718525

RANGE OF UNCERTAINTY OF MPC VALUES*

REPOSITORY ORNL/X-10
COLLECTION Office of Rad. Protection
BOX No. Snyder's Files
FOLDER

by
Walter S. Snyder
Health Physics Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee

Maximum permissible concentrations (MPC) of radionuclides in air or water as recommended by the National Committee on Radiation Protection and Measurements (NCRP) and by the International Commission on Radiological Protection (ICRP) are listed in the publications of these organizations mostly for the case of chronic exposure at a constant level and are primarily applicable for occupational exposure. Exposure at the MPC for 50 years of adult life is expected to result in a body burden, or organ burden, of the radionuclide which will produce a specified dose rate to the tissues of the organ. This limit on the dose rate is the primary standard for radiation protection in all cases except for exposure to Ra^{226}. The MPC values often are used for other conditions of exposure (short-term exposure, population exposure, etc.), and with appropriate modifications this is possible. The determination of the appropriate modifications essentially amounts to obtaining the data necessary for direct calculation so that such modifications should be regarded as a convenient means of presenting or publishing the selected values and not as a procedure for obtaining MPC on the basis of new principles. Because occupational MPC have been used and studied over a longer period of time than in the case of MPC for exposure of other

*To be presented at the Congressional Hearings on "Radiation Protection Criteria and Standards: Their Basis and Use," Washington D. C. (May 1960).

**Operated by Union Carbide Corporation for the U. S. Atomic Energy Commission.

1133872

A-00265

Human Studies Project

population groups, this discussion of uncertainties will be limited largely to occupational MPC. In principle, it would seem possible to study and determine the relevant factors entering into MPC estimation for other specified groups; and this is receiving much attention now, but long-term use of such MPC is largely lacking.

It is clear that an MPC for a specified type of exposure, e.g., chronic exposure at a constant level, involves two essentially different considerations: (1) There is a basic criterion which is to be selected, and (2) When this basic criterion is specified the metabolic factors which link the presence of the radionuclide in the environment with the criterion must be applied. Ideally, this basic standard should be the biological effects of the exposure. However, at the dose levels in question the dose-response relation generally is not known with sufficient precision to permit an estimate of the effects with a useful probable error for the estimate. Thus the NCRP and ICRP have expressed the basic criterion in terms of limits on dose (energy absorbed per gram of tissue) except in the case when bone is the organ of interest, in which case the criterion is expressed in terms of a comparison with Ra^{226} as discussed below. The uncertainty inherent in the selection of the basic criterion and the uncertainties involved in arriving at an MPC based on this criterion will be considered separately.

Beginning about 1924, cases of bone tumor associated with a body burden of radium began to be suspected, but it was only some five to eight years later that the evidence was considered conclusive by most doctors and more stringent protective practices were largely adopted in industry and medicine. Prior to 1930 many persons, perhaps thousands, accumulated body burdens of

1133873

Ra^{226} that we now consider to be significant. Some hundreds of cases with body burdens of 0.5 μc and higher have been studied. Bone changes characteristic of radium deposition are detectable in about 10 per cent of the bone samples in cases where the body burden was in the range 0.5-1 μg of Ra^{226}. Above 1 μg the majority of the specimens seem to show such changes.[1] The smallest body burden reported to have produced bone cancer is at the level of 0.5 μg,[2] and since this was a radium dial painter, it is possible, perhaps likely, that mesothorium also contributed to the dose. The NCRP recommended the value of 0.1 μg of Ra^{226} as a permissible body burden of Ra^{226} for occupational exposure in 1941. The same value was recommended by the ICRP soon after, and this recommendation has been continued by both organizations to the present.

It is difficult to assess the reliability of the value of 0.1 μg as the permissible body burden of Ra^{226} on an objective basis. As is usual in the area of internal dose estimation, the available data do not apply directly to the conditions of exposure that are under consideration. If we may digress momentarily to consider a maximum permissible intake for a single exposure or for short-term exposure during a few months or years, we need only to obtain the amount initially taken into the body rather than the body burden some 15-20 years later, and data from the radium dial painters and medical exposure cases would be more significant and would need only to be corrected for the possible presence of mesothorium. For such short-term exposure, an intake which would produce a long-term body burden in the range 0.5-10 μg or more would seem to be inadmissible since nearly 15 per cent of one group of humans studied in this range (mean of 3.4 μg) had bone sarcomas. Initially, when the body burden of 0.1 μg was

1133874

selected, it was considered that this would provide a factor of safety of at least 10. Exactly what incidence rate is considered tolerable depends on many factors (the balancing of benefits and risks), but in the case of such a severe effect as bone sarcoma, an incidence rate of 15 per cent, or even 5 per cent, would seem to be inadmissibly high for general occupational use. Based on studies of the Elgin cases,[3] a body burden of 0.5 μg 20 years after exposure might indicate an initial bone burden of about 2 μg, and the corresponding incidence rate might be of the order of 1 per cent since such a case did occur in a few hundred cases that are known. However, this neglects the influence of mesothorium. The medical cases would be less open to this objection and would indicate an initial burden of some 3 μg corresponding to 0.8 μg found 15-20 years later. What incidence rate of sarcoma a value 1/20 or 1/30 of these body burdens would produce, the available evidence does not indicate. Thus a value of 0.1 μg of Ra^{226} as permissible body burden for a short-term exposure is 1/5 to 1/30 of levels that have been thought to produce cancer, and the incidence rate is probably below 1 per cent, but it is not really well established.

