Current (1984) Status of the Study of ^{226}Ra and ^{228}Ra in Humans at the Center for Human Radiobiology*

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Running title: Status of the Argonne study of radium in man

SUMMARY

The Center for Human Radiobiology has identified 5784 persons by name and type of exposure to ^{226}Ra and ^{228}Ra. Included are 4863 dial painters (mostly women) and non-laboratory employees of the radium dial industry, 410 laboratory workers, 399 persons who received radium for supposed therapeutic effects, and 112 in other categories. Body contents of radium have been measured in 1916 of the dial workers and about one-half of the subjects in the other groups. Bone sarcomas, carcinomas of the paranasal sinuses and mastoids, and deterioration of skeletal tissue are still the only effects unequivocally attributable to internal radium. Excess leukemias have not been observed and other malignancies, if in excess, appear more likely to be related to external gamma radiation or radon than to internal radium. Positive correlations with radium burdens have been found for the incidence of benign exostoses among subjects exposed to radium before age 18 and for shortened latency of ocular cataracts.

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INTRODUCTION

The year 1984 is both the 60th anniversary of the first report [4] of deleterious effects ("radium jaw") of internally deposited isotopes of radium, and the 15th anniversary of the formation of the Center for Human Radiobiology (CHR) at Argonne National Laboratory (ANL). Ten years ago at a meeting held in Alta, Utah, R. E. Rowland [18] presented a paper with a title similar to ours. The present report is, in effect, a revision of Rowland's paper; it demonstrates the progress made in 15 years and suggests areas where work remains to be done.

THE POPULATION

It would be inappropriate to review here the early studies of the health effects of internal radium even if space permitted it; we merely draw attention to some major reports such as those by Martland et al. [11], Aub et al. [3], Evans et al. [6,7], Miller et al. [14], and that of the New Jersey Radium Research Project [17]. The latter four contain details of the numbers of persons, with their types of exposures, who constituted the population under study at the time of the formation of the CHR. Data collected from these reports are shown in Table 1. It can be seen that the number of persons for whom radium burdens have been measured has more than doubled since the formation of the CHR. All the subjects entered into Table 1 have had their radium contents determined, either in vivo or postmortem, and the health status of each person measured in vivo has been evaluated. For those measured postmortem and those who died after measurement, death certificates and medical records have been obtained.

Of almost equal interest to us is the mortality follow-up of the unmeasured subjects. Table 2 shows the current status of almost 6000 persons potentially exposed to ^{226}Ra and/or ^{228}Ra whose names we now have. These data may be compared directly with those in Table 1 of the 1974 review by Rowland et al. [18]. That review defined "studied" cases only as those with measured radium contents, even though medical records and/or death certificates had been obtained for many of the persons whose body burdens of radium had not been determined; in this paper we use the terms "measured" and "unmeasured" to avoid the implication that nothing is known about the health status of the latter. Our total of cases identified by name and type of exposure is 1981 more than that reported in the 1974 review. Of those reported in 1974, 46 persons have been lost from the follow-up. To keep this number to a minimum continual contact is necessary.

RADIUM IN THE POPULATION

Our methods for measuring radium in vivo have been described in detail [25]. The body content of radium decreases with time, so it is not a suitable parameter for use in comparing subjects who acquired their radium 30-60 years prior to measurement. We therefore apply the Norris retention function [16],

$$R_t = 0.54R_0t^{-0.52}$$

where R_t is the retention t days after intake to the blood of R_0 units (e.g. μCi) of radium. From the experimentally determined value of R_t we calculate R_0. Correction for radioactive decay of ^{226}Ra is small (2.2% for a 50-year period) but the correction for ^{228}Ra (half-life 5.75 years) is substantial, amounting to a factor of more than 400 for a 50-year period. Because of radioactive decay, in-vivo measurements of ^{228}Ra are rarely possible in subjects examined in recent years; instead, we estimate the intakes of ^{228}Ra from measurements of ^{226}Ra and knowledge of the ratios of ^{228}Ra to ^{226}Ra in persons with similar exposure histories or in radium materials to which the subjects were exposed. Because the power of ^{228}Ra to induce bone cancer is estimated to be 2.5 times that of ^{226}Ra on an activity basis [19], we calculate what may be called an "effective" systemic radium intake as the sum of the ^{226}Ra intake and 2.5 times the ^{228}Ra intake, both expressed in μCi. For various other effects, estimates of the relative effectiveness of ^{228}Ra have ranged from zero to six [1,2,10,19,24].

