffered from what we today suspect were acute radiation doses leading to early deaths. However, the great majority of exposed individuals went through life with

no recognizable consequences of their exposures. They lived as long as, and apparently in as good health as, their unexposed neighbors. This fact seems to have been little appreciated and seldom mentioned, but it may be the most important finding of the entire study."

Reviewed by

David S. Gooden

David S. Gooden, Ph.D., J.D. is the Director of Biomedical Physics at Saint Francis Hospital, 6161 South Yale Avenue, Tulsa, OK 74136.

Health Effects of Internally Deposited Radionuclides:

Emphasis on Radium and Thorium

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Editors

G. van Kaick, A. Karaoglou & A. M. Kellerer

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DOSE-RESPONSE RELATIONSHIPS FOR FEMALE RADIUM DIAL WORKERS: A NEW LOOK

R.E. Rowland

Environmental Research Division, Argonne National Laboratory

Argonne, IL 60439, USA

ABSTRACT

The values of initial systemic intake and of skeletal dose for all of the U.S. radium cases have recently been revised. This revision was required following the demonstrations by Rundo and by Keane that humans who were exposed to radium as adults lost radium at a rate that depended on the quantity of radium originally deposited within their bodies. These new values have been used to define new dose-response relationships for both the bone sarcomas and the carcinomas arising in the paranasal sinuses and mastoid air cells induced by internally deposited radium. The population examined was employed in the U.S. dial painting industry prior to 1950 and consisted of 1530 female dial workers for whom radium body burden measurements were available. By the end of 1990, 46 cases of bone sarcomas and 19 cases of head carcinomas had been diagnosed in this cohort. The head carcinoma incidence can be adequately fitted by a simple linear function, as was found in previous analyses. The bone sarcoma cases were previously fitted by a dose-squared-exponential function. With the revised values of systemic intake, the sarcoma results could not be satisfactorily fitted with this expression. When the exponent on D was increased to larger values, excellent fits were obtained.

Introduction

In previous publications, dose-response relationships for female radium dial workers and other radium populations were derived.[1,2] These publications examined the incidence of the bone sarcomas and head (paranasal sinus and mastoid air cell) carcinomas induced by very high levels of ^{226}Ra and ^{228}Ra deposited in the human skeleton. Both average skeletal dose and the initial systemic intake were used as measures of radiation insult. When these results were published, the retention of radium in the human body was calculated by means of a power function, the Norris retention function.[3] Since then radium body burdens have been determined for more cases, several more malignancies have appeared, and the Norris function has been replaced by a retention function[4] similar to that proposed by the ICRP.[5] These changes have made it necessary to re-examine the shape of the dose-response functions.

Systemic Intake

The systemic intake, the quantity of radium that entered the blood during the period of exposure, is a time-invariant measure of the radium hazard derived from a measurement of body content made long after the radium was acquired. The calculated

intake allows cases to be grouped by intake level, as is often done in laboratory animal studies. Systemic intake is the only radiation measurement considered in this study.

The radium dial paint first used in the United States contained only ^{226}Ra, but later the two radium isotopes, ^{226}Ra and ^{228}Ra, were mixed to reduce the cost. To express the radium intake as a single number, a ratio of effectiveness for the two isotopes was defined. We showed[1] that, for the induction of bone sarcomas in terms of systemic intake, a given activity of ^{228}Ra was about 2.5 times as effective as the same activity of ^{226}Ra. Therefore, for the induction of bone sarcomas, the systemic intake is the activity of ^{226}Ra + 2.5 × the activity of ^{228}Ra. In the case of the head carcinomas, which are thought to be induced by the daughter products of ^{222}Rn, only the ^{226}Ra content of the body is considered relevant, so the systemic intake is expressed as the activity of ^{226}Ra.

The Retention of Radium in the Human Body

The publications of Rundo et al.[6] and Keane et al.[7] demonstrated that radium retention in adult humans 30-60 y after intake depends on the quantity of radium deposited within the body. This was not an unexpected result, because an effect of dose level was reported by Lloyd et al.[8] in long-term studies of radium in beagles. Dogs with high-level radium injections had higher fractional retentions than those receiving lower doses. Lloyd et al.[8] attributed this effect in the beagle to radiation damage to the bone remodeling processes at high radium concentrations. Such a dose effect was also proposed by Rundo et al.[6] and Keane et al.[7] for the human radium cases.

To determine the initial systemic intake, one must calculate back, by means of an accepted retention equation, from the time when the body burden was measured to the time when radium was acquired. Stehney et al.[9] found that the average radium subject was measured about 40 y after first exposure to radium. Thus, apparently slight differences between two different radium retention functions can make large differences in the intake calculated from the measured body content.

Rowland[4] used the data of Rundo et al.[6] and Keane et al.[7] to define a modified retention function for low levels of radium in humans. The retention function proposed in the ICRP 20 document on the metabolism of the alkaline earths[5] in man was the logical starting point. The ICRP 20 document defined a parameter λ as the rate of apposition and resorption in compact bone, gave the value of λ as 2.5% y^{-1}, and stated that λ seemed to be a property of bone itself rather than a property of one of the radioelements in bone. However, in the ICRP 20 retention equation for radium, λ was given the value of 1.5% y^{-1}.

Schlenker et al.[10] subsequently modified certain parameters in the ICRP 20 equation to account better for the distribution of radium between soft tissue and bone. Rowland,[4] working from the modification of Schlenker et al.,[10] set λ at 2.5% y^{-1} and

derived a revised retention function for radium applicable to intake levels that do not result in radiation damage to bone. This function has now been used as the starting point for the recalculation of the intake and skeletal dose values for all of the U.S. radium cases. It should be noted that all of the previously published values of intake and skeletal dose were calculated by means of the power function retention equation proposed by Norris et al.[3]

The Study Population

For this report all female dial workers with body burden measurements who entered the industry before 1950 were examined; a total of 1530 such persons were found. In this cohort, 46 women were found to have had bone sarcomas, and 19 had one of the head carcinomas; 3 of these women experienced both a bone sarcoma and a head carcinoma. The follow-up of these women terminated at the end of 1990.

A previous analysis of dose response for bone sarcomas in the female radium dial workers[2] made use of the 42 bone sarcomas that had then appeared among the 1468 women first exposed to radium before 1950 for whom body content measurements were available. The previous analysis of head carcinoma induction in the female dial workers[1] was based on 759 women exposed before 1930, who experienced 17 of these malignancies.

The Bone Sarcomas

The 46 bone sarcomas in our cohort of 1530 women had appearance times ranging from 7 to 63 y (mean ± s.d. = 28 ± 14 y). The lowest systemic intake associated with a bone sarcoma was 3.70 MBq (100 μCi). This malignancy, diagnosed in 1981 in a dial worker who began painting dials in 1918, was thus detected 63 years later. The highest combined intake associated with a bone sarcoma was 234 MBq (6330 μCi), in a dial worker who started painting dials in 1917 and was diagnosed 10 y later.

In Table 1 the dial worker cases are arranged by intake levels in units of kBq ^{226}Ra + 2.5 × kBq ^{228}Ra. As was the case in previously published analyses,[1,2] the intake range covered several orders of magnitude. In the format of previous analyses, each decade of intake was divided into three groups defined by the numbers 1-2.5, 2.5-5, and 5-10. Previous analyses used μCi as the unit of intake, but here kBq are used. The intake level for the cases in each group is expressed as a weighted mean as follows:

$$\text{weighted mean} = \frac{\sum D_i y_i}{\sum y_i} \qquad (1)$$

Here D_i and y_i are the systemic intake and years at risk, respectively, for each individual in the intake group. Also included in Table 1 are the number of cases, the

number of person-years at risk, and the number of bone sarcomas for each group. Person-years at risk are calculated from the date of original employment to the date of death, diagnosis of a bone sarcoma, or end of follow-up, less an assumed 5-y development period from tumor induction to earliest possible diagnosis.[1]

Table 1. Case distribution, person-years of risk, and bone sarcoma experience by systemic intake level.