Returning to the case of chronic exposure, there are several considerations that indicate the value of 0.1 μg may cause an incidence rate somewhat less than in the case of the radium dial painters.

(1) For chronic exposure, this value of 0.1 μg would be reached only at the end of the exposure period, i.e., after 50 years of exposure, whereas in the case of the single intake the body burden of 0.1 μg could be the initial value. The total dose to the bone during an extended period, say 50 years, is much less in the case of chronic exposure than for the short-term

1133875

exposure of the radium dial painters and medical cases where the body burden starts out at 0.1 μg.

(2) The radium dial painters probably ingested considerable amounts of mesothorium (Ra^{228}) along with the Ra^{226}. Since Ra^{228} has a half-life of only 6.7 years, this was not observable at the time these people were studied, some 20 years after intake. This additional source of radiation exposure probably contributed substantially to the total dose and in particular increased the dose markedly during the early period of the exposure. On the basis of one study,[4] the dose from mesothorium may have been as much as 3 to 4 times the dose from Ra^{226}. It has been noticed that luminous dial workers had major skeletal changes at lower terminal levels of body burden of Ra^{226} than in the case of patients given radium medically.[5]

(3) The short-term deposition of large amounts of Ra^{226} produces areas of high concentration in bone, and the dose is correspondingly higher in these areas since the range of an alpha particle is quite short. Continuous exposure at a lower level of intake would probably produce a far more homogeneous distribution and bring the maximum dose levels closer to the average dose level in bone.

All of the above considerations would seem to favor the view that the value of 0.1 μg as body burden of Ra^{226} is a conservative value, especially for chronic exposure. However, we must recognize that we do not know what features of the dose distribution are directly linked to the malignancy. It is possible that the high dose in the early period due to the presence

1133876

of mesothorium, or that the areas of high dose (the "hot spots"), are not directly associated with the tumor. One can speculate that a high dose may kill cells and that a somewhat lower dose may be more effective in producing malignancies. Similarly, it is not known whether the long-term irradiation of bone is more effective than a short-term high dose rate which gives the same total dose. There is some evidence to suggest that a more nearly uniform dose distribution in time might be more effective.

The value of 0.1 μg of Ra^{226} as permissible body burden has been in use for almost 20 years without entailing a risk which is considered unacceptable, and the use of radium has certainly increased many fold during this period. However, it is possible that further experience and standards of acceptance might enforce a lowering of this value. On the basis of present knowledge, (1) the value seems below the level where deleterious effects are readily detectable, (2) but not so low that no evidence of any effect is seen, and (3) the recommendation does not largely impede the usefulness of the agent in question. These three criteria seem most desirable for any general standard for protection, though it may be necessary to give up one or more of these criteria in some cases.

The ICRP and the NCRP have recommended that dose limits for other bone-seekers should be based on a comparison with Ra^{226}. There are several bases for such a comparison and all involve some difficulties. However, the effort is warranted since the experience with radium is almost the only source of data on long-term exposure of bone to radiation, and further, these are data on human exposure which are of much greater value than data from animal experiments. The dose from Ra^{226} is preponderantly from alpha radiation. For other radionuclides that are primarily alpha emitters, the