Cohorts of former dial workers, although still incomplete, are far more complete than any of the other major exposure groups (medical cases, chemists, etc). We therefore concentrate on them in what follows. Figure 1 shows the intake of radium to the blood, calculated as described above, as a function of year of first exposure for the former dial workers whose body contents of radium have been measured. The 60 subjects who developed radium-related malignancies (see below) are identified by a distinctive symbol. Three main points are apparent. First, radium intakes dropped dramatically for persons whose year of first exposure was after 1925, when recommendations were made against the pointing of the radium-laden brush in the mouth [26]. Second, no dial worker with an intake of less than about 60 μCi developed a radium-related malignancy. Third, there are two distinct time-cohorts, before and after the 1930s, with the radium intakes for the later group still significant, but much lower than those of the early group.

EFFECTS OF RADIUM

The "Classical" Malignancies

At the time of writing, we know of 62 bone cancers (osteo- and fibrosarcomas) and 32 carcinomas of the paranasal sinuses or mastoids ("head" carcinomas) in 89 persons in the measured population, and 23 bone cancers and 5 "head" carcinomas in the unmeasured cases. These data and the sizes of the populations are set out in Tables 3 and 4 in the same format as Tables 5 and 6 in the 1974 paper by Rowland et al. [18]. In the studied population, since 1974 we have found eight more cases of bone cancer and six more "head" carcinomas. These differences can be attributed to new cases (three and five respectively), to exhumations of the remains of four previously unmeasured persons who had died with bone cancer between 1929 and 1946, to the revision of a 1957 diagnosis as mastoid carcinoma, and to acquisition of a 1959 death certificate showing bone cancer diagnosed two years earlier as a contributory cause of death. Despite the transfer of four cases to the measured category, the number of unmeasured bone cancer cases has only decreased by one, because four cases have been added to the list as a result of the review of medical records, while one exhumed body showed no evidence of bone cancer. The additional cases of bone cancer among the measured persons have no significant effect on the dose-response relationships reported in 1978 [19] and 1983 [20]. The most recent case occurred in 1981 (see Figure 2). A final value for the effective radium intake in this case awaits the completion of analyses for ^{228}Ra in bone samples obtained postmortem in 1983.

The time distribution of the appearance of the two types of tumor is shown in Fig. 2. The points plotted as circles and crosses are the same data as plotted by Rowland et al. in 1974, with some corrections and changes due to revision of records etc. The additions since then are shown as distinctive solid symbols. In 1974, Rowland wrote, "Noteworthy is the observation that no bone tumors have been diagnosed since 1969. Whether this 4-yr respite is a statistical fluke or an indication that the induction of these tumors is at an end remains to be seen." [18] We now know of three bone tumors that have appeared since 1969 and "head" carcinomas have continued to appear at a greater rate than bone cancers. We still can not write "Finis" to this sad episode in the experience of the radium dial workers.

Other Cancers

A study of the relationships of radium exposure to mortality from cancers of the stomach, pancreas, colon, rectum, liver, breast, lung, cervix, and corpus uteri, in 1285 female dial workers exposed before 1930, has been published recently [24]. In this study the observed mortality was compared with that expected from rates for U.S. white females, both with and without adjustment for local mortality rates. Mortality from cancers of the liver, pancreas, cervix, and corpus uteri was clearly unrelated to radium exposure. Because the gastrointestinal tract was exposed to radiation from the ingested radium, there is special interest in cancers in this region. However, cancers of the stomach, colon, and rectum appeared to be only indirectly, if at all, associated with exposure to radium. Lung cancer requires further investigation and the possibility that radon may have played a role must be seriously considered. In an earlier publication [1], a clear relationship was reported between radium intake and breast cancer in the early cohort. Further study [23,24] uncovered several observations that were inconsistent with a causal interpretation of that relationship. The three workplaces that contributed the great majority of observed and expected breast cancers showed a highly statistically significant heterogeneity. Thus, for one plant, the standardized mortality ratio (SMR) for breast cancer in women, both measured and unmeasured, and first exposed before 1930 was 0.15, while for the other two plants the SMR was about 2.0. Also, the SMR for breast cancer in the 1930-1949 cohort at this plant was 1.95.

Cuzick's conclusion [5] that internal alpha-particle emitters confer an elevated risk of multiple myeloma compared to external radiation, rested largely on the observation of 6 cases (2.15 expected) in the dial workers. It now appears [23,24] that duration of employment, a surrogate for external gamma radiation, rather than internal radium, is the more likely explanation for the association between dial work and multiple myeloma.