Systemic Intake			Number of		
Range (kBq)	Range (μCi)	Weighted Average (kBq)	Cases	Person-Years at Risk	Bone Sarcomas
≥ 50000	≥ 1351	73310	21	235	6
25000 - 49999	675.7 - 1350	37850	21	411	16
10000 - 24999	270.3 - 675.6	15100	51	2005	22
5000. - 9999.	135.1 - 270.2	7651	45	2237	1
2500. - 4999.	67.57 - 135.0	3498	53	3133	1
1000. - 2499.	27.03 - 67.56	1637	76	4166	0
500.0 - 999.9	13.51 - 27.02	702.2	76	4200	0
250.0 - 499.9	6.757 - 13.50	364.9	93	4861	0
100.0 - 249.9	2.703 - 6.756	153.3	168	8574	0
50.00 - 99.99	1.351 - 2.702	71.69	139	6459	0
25.00 - 49.99	0.676 - 1.350	36.40	167	7505	0
10.00 - 24.99	0.270 - 0.675	17.18	153	6589	0
<10.00	<0.270		467	21826	0
			1530	72101	46

The Head Carcinomas

The 19 head carcinomas in the measured female dial workers (Table 2) had appearance times of 19 to 59 y (mean ± s.d. = 41 ± 10 y). The lowest ^{226}Ra intake associated with a head carcinoma in this cohort was 2.9 MBq (78 μCi). This malignancy occurred in a woman who started painting dials in 1922 and was diagnosed 51 y later. The highest intake associated with a head carcinoma was 36.6 MBq (998 μCi), in a woman who started painting dials in 1918 and was diagnosed 39 y later.

Table 2. Case distribution, person-years of risk, and head carcinoma experience by systemic intake level.

Systemic Intake			Number of		
Range (kBq)	Range (μCi)	Weighted Average (kBq)	Cases	Person-Years at Risk	Head Carcinomas
≥ 25000	≥ 675.7	35110	14	166	3
10000 - 24999	270.3 - 675.6	11790	29	813	6
5000. - 9999.	135.1 - 270.2	7523	45	1625	6
2500. - 4999.	67.57 - 135.0	3648	47	1966	4
1000. - 2499.	27.03 - 67.56	1564	65	2887	0
500.0 - 999.9	13.51 - 27.02	731.9	62	3172	0
250.0 - 499.9	6.757 - 13.50	362.1	76	3601	0
100.0 - 249.9	2.703 - 6.756	154.2	210	9847	0
50.00 - 99.99	1.351 - 2.702	72.35	165	7096	0
25.00 - 49.99	0.676 - 1.350	36.68	188	7711	0
10.00 - 24.99	0.270 - 0.675	17.41	159	6192	0
<10.00	<0.270		470	19508	0
			1530	64584	19

In Table 2 the dial worker cases are arranged by ^{226}Ra intake levels in kBq. The same numerical intake level ranges are used as in the bone sarcoma analysis. All other quantities are the same as in Table 1 except for person-years at risk. Here a 10-y development time is assumed to be required between induction of the head carcinoma and the earliest possible diagnosis.[1]

Dose-Response Relationships

Various forms of a general dose-incidence expression,

$$I = (\alpha D + \beta D^2)e^{-\gamma D}, \qquad (2)$$

including the complete expression and simplifications obtained by leaving out the term containing the D, or the D^2, or the $e^{-\gamma D}$, were fitted to the data and subsequently tested by a χ^2 statistic. Here the incidence, I, is in malignancies per person-year, and α, β, and γ are constants to be found by the fitting procedure. Each equation was fitted to all data points with D greater than 10 kBq (12 points for the sarcoma data, 11 points for the carcinoma data). For the χ^2 analysis, the lower intake levels, where no malignancies were observed, were combined into a single intake group by summing the expected numbers calculated for the individual levels. When necessary, groups were further combined so that no group contained an expected number of less than three malignancies.[11] The weighted squares of the differences between the observed and the expected numbers of malignancies were calculated after the groups had been combined. The number of degrees of freedom was equal to the number of groups after combining, less the number of fitted parameters. The fitting procedure was applied to all the data points, and the goodness of fit was evaluated after the groups were combined.

The Sarcomas

No acceptable fits to the sarcoma data were found for any form of the general equation by the above procedure. To be acceptable the coefficients α, β, and γ would have to be positive, and the χ^2 analysis would have to result in a p value equal to or greater than 0.05.

Examination of the data suggested that the data might be fitted by a function that rose more rapidly than the square of the intake. To test this idea, the function

$$I = \beta D^{\delta} e^{-\gamma D} \qquad (3)$$

was fitted to the data. Here ß, γ, and the exponent, δ, were to be obtained from the fitting routine. In this case a satisfactory fit (p = 0.13) was found with the exponent equal to 3.15; the fitted function is

$$I = 2.132 \times 10^{-15} \times D^{3.15} \times e^{-7.055 \times 10^{-3} \times D}. \quad (4)$$

When the exponent, δ, was preselected, any value for the exponent between 2.7 and 4.1 was found to provide an acceptable fit to the sarcoma data set.

The general equation above, Eq. 2, and all its simplifications are based on the assumption that the fitted function goes through the origin; that is, when the intake is zero, the incidence is zero. When this restriction was lifted, so that the function to be fitted was

$$I = \text{Constant} + (\alpha D + \beta D^2)e^{-\gamma D}, \quad (5)$$

and the same simplifications were tried, no acceptable fits to the sarcoma data were found. However, when the exponent on D was changed from 2 to the value found above, 3.15, an acceptable fit was obtained. The fit was

$$I = -1.443 \times 10^{-4} + 2.142 \times 10^{-15} \times D^{3.15} \times e^{-7.056 \times 10^{-3} \times D}. \quad (6)$$

Setting the incidence, I, equal to zero and solving for D gives an intercept value of 2924 kBq (79 μCi). This fit to the data is shown in Fig. 1. On the scale shown in Fig. 1, little difference can be seen between Eqs. 4 and 6.

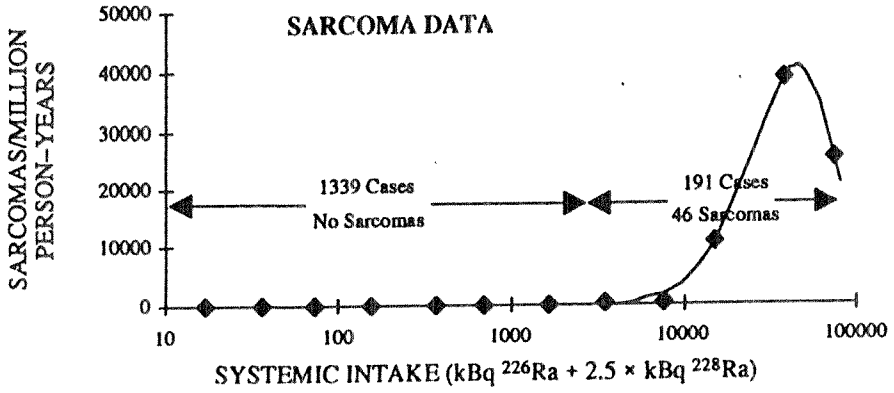

Figure 1. The dose-response function for bone sarcomas shown in Eq. 6 is plotted in units of bone sarcomas per million person-years versus systemic intake in kBq. The solid diamonds are the observed data points for the 12 intake groups from Table 1.

The Carcinomas

Various forms of the general dose-incidence expression, Eq. 2, were also fitted to the carcinoma data and tested by a χ^2 statistic. In contrast to the findings for the bone sarcoma data, several forms of this basic equation were fitted to the head carcinoma data; these fits are listed in Table 3. The linear, linear-exponential, and dose-squared-exponential functions provided acceptable fits. The linear and the dose-squared-exponential fits are shown in Fig. 2.

Table 3. Acceptable fits to the carcinoma data.

Function	Coefficients	p value	Intercept
	Forced through the origin; when D = 0, then I = 0.		
$I = \alpha D$	$\alpha = 5.24 \times 10^{-7}$	0.22	0
$I = \alpha D e^{-\gamma D}$	$\alpha = 5.89 \times 10^{-7}$ $\gamma = 3.72 \times 10^{-6}$	0.10	0
$I = \beta D^2 e^{-\gamma D}$	$\beta = 1.03 \times 10^{-10}$ $\gamma = 5.57 \times 10^{-5}$	0.88	0
	Fitted with a constant to determine an intercept.		
$I = \text{Constant} + \alpha D$	Const. $= -9.22 \times 10^{-5}$ $\alpha = 5.28 \times 10^{-7}$	0.55	175 kBq (4.7 μCi)
$I = \text{Constant} + \alpha D e^{-\gamma D}$	Const. $= -2.68 \times 10^{-4}$ $\alpha = 6.36 \times 10^{-7}$ $\gamma = 5.51 \times 10^{-6}$	0.24	422 kBq (11 μCi)

The fits in Fig. 2 are both forced through the origin; that is, the equations define the incidence as zero at zero intake. If this condition is removed and Eq. 5 is used as the function to be fitted, somewhat different results are obtained. These results are also listed in Table 3. Only the linear and the linear-exponential functions provided acceptable fits, suggesting the existence of a threshold. The apparent threshold values of 175 kBq (4.7 μCi) for the linear fit and 422 kBq (11 μCi) for the linear-exponential fit are quite small and statistically not significant.