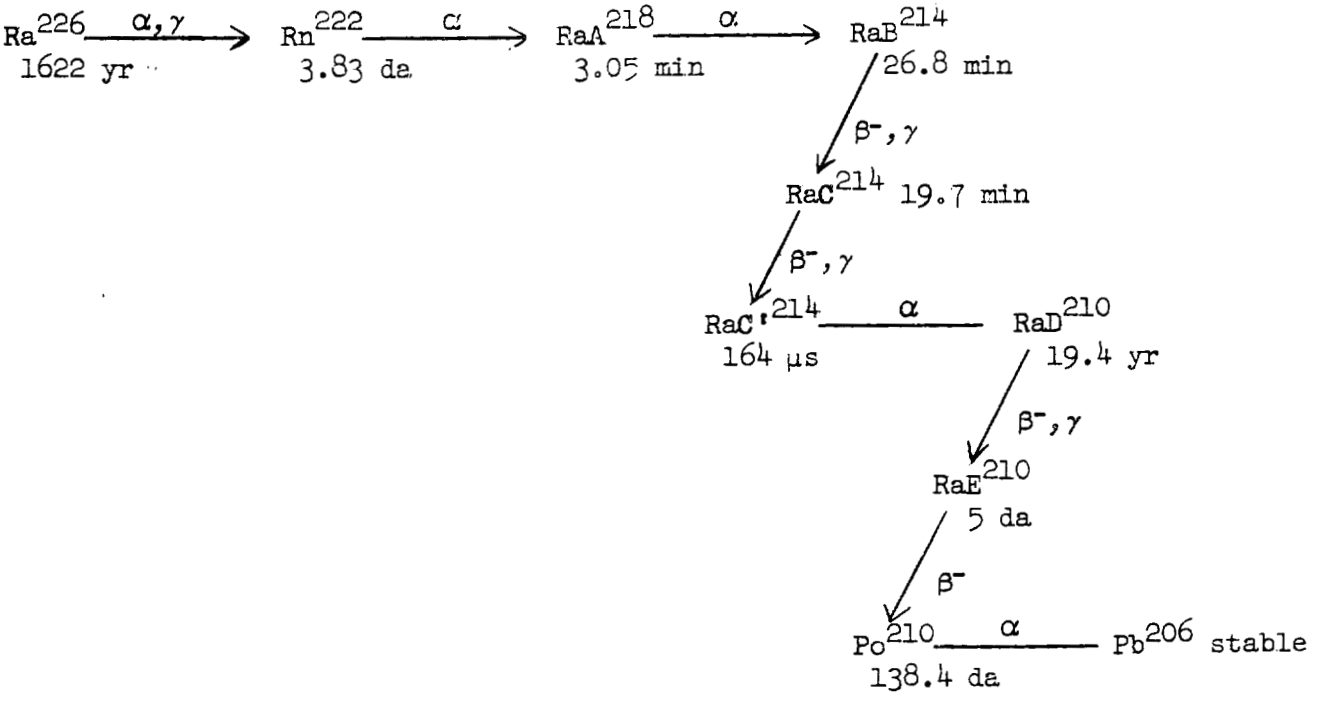
1133877

comparison is fairly straightforward and amounts to requiring that the dose level due to 0.1 μg of Ra^{226} in bone be not exceeded in the case of other alpha emitters. However, it was noticed early in the history of atomic energy that the heavy metals tended to deposit in bone in a distribution which was even less homogeneous than the distribution of radium. For this reason a "nonhomogeneity" factor of 5 was adopted for Pu and then extended to include all heavy metals. Thus it suffices to require that the average dose to bone from such alpha emitters as Pu^{239} be 1/5 the average dose to bone from 0.1 μg of Ra^{226}.

The estimation of the dose to bone from Ra^{226} is among the more complicated examples of a dose calculation when the organ burden is known. The reason is that Rn^{222} is produced by the radioactive decay of a Ra^{226} atom, and being a noble gas, the Rn^{222} tends to escape from the bone and from the body. Since the decay of Rn^{222} and its daughter elements contributes preponderantly to the total energy absorbed by bone, the fraction of Rn^{222} escaping from the bone matrix prior to radioactive decay will influence markedly the dose estimate in bone. Early work indicated that some 45 per cent of the Rn^{222} produced in bone escaped before decay[6], but later work[3,7] has indicated that 70 per cent of the Rn^{222} escapes without contributing to the dose. The estimate of dose to bone from a bone burden of 0.1 μg of Ra^{226} is outlined below. The decay schemes and the energy absorbed in bone per disintegration of an atom of Ra^{226} and of Sr^{90} are given in Tables I and II. It is assumed that the isotope is deposited in bone by chronic exposure over a 50-year exposure period.

1133878

TABLE I.



Radionuclide	Effective Energy (MeV x RBE) Absorbed in Bone per Disintegration of Ra^{226}			
	Type of Decay			
	γ	β^-	α	Atomic Recoil
Ra^{226}	0.0014		47.55	1.71
Rn^{222*}			16.46	0.60
RaA^{214*}			17.99	0.67
RaB^{214*}	0.014	0.060		
RaC^{214*}	0.092	0.22		
RaC'^{214*}			23.04	0.88
RaD^{210*}	0.0010	0.0007		
RaE^{210*}		0.025		
Po^{210*}			0.48	0.019
Totals	0.11	0.31	105.52	3.88
Total Effective Energy = 109.82 or ~ 110				

*Allowing for escape of Rn^{222} and degree of equilibrium

1133879

TABLE II

$$Sr^{90} \xrightarrow[28\ yr]{\beta^-} Y^{90} \xrightarrow[64.2\ hr]{\beta^-} Zr^{90}\ \text{stable}$$

Radionuclide	Effective Energy (MeV x RBE) Absorbed in Bone per Disintegration of Sr^{90}
Sr^{90}	0.21
Y^{90}	0.89
Total	1.1

When the radionuclide under consideration emits beta rays or gamma rays, the question is much more complex. The relative biological effectiveness (RBE) of different kinds of radiation has been extensively explored without finding any simple or unequivocal relationship. The RBE is generally defined with reference to 250 kv X-rays as the ratio of the dose from 250 kv X-rays to the dose of the given radiation when both doses produce the same effects. When so defined it is found that the RBE depends on many other factors such as the species and strain of animal used, end point selected to determine the effect, dose rate, environment, etc. In general it is found that heavy particle radiation (protons, alpha particles, neutrons) have an RBE greater than 1 and values in the range 10-20 have been found. With improvements in dosimetry, there has been a gradual lowering of RBE values for heavy particle radiation based on acute exposure. However, such delayed or long-term effects as cataract and shortening of life have indicated RBE of neutrons of the order of 10 and more. Unfortunately there is no known means of producing the same dose distribution of X-radiation and alpha rays in a single organ such as bone, and thus the direct determination of the RBE on the basis of bone cancer cannot be made. In the