No excess incidence of leukemia was observed in a recent detailed analysis [23] confirming the initial report of Spiers <u>et al</u>. [21]. Nine cases (seven fatal) were observed among the female dial workers, and six among radium-exposed males. Two cases of erythrocytic leukemia occurred among the males, and none among the females. A similar disproportionation between the sexes for this rare form of myeloproliferative disease can be observed when studies of the late effects of Thorotrast [15,27] in man, are reviewed. Chronically irradiated beagles at Argonne also show the same effect [9].

In conclusion, malignancies attributable to radium are still dominated by a huge preponderance of the "classical" tumors, bone sarcoma and carcinoma of a paranasal sinus or mastoid. However, the detailed studies that have been undertaken in recent years are uncovering some findings of considerable interest, although the only finding of outstanding importance relates to the relative lack of effects on hematopoietic tissues.

Non-stochastic Effects

Rarefaction of areas of bone, termed "radiation osteitis" by Martland [12], was described by Aub et al. [3] as "the fundamental lesion observed as a late effect of internally-deposited radium." A scoring method developed by Finkel et al. for quantifying radiographically observed changes [8], was modified to yield a uniform system that was used in an essentially unchanged fashion by the Massachusetts Institute of Technology (MIT), ANL (pre-CHR) and CHR radiologists. Recently Keane et al. [10] analyzed the x-ray scores in relation to systemic intake of radium; they observed a dose-response relationship between the average rate of accumulation of score (score divided by time from first exposure to radiography) and the systemic intake of radium. A very important finding was that on an equal activity basis, ^{226}Ra and ^{228}Ra produced essentially identical effects.

Other Effects

Effects have been attributed to ^{224}Ra [13,22], such as ocular cataract and benign exostoses, that have not been a prominent feature in our series. Adams et al. [2] reviewed ocular cataract incidence in 813 measured female radium dial workers first exposed before 1930 and noted that the lifetime incidence appeared not to be increased in subjects with high systemic intakes (>50 μCi) of radium (24 cataracts in 140 subjects versus 95 in 673 subjects with lower intakes). However, they noted a highly significant difference during the first 40 years after radium exposure: eight cataracts in 5412 person-years of follow-up in the high dose group versus only seven in 35975 person-years in the low-dose group. No further work has been done in this area.

Spiess [18] reported that exostoses occurred only in persons who received ^{224}Ra as juveniles. A very preliminary search of our records yielded similar results. For 482 females and 64 males first exposed to radium at age 17 or younger and whose radium content has been determined, reports of exostosis, osteoma, or osteochondroma in 22 of the females and 3 of the males were found, and there is a strong suggestion of a positive dose-response relationship. However, the numbers are small, and because the condition is benign we have not assigned its further study a high priority.

EXHUMATIONS

Figure 3, taken from reference [20], shows the dose-squared exponential dose-response function (lower bound of the shaded area) that best fitted the then-existing data on bone cancers in female dial workers exposed before 1950, and the linear-quadratic-exponential function (upper bound of the shaded area) that still fitted acceptably (p=0.05). The circular points represent zero values observed in intake intervals below 100 µCi, whereas the triangles show where each point would be if one malignancy occurred in that interval. Since there are 23 cases of bone cancer in unmeasured persons, (20 in dial workers, Table 4), there remains the possibility of one or more cases at radium intakes of less than 100 µCi and thus within the range plotted in Fig. 3. Exhumations of unmeasured bone cancer cases are needed to test this possibility and would provide data to improve confidence in extrapolation in this low-dose region.

An active program in which 69 persons were exhumed under the aegis of the CHR was shelved in late 1979, because of a reduction in available support. The program was reactivated in 1983, with efforts concentrated on the unmeasured persons with bone cancer. The current status of this program is summarized in Table 5. The exhumation of one of the cases in June 1984, leaves 23 cases (20 former dial workers) as shown in Table 4. The systemic intake of the recently exhumed case has been estimated at about 860 µCi, in line with the intakes that led to bone cancers in the dial workers plotted in Fig. 1. Although the exhumations of three other cases have been approved by next-of-kin, we are still some way from actually having the exhumations carried out. For those cases where next-of-kin have not responded or have not been located, it is conceivable that we might be able to carry out court-authorized exhumations.