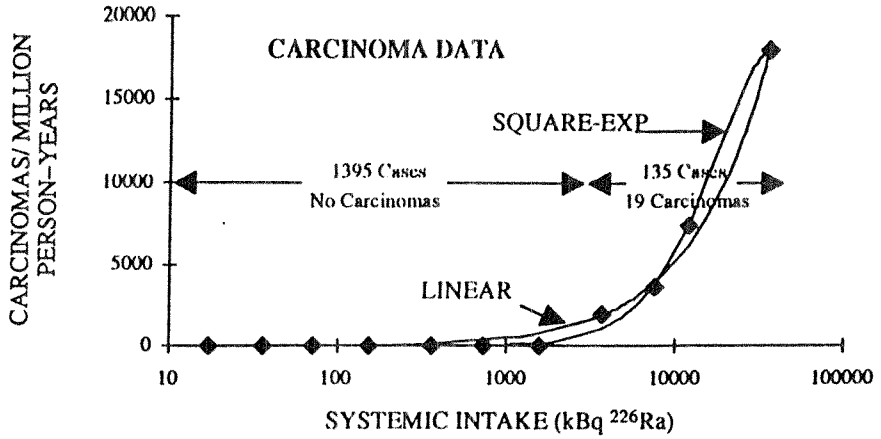

Figure 2. Two dose-response functions for head carcinomas from Table 3, the linear and the dose-squared-exponential function, are plotted in units of head carcinomas per million person-years versus systemic intake in kBq. The solid diamonds are the observed data points for the 11 intake groups from Table 2.

The 19 head carcinomas observed in this cohort are insufficient to allow us to differentiate between the various proposed response functions. In such a situation, it is probably best to accept the simplest result, the linear non–threshold function, in spite of the fact that a more complex function, the dose-squared-exponential function, appears to give a better fit to the data.

Discussion

The revised systemic intake values have altered the shapes of the dose-response functions from those found in earlier studies. The most evident change is in the fits to the bone sarcoma data. Past studies[1,2] showed that the sarcoma data could be fitted by a non-threshold function based on the square of the systemic intake, but not by a linear non-threshold function. The recalculated systemic intake values cannot be fitted by a dose-squared function, but they demonstrate a steep dose-response behavior that can be fitted with a larger value for the exponent. A mechanistic justification, other than a threshold, for such a form of a dose-response function remains to be found.

As a consequence of the threshold-like appearance of the dose-response functions for the bone sarcomas, very few of these malignancies are predicted at low intake levels. The head carcinomas, which do not demonstrate such a rapid drop with dose, are predicted to be more abundant than the bone sarcomas at low intake levels. This is in contrast to the observed frequency of the two malignancies at high intake levels; more than twice as many bone sarcomas (46) as head carcinomas (19) were observed in this cohort. This same pattern was observed for the entire population of cases with measured radium body burdens studied in the United States, for which the distribution is 64 sarcomas to 32 carcinomas among 2383 individuals exposed to radium from various sources. The dose-response functions derived here should be applied only over the range of intake values within which the malignancies were observed.

Conclusions

The recalculation of the intake levels for the measured radium cases has changed the distribution of radium-induced malignancies. The overall effect has been to raise the intake levels for the cases with lower intakes and to reduce them for the cases with higher intakes. This effect, while it is noticeable for the head carcinomas, does not result in significant changes to the previously published dose-response functions. The effect is more significant for the bone sarcomas and has resulted in a very steep dose-response relationship. Whether this result is actually a demonstration of a threshold or simply an indication of a very low probability of sarcoma induction below 2900 kBq remains to be seen.

Acknowledgments

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Bone Sarcoma in Humans Induced by Radium: A Threshold Response?

R.E. Rowland

Corporate address:
Environmental Research Division, Argonne National Laboratory, Argonne, IL 60439, USA

Home address:
700 W. Fabyan Parkway
Apt. 8C
Batavia, IL 60510, USA

Home phone: (708) 879-4554
FAX (708) 879 1153
E-mail rowland@inil.com

Abstract: The radium isotopes, ^{226}Ra and ^{228}Ra, have induced in humans, at sufficiently high levels in the body, malignancies in the skeleton, primarily bone sarcomas. They have also induced, at approximately half the frequency, carcinomas arising in the paranasal sinuses and mastoid air cells. There is no evidence that any leukemias have been induced by internally deposited radium, nor any other solid cancers. However, some radium cohorts have shown elevated levels of breast cancer, while others have not. It has been suggested, at least for the dial painter population, that breast cancer may be the consequence of external radiation from the radium dial paint.
Prior to the termination of the U.S. radium studies program in 1990, a concerted effort was made to verify, for each of the measured radium cases, the published values of the skeletal dose and the initial intake of radium. These were derived from body content measurements made, on the average, some 40 years after radium intake. Corrections to the assumed radium retention function resulted in a considerable number of dose changes. These changes, in turn, have changed the shape of the dose response function. It now appears that the induction of bone sarcomas is a threshold process; below the calculated threshold no malignancies have been seen, above the level the probability of the induction of a malignancy increases rapidly.

1. INTRODUCTION

Some thirty years ago Evans [1] proposed that a Practical Threshold existed for the induction of malignancies in humans by internally deposited radium. A review of the data that has accumulated since he made that proposal suggests a somewhat different interpretation for the bone sarcoma incidence in the now considerably enlarged population of radium cases.

What did Evans mean by a Practical Threshold ? In the abstract of a 1967 publication [2] he stated:

" When the cumulative skeletal dose in rads decreases, the tumor appearance time for the sarcomas and carcinomas associated with skeletal deposits of Ra or MsTh appears to increase. This leads to the identification of a "practical threshold" of dosage, below which the required tumor appearance time generally exceeds the life-span, and hence radiation-induced tumors appear with negligible frequency."

Today the accumulated data suggests that Evans was not entirely correct, there is not a Practical Threshold for the induction of bone tumors in the human $^{226/228}Ra$ cases. Instead there appears to be a real threshold, a dose below which such malignancies have not been seen. Evans suggested a practical threshold existed at a skeletal dose of 10 Gy (1000 rads) [2].When Evans made these statements he was studying the results made from about 450 cases, who had obtained their radium in a variety of ways. Of these, he concentrated on a group of 173 epidemiologically suitable cases

who experienced 26 bone sarcomas and 9 head-cavity carcinomas. Today we have a population of 2383 cases for whom we have reliable body content measurements; they experienced 64 bone sarcomas, none below 10 Gy. From this population we can draw a cohort with similar age, sex, method of exposure and period of exposure, the female dial workers. Further, we now limit the analysis to one malignancy, the bone sarcomas, instead of the two types of malignancies. This cohort of 1530 women experienced 46 bone sarcomas.

2. THE BONE SARCOMAS

The data that has been accumulated on these U.S. radium dial workers is unique in many aspects. The following points are relevant to the analysis of bone sarcoma incidence.

- These women were exposed to radium in the dial industry between 1913 and 1950. Those exposed after 1950 have not been included in this cohort.
- Their body content of radium was measured long after their exposure; the average time was 40 years after starting in the dial industry.
- From the measured radium body content the original intake of radium was calculated by means of an assumed radium retention function.
- The skeletal dose was calculated from the original intake and summed over the interval from exposure to diagnosis of a sarcoma, or death, or 1990 for those still living. The assumed retention function was a critical factor in this summation.
- Due to the long half-life of ^{226}Ra, and the slow release of radium from the skeleton, the irradiation of the skeleton continued throughout the life of the contaminated individual.
- The skeletal doses in this radium population range over almost five decades of dose.