1133880

absence of a direct determination, the ICRP and the NCRP have recommended that RBE be based on ion density along the track of the particle, and for alpha particles of the energies normally involved, the recommendations give a value of about 10. Actually the correlation with ion density is based on experimental results for particles giving a high ionic density and thus is only a convenient summary of their judgment of the biological potency of such radiation.

If an RBE factor is accepted, say for alpha radiation and also for beta rays, then it is possible to calculate what amount of a given beta emitter, say Sr^{90}, will give the same average dose to bone as 0.1 μg of Ra^{226}. Even then the distribution of dose will probably differ in the two cases, since the beta radiation from a given site of deposition will be spread over a greater volume than in the case of alpha radiation.

There is an alternative way of making the comparison and that is by directly determining the effects of the two radionuclides when present in the skeleton of some animal. This method has been tried in the case of several bone-seekers, in particular for Sr^{89} and Ra^{226}.[8,9] This method is attractive if the relevant experimental results are available. Unfortunately such experimental results generally are not directly applicable and require extrapolations for a lower dose level, for a longer period of exposure, and for the difference in species. Most of the data available are concerned with a high dose level administered to mice or rats, giving a rather high incidence of bone tumors in a period of 1-2 years. Longer-term studies are now under way using dogs, and when these have reached their term, it will be possible to reappraise the relative potency of bone-seekers. If it is assumed the relative potency will be the same for

1133881

the long-term, low-level effects in man, and if corrections are made for the metabolic differences of Sr and Ra in mouse and man (for example, the fraction of Rn^{222} escaping from the bone of the mouse is considerably higher than in the case of the human), then it appears that Sr^{90} is about 5 times as carcinogenic as Ra^{226}. This factor of 5 might be termed a relative damage factor, and its precise interpretation for the production of bone cancer is not known. It is possible that at the rather high dose levels of these experiments the RBE of the radium alpha particles should be taken as less than 10, and the relative damage factor, often termed the n factor, is correcting for this high RBE. It may represent an increased efficiency of the radiation from strontium which is distributed much more homogeneously throughout the bone than in the case of radium.

If the relative damage factor, or n factor, of 5 is considered as applicable and is included in the calculation of effective energy, then the two methods give essentially the same resulting body burden as they should. The inclusion of this factor amounts to saying that the rem dose, i.e., dose x RBE, is held to 20 per cent of the average dose delivered to bone from 0.1 μg of Ra^{226}. Thus the body burden q of Sr^{90} which would be expected to be equipotent with 0.1 μg of Ra^{226} is determined by $(qf_2)_{Sr} = (qf_2)_{Ra} \times \frac{110}{n \times 1.1}$ where qf_2 is the organ burden and 110 and 1.1 are the effective energies of Ra^{226} and Sr^{90} respectively. Since the skeleton contains nearly all the Sr^{90} and Ra^{226} deposited in the body by chronic exposure, the values of f_2 are near 1. Specifically, f_2 is taken as 0.99 for Ra^{226} and as 0.95 for Sr^{90}. On this basis, q = 2.1 μc for Sr^{90}.

There is a strictly dosimetric approach which has been suggested by some[10] which would restrict the bone to the same dose level as recommended

1133882

for most other tissues, i.e., 0.3 rem/week. This would give a value of 5.7 μc as permissible body burden if the 0.3 rem/week is interpreted as an average dose to bone. The local dose is not very precisely known. Perhaps the best evidence is that given in Reference 10. Figure 1 gives the distribution of dose in bone from Sr^{90} and Ra^{226} as estimated by Hindmarsh, et al.[10] As expected, the dose distribution from Sr^{90} is estimated to be much more homogeneous than the dose from Ra^{226}, the maximum found being above the mean by a factor of 3.1. This would give 5.7/3.1 = 1.8 μc as the permissible body burden of Sr^{90} which would give a maximum dose of 0.3 rem/week in the skeleton, and this value is essentially in agreement with that obtained by comparison with Ra^{226}.

The method of basing the value on a recommended dose rate is only as valid as the dose rate selected. The use of 0.3 rem/week as a permissible limit for dose to various body tissues dates from 1949 and has not been based on a specific study of bone cancer. Rather, it reflects a general judgment concerning a level that might be considered as appropriate in the absence of more specific and detailed data concerning the kinds of effects and rates of incidence to be expected. Nevertheless, the 0.1 μg of Ra^{226} corresponds to an average bone dose of 0.56 rem/week, and the agreement of the above estimates is probably not entirely fortuitous. The estimates of dose to bone from 0.1 μg of Ra^{226} and the distribution of such dose in bone probably was one basis among many for the selection of the value of 0.3 rem/week. While our present estimates of this dose and dose distribution are probably more accurate than earlier estimates, the differences probably would not produce a major change in the type of judgments involved in selecting a dose limit for general application. The dose distributions

1133883

from Sr^{90} indicated in Figures 2 and 3 are based on a single sample of bone from a human whose period of exposure to Ra^{226} was of the order of a year. The dose estimates given in Figures 2 and 3 are based on the assumption that Sr^{90} and Ra^{226} will have the same distribution in bone. It is possible that the dose distribution for chronic exposure might be more homogeneous than is indicated by these estimates.