CONCLUDING REMARKS

Progress in this study since 1974 has been substantial. Almost 2000 persons have been added to the total, and of these, we have been able to measure the radium contents of nearly 800. The number of unlocated persons has remained unchanged despite the 52% increase in the known population.

Bone sarcomas and carcinomas of the paranasal sinuses or mastoid air cells are still appearing, the latter at a rate that indicates that there are more to come. We can be less dogmatic about eventual future bone sarcomas. The existence of other radium-related cancers is still equivocal, although we can say that major carcinogenic effects on the hematopoietic system have not occurred. Non-stochastic effects on the skeleton ("radiation osteitis") have been quantified and a dose-response relation determined, but the relationship of this damage to eventual sarcomagenesis is obscure.

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Table 1. Numbers of persons with measured radium contents, by class of exposure, September 1969 and June 1984.

Source of Data	Dial workers	Medical cases	Chemists & other exposures	Totals
MIT [6,7]	367	69	168	604
ANL/ACRH [14]	277	71	16	364
NJRRP [17]	113	1	47	161
Totals	757	141	231	1129[a]
CHR 1969	734	139	226	1099
CHR 1984	1916	166	292[b]	2374

[a]Some cases were included in reports from more than one laboratory
[b]239 were chemists, or other laboratory or clinical personnel

Table 2. Radium cases, by class of exposure, June 1984, for comparison with the situation in April 1974 [18].

Radium Cases	Dial work	Laboratory	Medical	Other	Totals
Located & measured					
Living	1410	99	18	39	1566
Dead	497	137	144	13	791
Lost	9	3	4	1	17
Located & not measured					
Living	1269	17	44	3	1333
Dead	856	78	88	17	1039
Lost	19	2	7	1	29
Not located	803	74	94	38	1009
Totals	4863	410	399	112	5784

Table 3. Radium-induced malignancies in the measured population.

Measured cases	Persons	Bone tumors	Sinus or mastoid carcinomas
Total population			
Living	1566	1	1
Dead	791	61	31
Totals	2357	62[a]	32[a]
Dial workers			
Living	1410	1	1
Dead	497	43	18
Total	1907	44[b]	19[b]

[a]Five persons developed malignancies of both kinds

[b]Three dial workers developed malignancies of both kinds

Table 4. Probable or confirmed malignancies in the unmeasured radium cases.

Unmeasured cases	Persons	Malignant bone tumors	Sinus or mastoid carcinomas
Total population			
Located			
Living	1333	0	0
Dead	1039	23	5
Not located	1009	--	--
Totals	3381	23	5
Dial workers			
Located			
Living	1269	0	0
Dead	856	20	5
Not located	803	--	--
Totals	2928	20	5

Table 5. Status of program reactivated in 1983 for exhumation of 21 unmeasured former radium dial painters with probable or confirmed bone sarcomas.

Status	Number of cases	Exposed	Died
Exhumed	1	1924	1946
Exhumation approved by next-of-kin	3	1920-24	1940-58
Awaiting permission by next-of-kin	4	1917-23	1931-62
No response from next-of-kin	5	1917-24	1924-47
No relatives located	3	1917-23	1931-39
Exhumation refused by next-of-kin	5	1917-24	1930-56

Captions for diagrams

Fig. 1. Effective systemic radium intake, defined as the sum of the ^{226}Ra intake, and 2.5 times the ^{228}Ra intake, both expressed in μCi (see text), as a function of year of first exposure for 1916 dial workers. Not plotted are 9 cases with measurable radium first exposed after 1970 and a number of cases with intakes of less than 0.01 μCi. Points plotted as upright triangles are for persons who developed bone sarcomas, while inverted triangles represent persons with "head" carcinomas.

Fig. 2. The year of diagnosis for each of the 62 malignant bone tumors and 32 "head" carcinomas in the total measured population. Compare with Fig. 5 in reference [18]. Solid symbols are for malignancies that have arisen or been discovered (see text) since the 1974 review.

Fig. 3. Bone sarcomas per person-year at risk versus systemic intake on a logarithmic scale for the dose region where these tumors have not been observed. See text for explanation.