In the late 1980s sufficient evidence had accumulated to show that, as previously demonstrated in studies with dogs [3], radium retention in humans was dose dependent [4, 5]. High dose cases retained radium more tenaciously than lower dose cases. This led to a complete recalculation of the initial intakes and skeletal doses, making use of the ICRP 20 retention function for radium [6, 7], modified for the effect of the radium intake level. It is with these revised radium doses that the evidence for a bone sarcoma threshold becomes evident.

The time from first exposure to radium to the time of sarcoma diagnosis is plotted against the skeletal dose for each of the 46 bone sarcoma cases in Fig. 1. Also shown on this plot are the cumulative doses for remainder of the 1530 dial workers in the cohort, indicated by the number placed in each decade of dose.

It is evident that no sarcomas appeared in the 1370 dial workers who accumulated less than 10 Gy to the skeleton. Had we performed this analysis on the total number of measured radium cases, 2383, the general appearance would have been the same. All 64 bone sarcoma cases occurred in the 264 cases with more than 10 Gy, while no sarcomas appeared in the 2119 radium cases with less than 10 Gy.

Dose response functions may be calculated for this cohort of female radium dial workers. Previous analyses of these radium cases used numerical fits to a general dose-response function that related the probability of the induction of a bone sarcoma to the magnitude of the radium insult. The functions tested have been continuous functions that passed through the origin (zero probability at zero dose) and included the full range of measured skeletal doses. Dose response functions of the form

$$\text{Incidence} = a\, D^2\, e^{-b\,D}$$

have been proposed in previous reports [8, 9]. Such functions describe the data well and were proposed as reliable predictors of future radium-induced bone sarcomas. Here Incidence was in

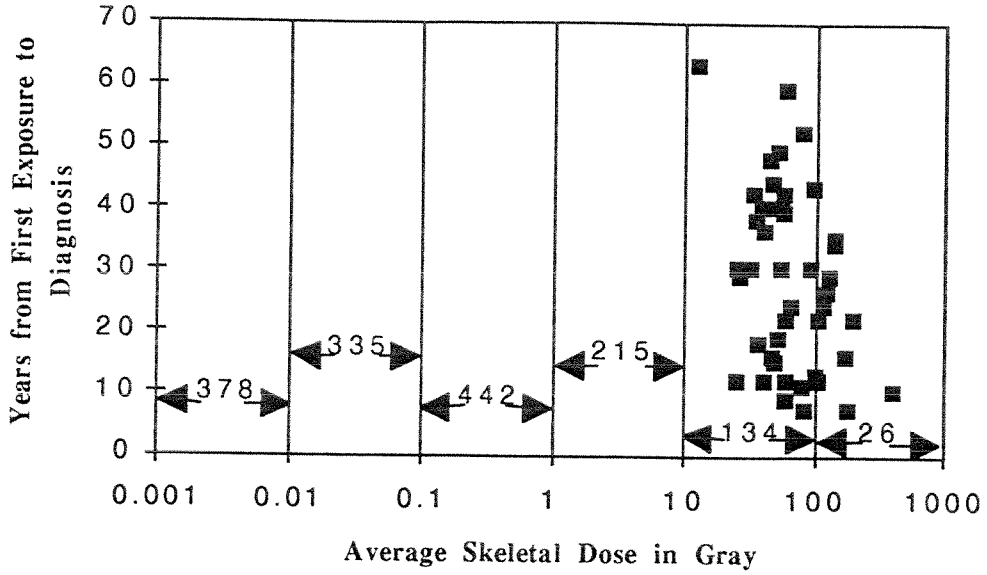

Figure 1. The 46 bone sarcomas in the cohort of 1530 female dial workers are plotted as black squares, indicating their appearance time and dose for each sarcoma case. The total number of cases in each decade of dose are also indicated.

units of sarcomas per person year at risk, D was in units of skeletal dose or units of systemic intake, and a and b were constants determined by the fitting procedure.

The most recent presentation [10], in contrast, postulated that a threshold might exist for radium-induced bone sarcomas. It suggested that there was zero risk up to a threshold dose, above which the risk increased at a rapid rate. It was shown that a continuous dose response function that passed through the origin for bone sarcomas could only be fit to the data with an expression of the form

$$\text{Incidence} = a\, D^{\text{exponent}}\, e^{-b\,D}.$$

Here the numerical value of the exponent had to be in the range 2.7 to 4.1, with the value 3.15 for the exponent appearing to be the best fit to the data. Needless to say, it is difficult to find any physical meaning for such a dose response function.

It appears that instead of a continuous function from the zero-zero point up to the observed data points, a pair of functions should be considered, with zero incidence up to a threshold value, and a steeply rising curve above that point. This published analysis [10] used systemic intake as the measure of radium risk. Systemic intake, the quantity of radium that entered the blood during the period of exposure to radium, has been a useful parameter. It is time invariant, in contrast to skeletal dose, which increases as long as the radium-exposed subject lives. The U.S. radium cases were long-lived; approximately 1000 were still living when the study was terminated in 1990. It correlates quite well with skeletal dose, as is shown in Fig. 2, where log skeletal dose in gray is plotted against intake in log kilobecquerels.

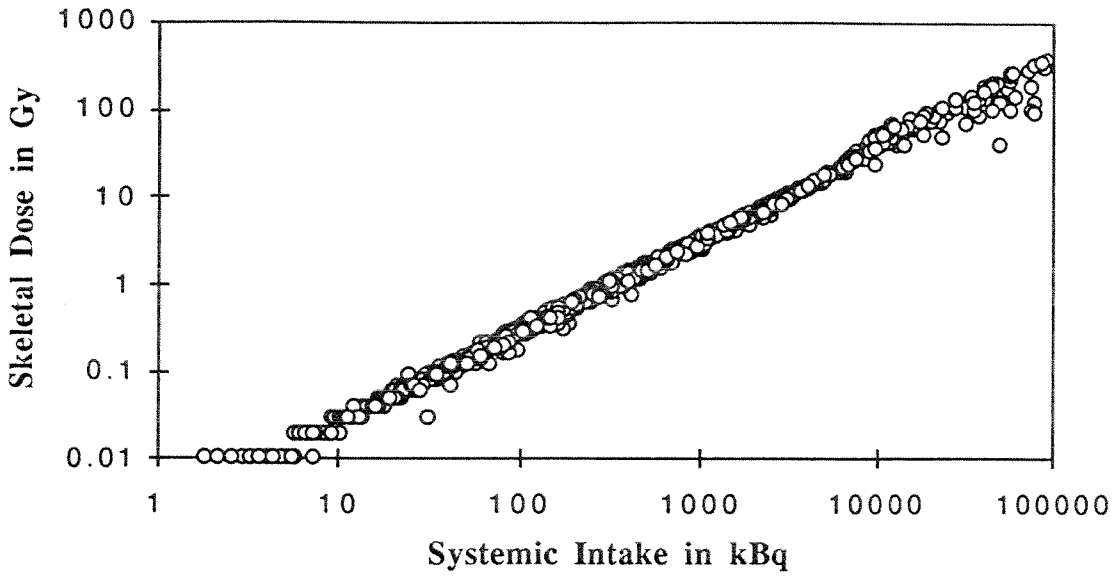

Figure 2. Each of the 1530 female workers is plotted to show the relation between their systemic intake and their skeletal dose. The correlation coefficient for dose in gray and intake in kBq is 0.93.

In the above referenced publication [10] the threshold for bone sarcoma was found to be 2924 kBq. From the relationship between systemic intake and skeletal dose shown above, this translates into a skeletal dose threshold of 7.5 Gy.

Alternatively, the female dial cohort can be divided into dose groups and fitted to a dose response function directly. Table 1 shows the dose distribution of the 1530 dial workers and their bone sarcomas.