The ICRP and the NCRP have indicated that Ra^{226} be used as a standard for bone-seekers, thus expressing some preference for a close link with the data on chronic exposure to Ra^{226} in man. After the review of the available data, the Committees on Internal Dose of these two groups voted that the comparison with radium be made on the basis of average dose to the skeleton but that the n factor of 5 be applied to all particulate radiation (β, α, atomic recoils) except when the parent isotope was radium in which case n is taken as 1. It was agreed that no specific interpretation be given for the n factor which might in some cases be more directly related to inhomogeneity and in other cases to a direct experimental demonstration of relative damage. It was agreed to designate it as the relative damage factor. On this basis the permissible organ burden in bone is given by

$$(qf_2)_{bone} = 0.1 \times \frac{110}{\mathcal{E}} \mu c \qquad (1)$$

where $\mathcal{E}$ is the effective energy of the isotope considered, i.e., energy absorbed in bone per disintegration of the parent and with the energy contributions from all particulate energy weighted by 5.

The range of uncertainty of the bone burden values based on a comparison with Ra^{226} is probably large. That is to say, it is not demonstrated on the basis of the procedures used that the estimated amounts are equivalent

1133884

UNCLASSIFIED
ORNL-LR-DWG 43911

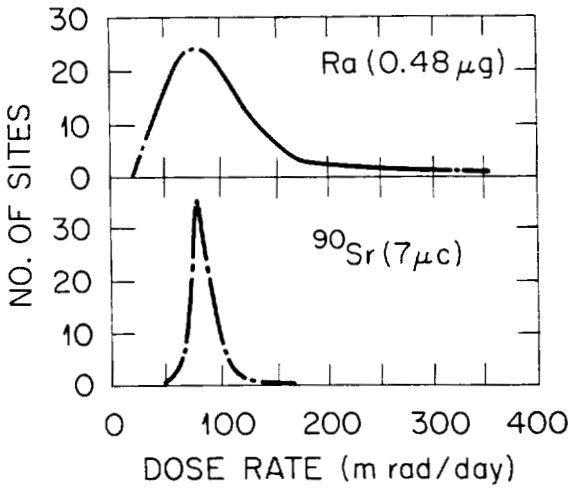
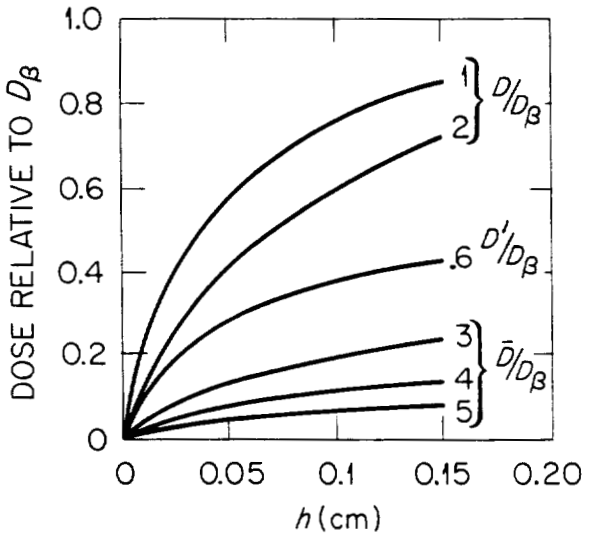


Fig. 1*. Dose distribution among concentration sites for same distribution of activity of Ra and ^{90}Sr.



(1) Small tissue volume in bone slab.
(2) Small tissue volume in bone cylinder.
(3) Average dose across marrow. Diameter 0.5 cm.
(4) Average dose across marrow. Diameter, 1.0 cm.
(5) Average dose across marrow. Diameter, 2.0 cm.
(6) Dose at edge of marrow. Diameter, 0.5 cm.

Fig. 2*. Results of calculations for a slab and cylinder in bone tissue system.