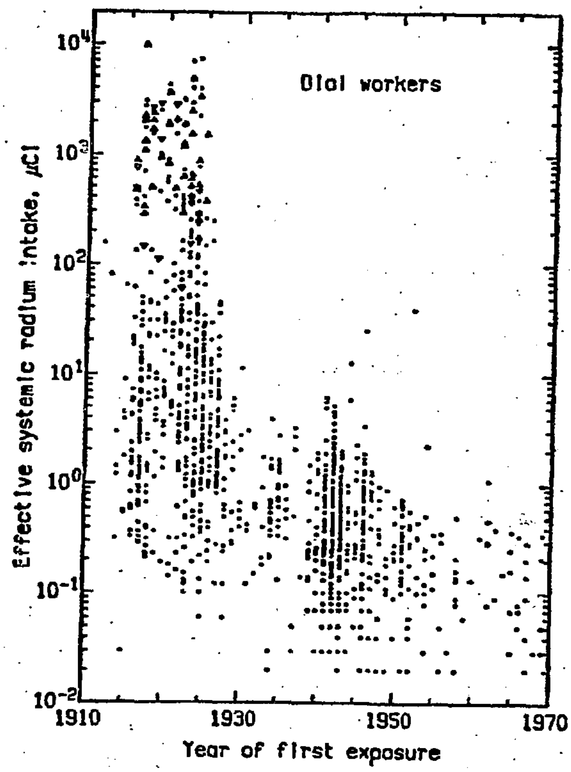

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Figure 1

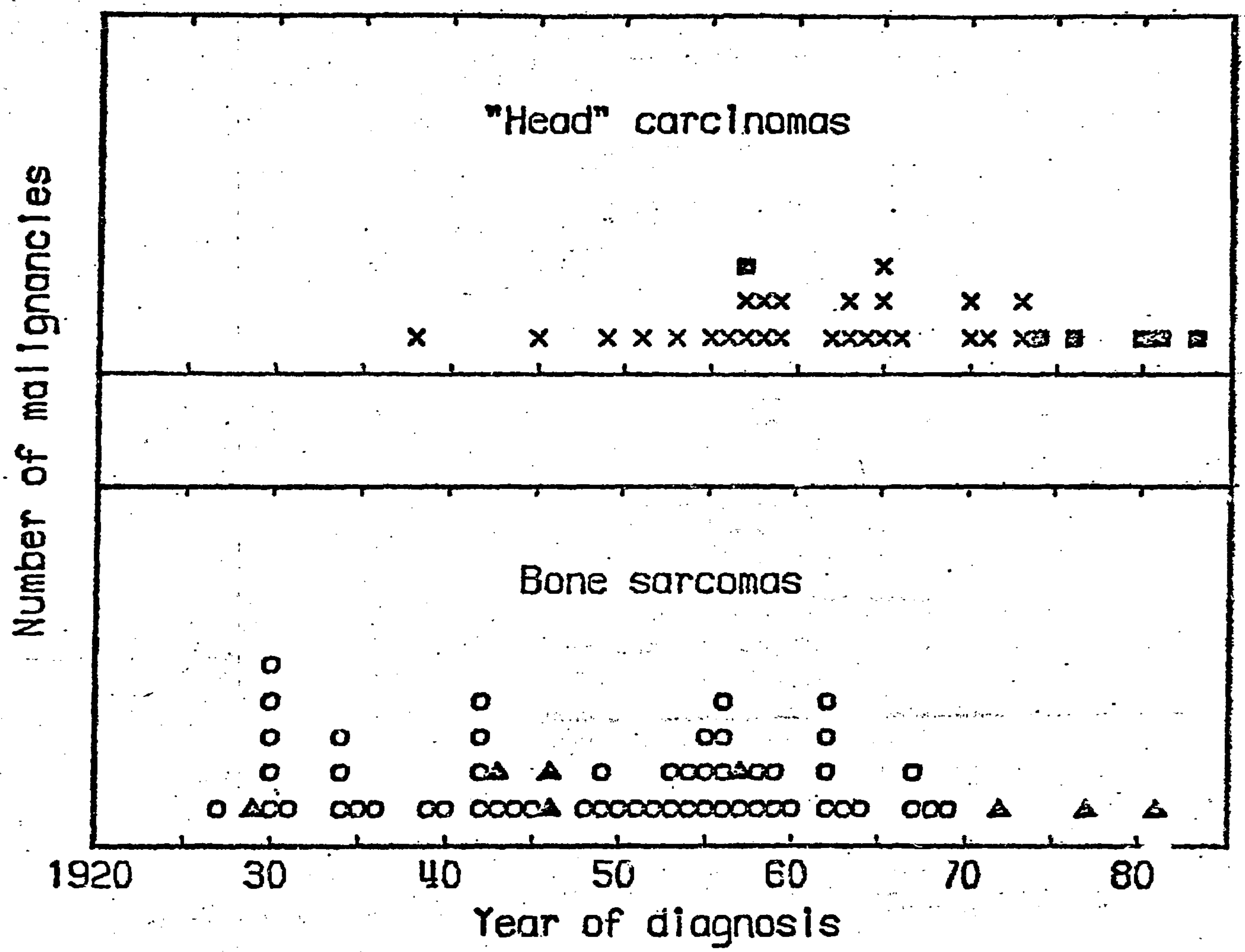