TABLE 1. DISTRIBUTION BY DOSE OF 1530 MEASURED RADIUM CASES

Dose Range Gy	Weighted Dose Gy	Cases	Sarcomas	Person Years at Risk	Incidence: Sarcomas/ Person Yr
>100	156.78	26	13	494	0.0263
≥50.0 <100	62.72	38	17	1,176	0.0145
≥25.0 < 50.0	37.19	47	15	1,937	0.0077
≥10.0 < 25.0	15.92	49	1	2,537	0.0004
≥5.00 < 10.0	7.046	52	0	2,918	0
≥2.50 < 5.00	3.520	57	0	3,162	0
≥1.00 < 2.50	1.584	106	0	5,856	0
≥0.50 < 1.00	0.705	96	0	5,015	0
≥0.25 < 0.50	0.352	141	0	7,103	0
≥0.10 < 0.25	0.156	205	0	9,422	0
≥0.05 < 0.10	0.067	167	0	7,314	0
≥0.025< 0.05	0.035	80	0	3,419	0
< 0.025		466	0	21,748	0

Several different continuos functions can be fit to this data. One of the best fits is given by

$$\text{Incidence} = A \times (D^{+X}) \times e^{(-B \times D)}$$

where $A = 1.53 \times 10^{-6}$

$B = 1.84 \times 10^{-2}$

$X = 2.5$

and D = Dose in gray

with a χ^2 probability of $p = 0.31$.

Several other values of the exponent on the dose will also give acceptable fits for such continuous functions that pass through the origin.

When these dose groups are plotted in Fig. 3 the evidence for a threshold is marked. Dividing the dose groups up in this manner suggests that a threshold exists in the neighborhood of 10 Gy.

Functions of the form

$$\text{Incidence} = \text{Constant} + A \times (D^{B})$$

and

$$\text{Incidence} = \text{Constant} + A \times (D^{(\text{a specified exponent})}) \times e^{(-B \times D)}$$

were fit to the data, and some acceptable fits were found. These allow the constant term to define the threshold value when the Incidence equals zero, tbut all have a non-integer exponents on the dose term. The best fit was

$$\text{Incidence} = -3.201 \times 10^{-2} + 1.575 \times 10^{-2} \times D^{0.259}$$

which yields a threshold at 15.4 Gy

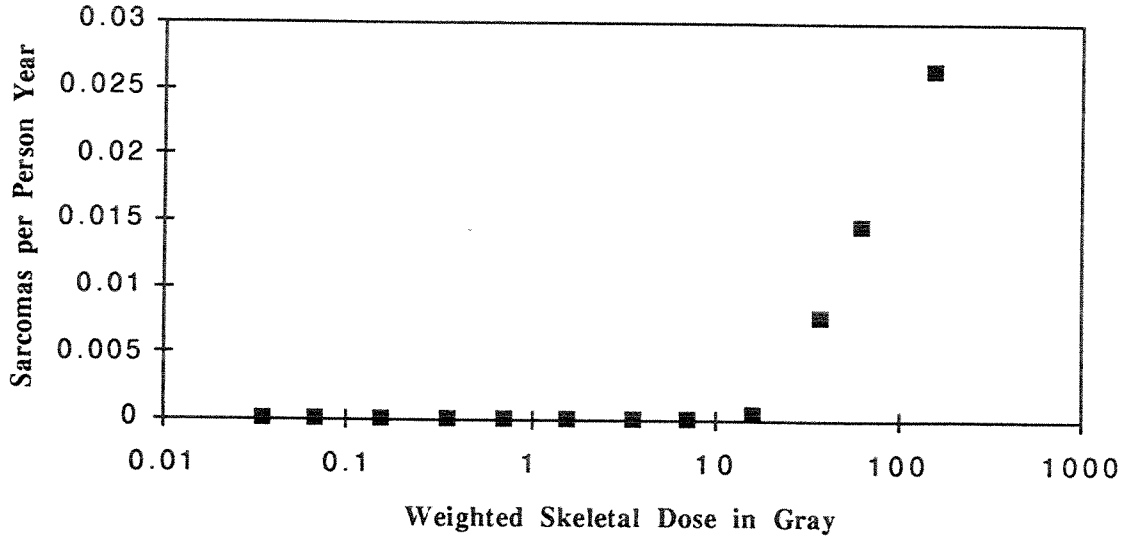

Figure 3. The solid points show the sarcoma incidence in each of the 12 dose groups from Table 1.

One should be aware that changing the size of the dose groups can have a marked effect on the shape of the dose response plot. It is not my purpose to specify precisely where the threshold is, it is only to point out that this data set strongly suggests that there is a threshold. Indeed, it would be very difficult to determine precisely the location of a threshold, if one exists.

3. THE HEAD CARCINOMAS

In addition to the bone sarcomas, radium deposition in humans is known to be responsible for the induction of head carcinomas, carcinomas that arise in the paranasal sinuses or mastoid air cells. These malignancies take longer to appear than the bone sarcomas, the earliest appearance time was 19 years after first exposure to radium, in contrast to only 5 years for the sarcomas. Both appear at very long times after exposure, as late as 63 years. There have been only half as many of the head carcinomas as bone sarcomas. In the total measured population, there were 32 carcinomas to 64 sarcomas; in the dial worker cohort the ratio was 19 to 46. As a consequence of the small number of the head carcinomas, there is insufficient statistical power to differentiate between alternate forms of dose response functions. It probably would be appropriate to calculate the risk of bone sarcoma for a given radium exposure, then reduce this risk by half to predict head carcinoma risk for a given exposure.

These radium induced malignancies have occurred more often in women than in men, in large part due to the much greater number of women employed in the dial painting industries. However, there were many males who received high levels of radium from medical treatments or exposure in chemical plants. When the dose response relation for bone sarcomas derived from female dial workers is applied to this population, it predicts significantly more sarcomas than were observed [11]. This suggests, but does not prove, that males may be less likely than females to develop bone sarcomas from internally deposited radium.

Before leaving the subject of radium-induced malignancies, it should be noted that no one who entered the dial painting industry after 1925 has developed either of the radium induced tumors. It was in 1925 that the request was made that dial painters were not to tip their brushes with their mouths. The dial painting studios had no rules for cleanliness, no attempts were made to clean up the spilled radium, and of course there were no health physicists monitoring their activities in those days. However, just the simple instruction, "Don't put the brush in your mouth" was sufficient to stop completely the induction of malignancies.

Note, however, that this did not put an end to the use of radium for intravenous injections as a medication or its use as an additive for bottled drinking waters. These sources of internal radium deposition continued to exist, and accounted for the induction of radium-induced malignancies in additional persons exposed after 1925.

4. OTHER MALIGNANCIES

Radium-induced leukemias have always been an expected consequence of radium deposition in bone. However, they have not been seen in excess of expected numbers in any cohort of radium cases [12].

Two other malignancies have been at times associated with internal radium, multiple myeloma and female breast cancer. The number of multiple myeloma cases is too small for any decision to be reached at this time. In regard to the breast cancers, the numbers are larger, but the studies are confounded by uncertainties. For example, dial painters as some sites had clear excesses of breast cancer, while at other sites the numbers observed were considerably lower than expected. In addition it has been recognized that external radiation to the breast tissue from the radium in the paint being used could have delivered a significant dose to the breast tissues, and thus might be the cause of some of the breast malignancies.

5. LIFE SHORTENING

The measurement of life shortening among the female dial workers should be mentioned in this summary. In two studies [13, 14] it has been shown that the malignancies induced by radium, the

bone sarcomas and the head carcinomas, are the only causes of life shortening. Stehney et al. [13] summarized their findings as follows:

"This study has demonstrated that when the radium tumor deaths are removed, the average survival of the dial worker population is indistinguishable from estimates of the survival of contemporary white females of the same age. This is a remarkable result, for it implies that, to the precision obtainable with a population of some 1000 persons, the life expectancy of the remaining population was unaffected by radium burden."

6. CONCLUSIONS

The study of the U.S. radium cases has been terminated, and it is unlikely that it could or would be reinstated before the majority of the still-living cases will have died. Thus the data that now exists are all that will ever be available in the future. No data is being collected at this time, nor is anyone funded to examine the existing patient files. It is the hope of those of us who have been involved in the collection of the radium records that the knowledge gained, imperfect as it is, will at least become part of the basic knowledge of the field of radiation research. Toward this end, the Department of Energy has funded the publication of a book that summarizes primarily the work on radium at the Argonne National Laboratory. However, it also includes a brief review of earlier studies in the U.S., particularly of the dial painters, and also describes some of the early medical uses of radium [15]. I would hope copies of this volume could be made available in the libraries of major research laboratories and universities.

It is appropriate to conclude with a quotation from the author's preface to this book.

"Given the number of people who acquired radium internally, it is remarkable how few suffered significant damage. To be sure, those who eventually developed radium-induced malignancies suffered severely. Those who acquired very large internal quantities of radium, as did many of the early dial painters, also suffered from what we today suspect were acute radiation doses leading to early deaths. However, the great majority of exposed individuals went through life with no recognizable consequences of their exposures. They lived as long as, and apparently in as good health as, their unexposed neighbors. This fact seems to have been little appreciated and seldom mentioned, but it may be the most important finding of the entire study".