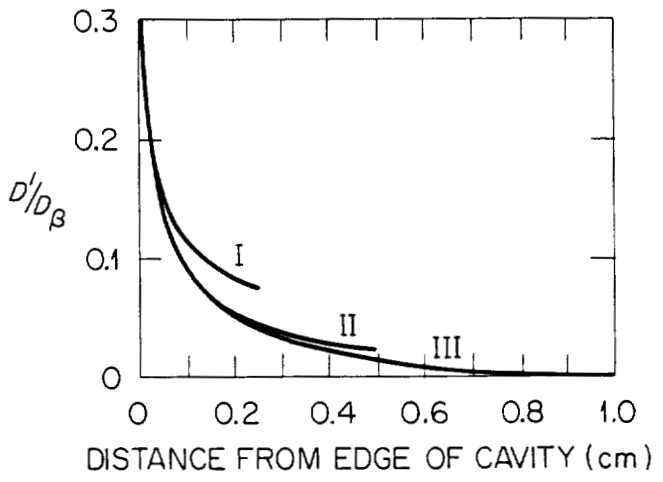


Fig. 3*. Variation in radiation dose across a marrow cavity surrounded by a deposit of ^{90}Sr 0.05 cm thick on the endosteal surface. Diameter of cavity I, 0.5 cm, II, 1.0 cm; III, 2.0 cm.

* Margaret Hindmarsh, *et al.*, "The Relative Hazards of Strontium 90 and Radium 226," Brit. J. Radiol. XXXI, No. 370, 518-533 (October 1958)

—1133885

to 0.1 μg of Ra^{226} in bone. The range of uncertainty referred to here is only that involved in making the comparison. Whether the standard itself, i.e., 0.1 μg of Ra^{226} as permissible bone burden, is too high or too low is not considered at this point. This large measure of uncertainty in making the comparison arises primarily from the extrapolations that must be made on the basis of the existing data and from the lack of any adequate theoretical basis for the extrapolations. There is little, if any, human data on long-term, low-level exposure to isotopes other than radium. As mentioned earlier, it is necessary to extrapolate the data in species, in exposure time, and in dose level, and there is no available theoretical basis for these extrapolations at the present time. The cause of cancer is not known nor is it known how its occurrence is linked with radiation in the case of Ra^{226} or other bone-seekers. Is it the total dose to a particular site or cell or the average dose in the skeleton during a long period that correlates with the occurrence of bone cancer? Since the dose-response curve is not established, it is not evident that in extrapolating from a high dose level to a lower level that the equivalence of two bone burdens is preserved. Similar remarks apply to the other extrapolations. There is little experimental or theoretical basis for converting results of short-term exposure to chronic exposure or for estimating the incidence of bone cancers in man from data on mice. It is difficult to attach any numerical value to these uncertainties since even the relevant parameters are not known. As discussed earlier, the value of 0.1 μg of radium seems on the whole to be a conservative one, and one may hope that this value is conservative enough to make some allowance for the present range of uncertainty of the methods used for comparison of effects. It is likely that the next few years will

1133886

bring to completion or near completion several long-term studies that will give additional information. Occupational exposure to presently permitted levels will continue to provide some data. To date the industrial experience is reassuring. However, it is fair to point out that the average exposure of most employees, even of those working with radiation, is generally well below the MPC level. The group exposed at or above MPC levels for considerable periods on a particular operation is generally small, and the actual intake of the material is usually very difficult to estimate. Thus it is not clear to what extent operating experience really tests these estimates. Moreover, experience with most of these isotopes is coextensive with the use of atomic energy. It may be we are only now approaching the period when late effects may be expected to appear. In summary, the body burden of 0.1 μg or Ra^{226} appears to be a well-established, conservative value so far as its use for Ra^{226} is concerned. The basic standards for other isotopes involve greater uncertainties and are essentially comparisons on the basis of dose rates, since the relevant human data on these effects are extremely scanty and difficult to interpret.

For organs where the dose limit is specified directly in terms of a rem dose, e.g., thyroid, 0.6 rem/week, or kidney, 0.3 rem/week, the estimation of organ burden is given by

$$(qf_2) = \frac{Rm}{2.2\text{x}10^{10} \text{ x } 1.6\text{x}10^{-8}\mathcal{E}} \ \mu c \qquad (2)$$

where R is the specified RBE dose in rem/week, m is the mass of the organ in grams, $2.2\text{x}10^{10}$ is the number of disintegrations per week from one microcurie, and $1.6\text{x}10^{-8}$ is a factor used to convert from units of MeV in the effective energy $\mathcal{E}$ to rem.

1133887

Once the dose rate standard is accepted, body burden or organ burden values based on the specified dose rate are rather accurate inasmuch as they only purport to give an amount which produces a given dose. The major sources of uncertainty are the degree of inhomogeneity of the deposition of the isotope within the organ, and individual variations in size and weight of the organ. The recommendations of NCRP and ICRP permit the dose to be averaged over volumes of tissue of the order of 1 cm^3, and this goes far toward de-emphasizing the importance of nonhomogeneity so far as the recommended levels are concerned. Whether smaller volumes at a higher concentration and a correspondingly higher RBE dose rate are significant is not known in general, and this implies some uncertainty. Likewise, the NCRP and ICRP have based their recommendations on a "standard man," thus largely neglecting individual variations. In 1959 the ICRP did suggest a maximum dose limit for population exposure, in effect allowing the maximum to be higher than the average by a factor of 3. Taking into account the averaging over a cubic centimeter of tissue as well as the averaging over a year suggested for population exposure, this factor of 3 may prove to be too small.