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Figure 2

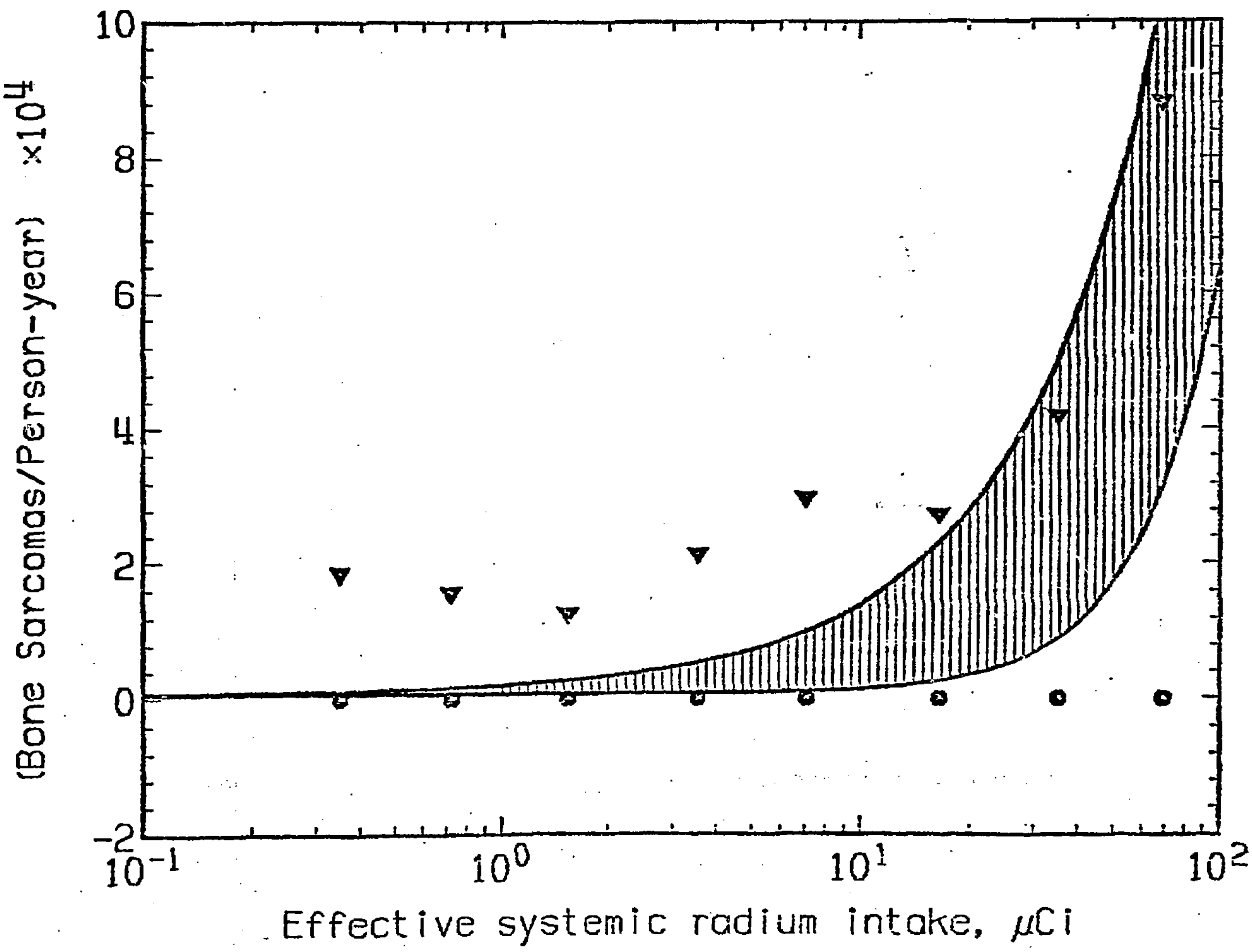

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Figure 3