Acknowledgment

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RADIUM IN DRINKING WATER
A Review of the Studies of the Toxicity of Radium as they Apply to Very Low Intakes of Radium

This document was prepared by Dr. Robert E. Rowland. Dr. Rowland holds a Ph.D in Radiation Biology, and has spent most of his professional career at the Argonne National Laboratory studying and publishing scientific papers on various aspects of the toxicity of radium in humans. He joined the Laboratory in 1950, became Associate Director of his research division in 1964, Director in 1967, and was appointed Associate Laboratory Director for Biology and Medicine of the Argonne National Laboratory in 1981. He retired in 1983, and has worked as a consultant to the Laboratory and other organizations since that time. He has recently written a book on the history of the use of radium in the United States which summarizes the current knowledge of the toxicity of this radioelement in humans[1]. He was a member of the National Council on Radiation Protection and Measurements (NCRP) from 1971 until his resignation in 1983.

In 1969 the Atomic Energy Commission combined all of its funded research studies on radium in humans into one program, the Center for Human Radiobiology, and placed that program at Argonne under the direction of Dr. Rowland. The files in the Center for Human Radiobiology at the Argonne National Laboratory contain the names of approximately 6000 people who acquired the element radium internally. Many of these people acquired radium when internal radium was prescribed by members of the medical profession, a practice popular in the 1920s and early 1930s. Others acquired radium as a consequence of buying and drinking water to which high levels of radium had been added. The greatest number, however, acquired radium when they worked in the watch-dial industry, where a radium-containing paint was applied to watch and clock dials so that the hands and numerals would glow in the dark.

More than 2400 of these radium-containing individuals have been carefully studied in the laboratory, both for their radium content and their health status. The ultimate cause of death has been determined for the deceased cases by autopsy or at least by means of a death certificate. (More than 1000 of the these studied individuals were still living in 1990, even though most received their radium between 1920 and 1950.)

It should be recognized that all humans carry radium in their body, as a consequence of the radium ingested daily from food and water. The amount in any given person varies, depending upon their diet, but is usually of the order of 30 to 40 pCi. Similarly, radon is present in the air we breathe every day. Radon is a gas formed when radium atoms decay; its source is the radium everywhere in the soil. It is at far greater concentrations in the air than in the body from our deposited radium.

The lowest level of radium that can be measured in the body by whole-body counters is about 4000 pCi or 4 nCi. This limit is the consequence of a much more abundant form of natural radioactivity in man, that from potassium. Potassium, a normal and necessary component of the human body, contains a

Ex. 10

long lived isotope, ^{40}K. Of the body's roughly 140 grams of potassium, a small fraction, 0.012 %, is ^{40}K, which expressed as radioactivity in the human body, is 117,000 pCi, or 0.12 μCi. The decay of ^{40}K contributes so many gamma rays that body-counters are flooded with these counts, limiting their sensitivity to radium.

Exposure to radiation is feared because of the well-known ability of high levels of radiation to cause malignancies. What is seldom recognized is the fact that all humans are exposed to low levels of natural radiation at all times. The difference between the "high" and the "low" may be a factor of a million or so. It is known that two distinct malignancies can be induced by very high levels of radium in the body, bone sarcomas and carcinomas originating in the mastoid air cells or paranasal sinuses. These latter malignancies have been called "head carcinomas" for brevity. Dose response relationships have been derived and published [2,3,4] for each of these malignancies. No other malignancies have been proven to be induced by radium in the human body. A number of studies have examined all the other malignancies observed in the studies of radium in humans, but no other malignancies have been found to be consistently and statistically elevated.[5,6,7]

In 1975 the Environmental Protection Agency (EPA) proposed interim standards for radium in drinking water, and in 1976 published the National Primary Drinking Water Regulations, containing Maximum Contaminant Levels (MCLs) for radium. These MCLs were set at 5 pCi per liter for the sum of the ^{226}Ra plus ^{228}Ra activity in the water. These levels are still with us today, but much new information has been developed in the meantime which makes these standards unnecessarily stringent.

As a consequence of the large study of the toxicity of radium in humans, radium standards may now be based on human experience with radium, not derived from laboratory animal studies. Further, there is no need to attempt to deduce the effects of radium deposited within the human body from the experience of those exposed to the whole body gamma and neutron irradiations from atomic bomb detonations. Thus there is no need to introduce modifying factors in an attempt to translate animal results into predictions of human effects, or to attempt to predicted the effects of radium deposited in bone from estimates of bone dose from whole body irradiations. This is very important, for from animal studies it has been observed that radium is absorbed, retained, and eliminated quite differently in various species, and that in no species does radium adequately mimic the observed behavior in humans. Likewise, many more radium-induced bone sarcomas have been observed in our radium studies than radiation-induced bone malignancies were observed among the atomic bomb survivors.

In the Federal Register for July 18, 1991[8] MCLs for drinking water of 20 pCi for both ^{226}Ra and ^{228}Ra were proposed. The risk of drinking water containing these levels of radium can be calculated by reference to actual human experience, without reference to any hypothesis or arbitrary standard. It can be done as follows:

What would the total radium intake be after drinking water containing ^{226}Ra at a level of 20 pCi per liter for a period of 50 years? For this estimate take the EPA recommendation level of consumption, 2 liters of water per day at the proposed MCL for ^{226}Ra, 20 pCi per liter, times 365 days per year multiplied by 50 years. Of this total oral intake 20% will be absorbed into the systemic circulation[9] and circulated throughout the body. The calculation thus yields:

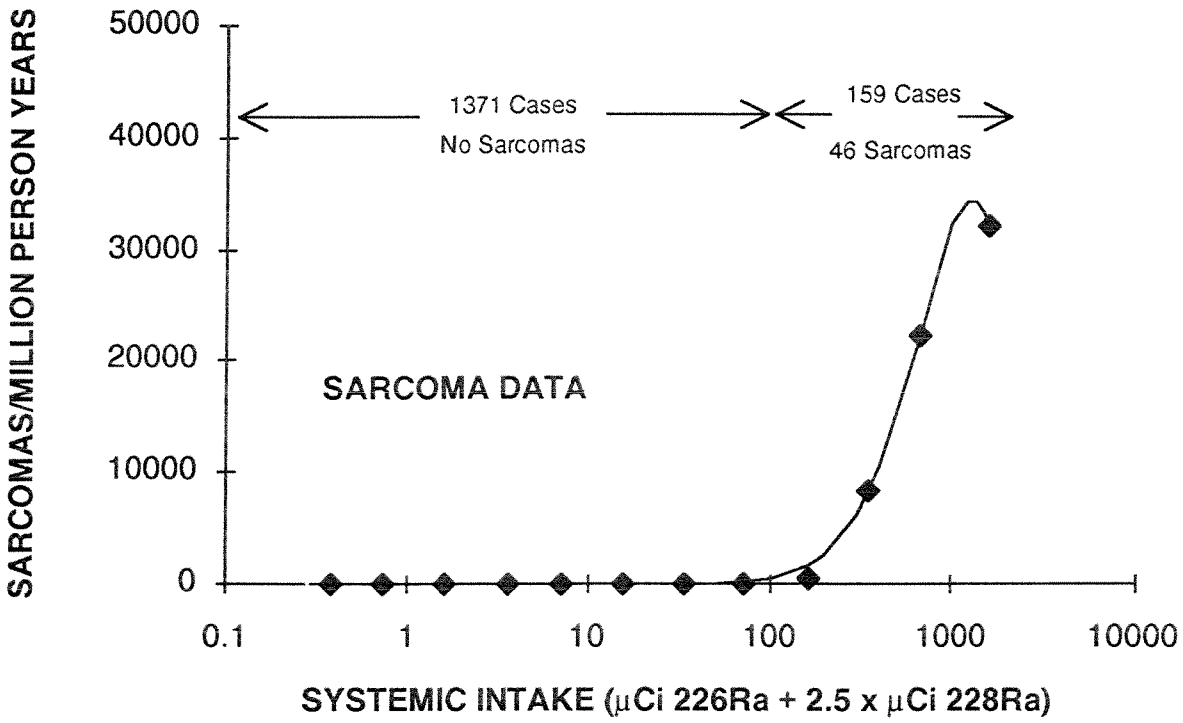
$$(20\ pCi/l \times 2\ l/d \times 365\ d/y \times 50\ y) \times 20\ \% = 146{,}000\ pCi$$

Thus after 50 years the total intake will be of the order of 150,000 pCi or 0.15 μCi of radium, or 0.3 μCi if both radium isotopes were present at the proposed maximum level.