The estimation of MPC values, or equivalently, maximum permissible daily intakes MPI, involves consideration of the metabolism of these isotopes in the body. Here again radium and strontium are among the isotopes that have been studied most, and yet the necessary information is not unequivocally established. The problem is that of describing quantitatively the growth of the organ burden for a given type of exposure. As an example, consider the ingestion of Ra^{226} or Sr^{90}.

1133888

It is necessary to estimate the retention in the critical organ following ingestion or inhalation of the radionuclide. A few experiments on chronic exposure are available, but most experimental work is done on the basis of a single dose or a short-term exposure. In using such data it is necessary to integrate the retention formula to obtain the organ burden resulting from chronic exposure. Thus if R(t) denotes the fraction of ingested material that remains in the critical organ at time t following ingestion, then following chronic exposure at an intake level of I μc/day, one might expect to find in the critical organ at time T after exposure begins an amount

$$A(T) = I \int_0^T R(t)dt \ \mu c \tag{3}$$

Formula (3) assumes complete additivity, i.e., that an early intake does not affect the metabolism of later intakes. At the low level of intake to be expected in these applications, it seems a reasonable assumption. Experimental checks have been carried out and indicate good agreement in the instances checked.[11] In the few cases where long-term chronic exposure data are available, it is possible to estimate A(t) directly, but these cases are few, and in no case do they extend over a period approaching 50 years. Thus the estimations made always involve extrapolations in exposure time, and this is a major source of uncertainty. In many cases estimates of the retention function must be based on rather short-term experiments with small mammals, and in some cases even for a chemically similar but different isotope. In many cases data are available on several species but for different modes of exposure, or differing exposure periods, and at different dose levels. The choice of a retention

1133889

function R(t) from such data becomes a matter of judgment rather than the precise application of a validated theory. Specific cases discussed below will illustrate the situation.

Before taking up these specific cases, it may be well to indicate that the choice of the retention function R(t) or A(t) is the essential step in the passage from an organ burden value to an MPC. If A(T) is known, then the daily intake I is obtained from

$$I \int_0^T R(t)dt = qf_2 \tag{4}$$

In equation (4) q is the permissible body burden, f_2 is the fraction of the body burden in the critical organ, so that qf_2 is the permissible organ burden. Dividing I μc/day by the average dialy intake of the carrier (air, water, a particular food), the MPC is found. Except for individual variations in the intake of the particular carrier, the accuracy of the estimate depends only on the accuracy of the retention function.

<u>Ra^{226} and Sr^{90}</u>

As a first example of such a derivation, consider the estimation of $(MPC)_w$ for Ra^{226} and Sr^{90}, i.e., the radionuclide is assumed to be present in the water used for drinking as well as in the water used for the preparation of food. It is advantageous to consider these two isotopes together since their chemical properties are similar and the data used for one may profitably be compared with data for the other. Early studies of the radium dial painters and patients given radium for therapy led to an estimate that chronic deposits of Ra^{226} in bone showed a 45-year half-life.[12] That is to say, assuming that a constant fraction of the bone burden is eliminated from the skeleton per day, the rate of elimination was such that in 45 years

1133890

half the burden of Ra^{226} would be eliminated. Since the half-life for radioactive decay of Ra^{226} is 1622 years, this 45-year half-life would represent elimination due to biological processes alone, and thus 45 years is designated as the biological half-life of Ra^{226} in bone. This estimate of the biological elimination of Ra^{226} from bone is still retained by the Internal Dose Committees of NCRP and ICRP, although animal experiments generally indicate a faster rate of elimination.

The entire model may be doubted and indeed was never advanced except for long-term deposits of radium in bone. Following ingestion of Ra^{226} or Sr^{90}, a certain fraction f_1 of the amount ingested is absorbed into the blood, and this amount is taken up by the skeleton within a few hours.(13) The rate of elimination from bone decreases rather rapidly during the first few days, but this elimination rate decreases with time. Several models have been suggested and used to interpret such data. One model assumes that there are several "compartments" or categories of deposition, the material being eliminated from each compartment at a rate characteristic of that comparmment. As the time after exposure increases, the compartments with a rapid turnover time are largely depleted, and only the compartments with a long half-life contain a significant amount of the material. One may speculate that these compartments might represent material deposited in different tissues, e.g., Haversian systems, endosteal bone, bone mineral, etc., but no such interpretation has been experimentally verified. Figure 4 gives data on retention of Sr^{90} in monkeys(14) and has been fitted by four exponentials each of which might be considered to represent a compartment. The half-times for the respective compartments are approximately 1 day, 10 days, 50 days, and 980 days. In general, the turnover time tends