A recent study[4] of the risk from internally deposited radium demonstrated that the probability of a radium-induced malignancy was very low in those cases where the total radium that had entered the systemic circulation was less than 75 μCi. Indeed, more than 2400 individuals exposed to radium from all sources have had their body contents measured and their radium intakes calculated[1], and not one radium-malignancy has been observed in any case with a total radium intake of less than 75 μCi. Thus at the maximum proposed radium concentration in drinking water, ingested continually for 50 years, at an ingestion rate (two liters per day) that is seldom achieved, with no other source of liquids (milk, bottled soft drinks, beer, etc.), one would accumulate less than 0.5 % of the lowest intake associated with a malignancy.

It has been observed that malignancies are induced at lower levels than any other symptom associated with high radium intakes. Such symptoms, such as bone necrosis or spontaneous fractures, are not seen until intakes levels of more than 100 μCi are achieved. Above such levels there is a high risk of a malignancy or other damaging symptoms of radium poisoning. Thus no effects from radium deposited within the body can be expected at the levels that would be obtained by drinking water containing the radium isotopes at the proposed MCLs.

The following graph of the observed bone sarcomas in a population of female dial workers who started work in the radium dial industry before 1950[4] shows the abrupt rise in the occurrence of bone sarcomas as the systemic intake approaches 100 μCi.



There were 1530 female dial workers in this study who experienced 46 bone sarcomas. It is the best group for analysis, for we have a single sex, similar occupation, identical route of entry of radium into the body (oral), and nearly all of the same age, 20.4 ± 2.1 years. Were we to take all the measured radium cases, there would now be 2403 cases with 64 bone sarcomas, but the plot of incidence against dose would look exactly the same, for there were no bone sarcomas observed below 100 μCi. The only difference would be the number of cases below the lowest level malignancy observed; that number is greater than 2100 for the population of all measured cases.

Radium is also known to induce another type of malignancy, which have been called head carcinomas. They are not as abundant as the bone sarcomas. Only 19 were observed among the 1530 radium dial workers vs. 46 bone sarcomas, while the total radium exposed population of 2403 measured cases experienced 32 vs. 64 bone sarcomas. None appeared at intake levels less than 75 μCi.

It should be noted, however, that some studies have concluded that other cancers are induced by radium at very low levels such as occur in natural drinking water. Lyman and co-workers[10] have published on an association between groundwater radium levels and the incidence of leukemia in certain Florida counties. These counties have substantial deposits of phosphate, which contain ^{238}U, the source of ^{226}Ra. This radium may ultimately enter the groundwater. Similarly, Bean and co-workers[11,12] have published associations between groundwater radium in Iowa and certain malignancies, and while no increase in leukemia was found, other malignancies were elevated, specifically bladder, lung, and breast cancer, malignancies not mentioned in the Lyman

study in Florida. If radium was the culprit, it would be expected to induce the same results in each location, not a spectrum of different results. Further, if these malignancies were indeed caused by ingested radium, surely they would be expected to be observed in the much larger study of radium cases, many with much higher intakes of radium.

All of these studies have been reviewed and discussed in a document written by a committee of the National Research Council, Health Risks of Radon and Other Internally Deposited Alpha-Emitters, also know as BEIR IV.[13] On page 228 of the BEIR IV document the following statements are found:

> "Lyman et al. show a significant association between leukemia incidence and the extent of groundwater contamination with radium. The majority of the leukemias were acute myeloid leukemias, Further, a dose-response relationship is suggested for total leukemia with increasing levels of radium contamination.
>
> "Lyman et al. do not claim, however, to have shown a causal relationship between leukemia incidence and radium contamination. They point out that there is no information on individual exposure to radium from drinking water, nor to other confounding factors. Since leukemia rates are not elevated in the radium-dial worker studies, where the radium exposures ranged from near zero to many orders of magnitude greater than could be attributed to drinking water, it is difficult to understand how radium accounts for the observations in this Florida study."

The point is that there was no indication of how many of the cases with leukemia were actually drinking water containing radium, or if they were drinking water with elevated radium how long they might have consumed it.

The reader should note that radium is often found in water from deep wells; surface water usually contains very little radium, and that home water softening processes effectively remove radium from water. These comments are relevant to the next quotation from page 231 of the BEIR IV document, where the following statements are found:

> "A pair of studies relating cancer to source of drinking water in Iowa were reported by Bean and co-workers. The first of these examined the source of water, the depth of the well, and the size of the community. This study was aimed at the role, if any, of trihalomethanes resulting from the disinfection of water by chlorination. The second, which used the deep-well data from the prior study, examined cancer incidence as a function of radium content of the water. Twenty-eight towns met the three criteria for the second study: a population between 1,000 and 10,000, water is obtained solely from wells greater than 500 ft (152 m) deep, and no water softening. These 28 towns had a total population of 63,689 people in 1970.

When the water supplies were divided into three group levels of 0-2, 2-5, and > 5 pCi of ^{226}Ra per liter and the average annual age-adjusted incidence rates were examined for the period 1969-1978 (except for 1972), certain cancers were found to increase with increasing radium content. These were bladder and lung cancer for males and breast and lung cancer for females. Their data, plus the incidence rates for these cancers for all Iowa towns with populations 1,000 to 10,000 are shown in Table 4-6.

TABLE 4-6 Cancer Incidence Rate among Persons Exposed to Different Concentrations of Radium in Drinking Water

	Age-Adjusted Incidence Rate/1,000,000				
	pCi/liter			Water Supply from:	
Cancer Site	0-2	2-5	5	Surface[a]	Ground[b]
Male lung	64.9	85.6	108.8	82.8	78.2
Female lung	13.2	18.7	19.2	19.9	15.6
Male bladder	24.6	27.6	33.7	29.9	29.8
Female breast	75.0	89.4	101.5	104.5	95.6

[a]All towns, 1,000 to 10,000 population, with surface water supplies.

[b]All towns, 1,000 to 10,000 population, with groundwater supplies.

When examined in this fashion, questions arise. There is no doubt that male and female lung cancers appear to increase with an increase in the radium content of the water, but in the case of the female lung cancers the levels were never as great as observed for those who drank surface water. A similar situation exists for female breast cancer. For male bladder cancer only, the highest radium level produced a higher cancer rate than was observed for those consuming surface water. Were it not for the fact that these cancers were not seen at radium intakes hundreds to thousands of times greater in the radium-dial painter studies, they might throw suspicion on radium. However, it is difficult to accept this hypothesis without an explanation of the lesser number of cancers found at higher radium intakes."

Thus the prestigious and respected BEIR IV report clearly concludes that no studies of natural radium in drinking water have ever been shown to pose a risk to the populations drinking such water. It is known that very high levels of ingested radium are capable of inducing malignancies, but due to the short range of the emitted radiation and to the fact that radium deposits only in bone, only two types of cancer have been induced in humans by radium. Other types have been alleged to have been induced, but there is no evidence to support these allegations. What other problems might internally deposited radium account for?

It has been suggested by several authorities that all levels of radiation are harmful, and if this is true then there should be some visible effects. One often suggested effect is a general, non-specific damage to the body, which will

result in a shortened life span. The radium cases that have been studied have now lived long enough that one can examine their life spans. This has been done twice, once in 1978 by Stehney and co-workers[14], who examined the survival of pre-1930 radium dial workers and again in 1994 by Stehney[15] who expanded the study to include pre-1950 dial workers. In each case the results were the same; life shortening is visible, but when those cases who developed the well known radium-induced malignancies are removed from the study, so no radium-induced cancer cases are included, there is no life shortening. No matter how large an internal burden was acquired, those cases that did not have a bone sarcoma or a head carcinoma showed no life shortening. Since these malignancies occur only after very large radium intakes, which could be achieved only if drinking water contained about 1 μCi per liter, they are not relevant to the present concern about MCLs set at 20 pCi per liter.

Three recent publications deserve mention. Two of these came from Dr. Finkelstein of Toronto, Canada[16, 17]. He studied the relationship between the radium content of drinking water at the birthplace of children who ultimately developed childhood bone malignancies. The first of these studies[16] identified deaths of people 25 years of age or less in Ontario due to bone cancer between the years 1950 and 1983. There were 283 usable bone cancer cases. Their birthplace water was sampled for radium between 1987 and 1992. Radium at a concentration of more than 0.19 pCi/l was found in the birthplace water of 15.2 % of those dying with bone cancer (this group of 43 cases is called the exposed group, the remaining 240 bone cancer cases from birthplaces with lower radium levels in the water are called the reference cases) but only 10.2 % of the controls (256 deaths from other causes than bone cancer) were found to have birthplace water above this level. This suggests that the radium level in the water might be the cause of the bone malignancies.

The following data for the bone malignancy (exposed plus reference) cases are taken from Table 3 of Finkelstein's publication.

	Exposed Bone Cancer Cases	Ratio	Reference Bone Cancer Cases	Ratio
Osteosarcoma	20	20/43 = 0.47	125	125/240 = 0.52
Ewings sarcoma	15	15/43 = 0.35	93	93/240 = 0.39
Chondrosarcoma	3	3/43 = 0.07	9	9/240 = 0.04
Other	5	5/43 = 0.12	13	13/240 = 0.05
Total malignancies	43		240	

Radium is known to induce osteosarcomas, but not Ewings sarcoma, chondrosarcoma, or other bone malignancies[18]. Thus one might expect to see a higher ratio of osteosarcomas in the exposed group than in the reference group. Instead we find in the exposed population 47 % of the bone malignancies were osteosarcomas while in the reference group 52 % were osteosarcomas, contrary to our expectations.

The second study by Finkelstein and Kreiger[17] examined people under the age of 26 years born in Ontario who were diagnosed with primary bone sarcoma during the period 1964 to 1988; subjects in the previous study were excluded. (It is not clear how the cases in the two studies were selected; evidently not all cases were used, otherwise the cases in the two studies would overlap.) These were matched with control subjects diagnosed with other cancers. Radium levels in drinking water from birthplace homes were measured for all cases. Cases with birthplace water containing more than 0.19 pCi/l were classified as exposed, the mean birthplace exposure was 0.7 pCi/l. Of the subjects with osteosarcoma 17 % were exposed at birthplace but only 10 % of the cancer cases were exposed at birthplace. However, in this study there was no increase in bone sarcomas with increasing dose, that is, no dose response trend. The authors conclude "Our findings are compatible with the absence of risk at low doses, but they might also reflect inadequate statistical power to measure a true risk at environmental exposure levels".

In this second document the authors correctly point out that radium is not only acquired from drinking water, but also from food. Indeed, they note that food is a more important source than water, and estimate that "The average daily intake in food is about 1.1 pCi/day, although most residents of Ontario ingest less than 0.3 pCi/day from water." What they did not address is the fact that there are other sources of radiation in human bone. Good values for these quantities can be obtained from the NCRP[19]. For the radium isotopes they are 1.4 pCi per day for ^{226}Ra and 1.0 pCi per day for ^{228}Ra from food. The mean birthplace exposure of the exposed subjects was given as 26 mBq/l or 0.7 pCi/l. At an intake of one liter of water per day the mean ^{226}Ra intake is increased from 1.4 pCi/d to 2.1 pCi/d, or by 0.7 pCi per day.

The following table was taken from NCRP 94[19], Table 9.2, page 142. It summarizes the dose equivalent rates to bone surfaces from naturally occurring radioisotopes in the body. Bone surfaces are considered to be the critical tissue for the induction of osteosarcomas.

Radionuclide	Dose Equivalent Rate (μSievert per year) to bone surfaces
^{14}C	8
^{40}K	140
^{87}Rb	14
^{238}U - ^{234}Th	3
^{230}Th	6
^{226}Ra	90
^{222}Rn	14
^{210}Pb - ^{210}Po	700
^{232}Th	2
^{228}Ra - ^{224}Ra	120
^{220}Rn	<0.1
Total	1,100

The total dose equivalent to the bone surfaces is the sum of that delivered by these internal radionuclides plus that delivered by external radiation. The total bone surface dose equivalents listed below are from NCRP 94, Table 9.3, page 142.

Source	Dose Equivalent Rate (μSievert per year) to bone surfaces
Cosmic	270
Cosmogenic	10
Terrestrial	280
In the body	1,100
Rounded Total	1,700

Thus the contribution from environmental ^{226}Ra is seen to be a very small fraction (90/1700 = 0.05) of the total. When that small fraction is increased by 0.7 pCi per day, the net increase in bone surface dose equivalent is insignificant, indeed, less than the rounding error in the above summation, i. e., less than 3 % of the total. Thus it is difficult to see how this small addition to the total bone radiation dose could be responsible for an easily detectable increase in bone malignancies.

At one point in this second publication Finkelstein and Kreiger refer to a epidemiological study by Petersen et al[20]. In this study covering 13 years (1950-1962), 111 communities whose population grew from 708,000 to 908,000 people in that period in Illinois and Iowa were found to be consuming water containing more than 3 pCi/l. Note that this is a factor of 15 greater than the lower level used in the Finkelstein studies. These were matched with controls from similar communities where the water contained less than 1 pCi/l, which is a factor of five greater than the lower limit of the exposed level in the Finkelstein study. The authors reported that, using all malignant neoplasms involving bone as their criteria, in the elevated radium water communities the mortality rate was 1.41 deaths per 100,000 people vs. a rate of 1.14 deaths per 100,000 in the control communities. They did mention that the rate in Chicago, where the water contained only 0.03 pCi/l, was significantly greater than the control rate.

The authors wrote, but did not publish, an interim report, based on the same data set, which was obtained from the EPA Region 5 Library in Chicago[21]. In this report it states that only one third of the cases with deaths due to "malignant neoplasm involving bone" on their death certificates actually died of osteosarcoma of bone, and that only certificates mentioning sarcoma of bone should be used for bone sarcoma deaths. In this interim report they found that the osteosarcoma rate per million man years was 5.6 in Chicago, 5.5 in the elevated radium towns, and 4.9 in the control towns. They concluded that "no significant difference could be detected between the osteosarcoma mortality rate in towns with water supplies having elevated levels of Ra-226 and matched control towns with water supplies having negligible levels of Ra-226."

The importance of the Petersen paper lies in the fact that if radium in water was as dangerous at low levels as implied in the Finkelstein studies, then much larger rates would have seen in both the elevated communities and in the control communities relative to the rates in Chicago. Since in this large survey of bone sarcoma cases there is no evidence of an epidemic of bone sarcomas in the higher radium water areas, nor in the control communities, and since the radium levels in Illinois and Iowa waters are much higher than found in Ontario, then the must be some other explanation for the results found in the Finkelstein study.

The final study to be mentioned was an invited paper given by Rowland at the 27th Annual Meeting of the European Society for Radiation Biology, entitled Bone Sarcoma in Humans Induced by Radium: A Threshold Response?[22] At that I meeting I proposed that a threshold existed for the induction of bone sarcomas by internally deposited radium in humans, and that threshold was approximately 1000 rad or 10 Gy. In terms of initial systemic intake the threshold was approximately 79 μCi or about 400 μCi by oral ingestion. Below these thresholds there will be no malignancies induced by internally deposited radium. Previously in this document I calculated that a fifty year intake of water containing 20 pCi per liter of both radium isotopes would be equivalent to a total radium intake of 0.3 μCi. This is less than one thousandth of the oral threshold of 400 μCi and implies that there is no risk from drinking water containing radium at these levels.

The U.S. EPA, in 1991[8], stated that the lifetime risk of drinking 2 liters of water per day containing 1 pCi/l of ^{226}Ra was 4.4×10^{-6}, and that the lifetime risk of drinking 2 liters of water per day containing 1 pCi/l of ^{228}Ra was 3.8×10^{6}. These were derived using a linear, non-threshold dose response, or risk function. At the proposed MCLs of 20 pCi/l for each radium isotopes, the lifetime risks for radium induced cancer deaths are, respectively 8.8×10^{-5} and 7.6×10^{-5}. While these are very low risks for the world we live in, I think the actual risk, from this source, are much lower. I think that there is no risk from drinking water containing radium at these levels.

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