1133891

UNCLASSIFIED
ORNL-LR-DWG-47560

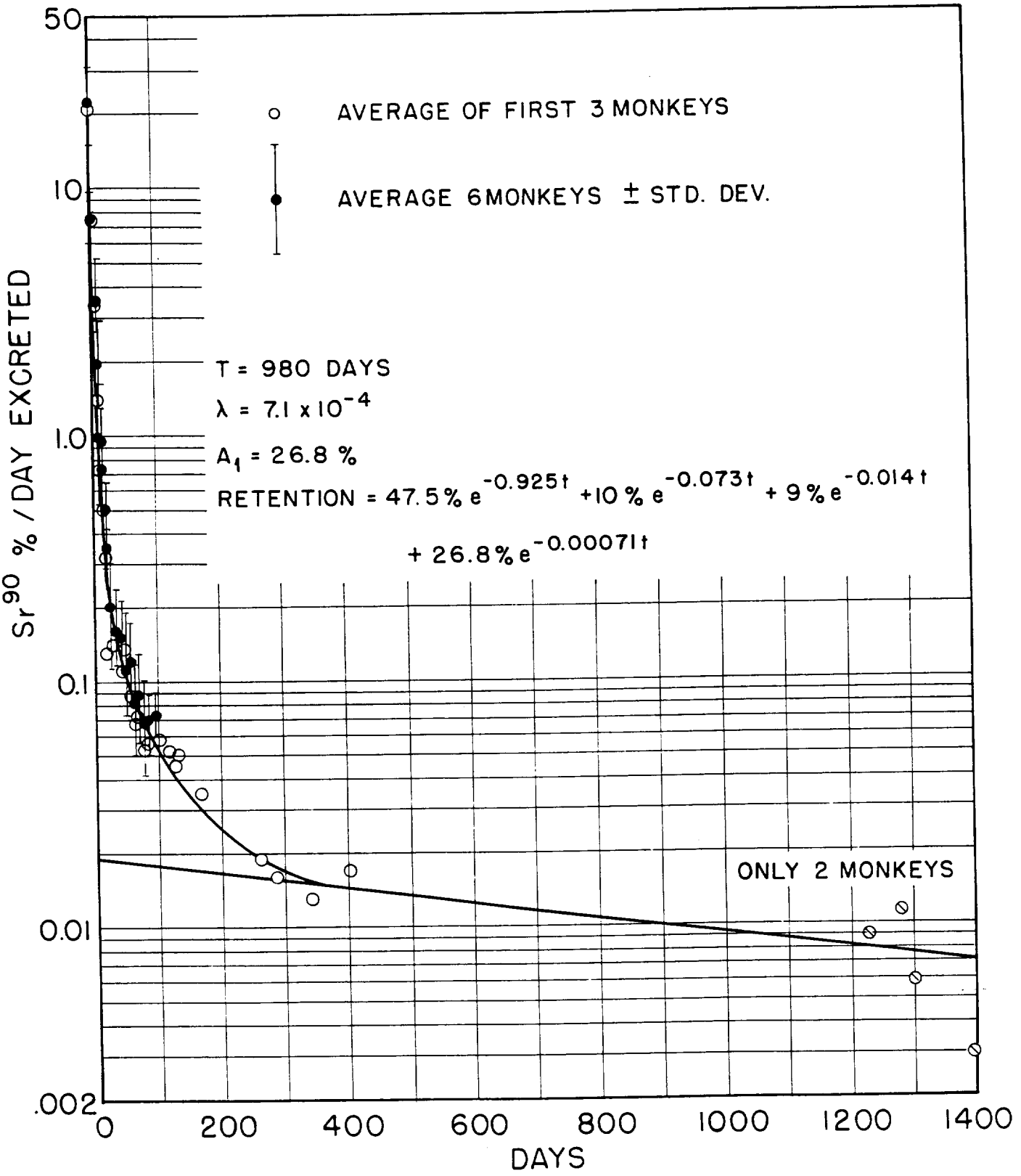


FIGURE 4. EXCRETION AND RETENTION OF Sr^{90} IN MONKEYS.

1133892

to increase with the size of the animal, but there is no validated theory for extrapolating from monkey or dog to man. In recent years there has been work, particularly by Langham and Richmond, which may lead to such an adequate theory. However, at the present time, it is not possible to say definitely whether the monkey data and other similar data on dogs, mice, etc., are inconsistent with the 45-year half-life in man or not. Figure 5 from Reference 15 shows the variation of turnover time, or biological half-life, of Cs, Rb, and Na in mice, rats, monkeys, dogs, and man. It will be noted that the lines are not parallel, and thus the extrapolation law varies according to the isotope under consideration. We may hope that more data will be available in the years ahead and that the use of the whole body counter and other techniques may provide data directly on man in some cases.

Another model frequently used to interpret retention data assumes that the retention varies as a power of the time following intake,

$$R(t) = At^{-n} \tag{5}$$

Such a function yields a graph which is a straight line on a log-log plot. Figure 6 shows data on retention of Sr^{85} in man presented in this way.[16]

Some of the most accurate human data on radium retention is that relating to the Elgin Hospital patients. In contrast to the radium dial painters, these patients received known amounts by injection over a period of about a year, the body burden was estimated on the basis of expired radon within a period of about a year, and a careful estimate of their body burden was again obtained some 20 years later. These data are shown in Figure 7.[3] It will be noted that there is considerable scatter in the data. Unfortunately no data are available during the intervening years

1133893

UNCLASSIFIED
ORNL-LR-DWG-47843

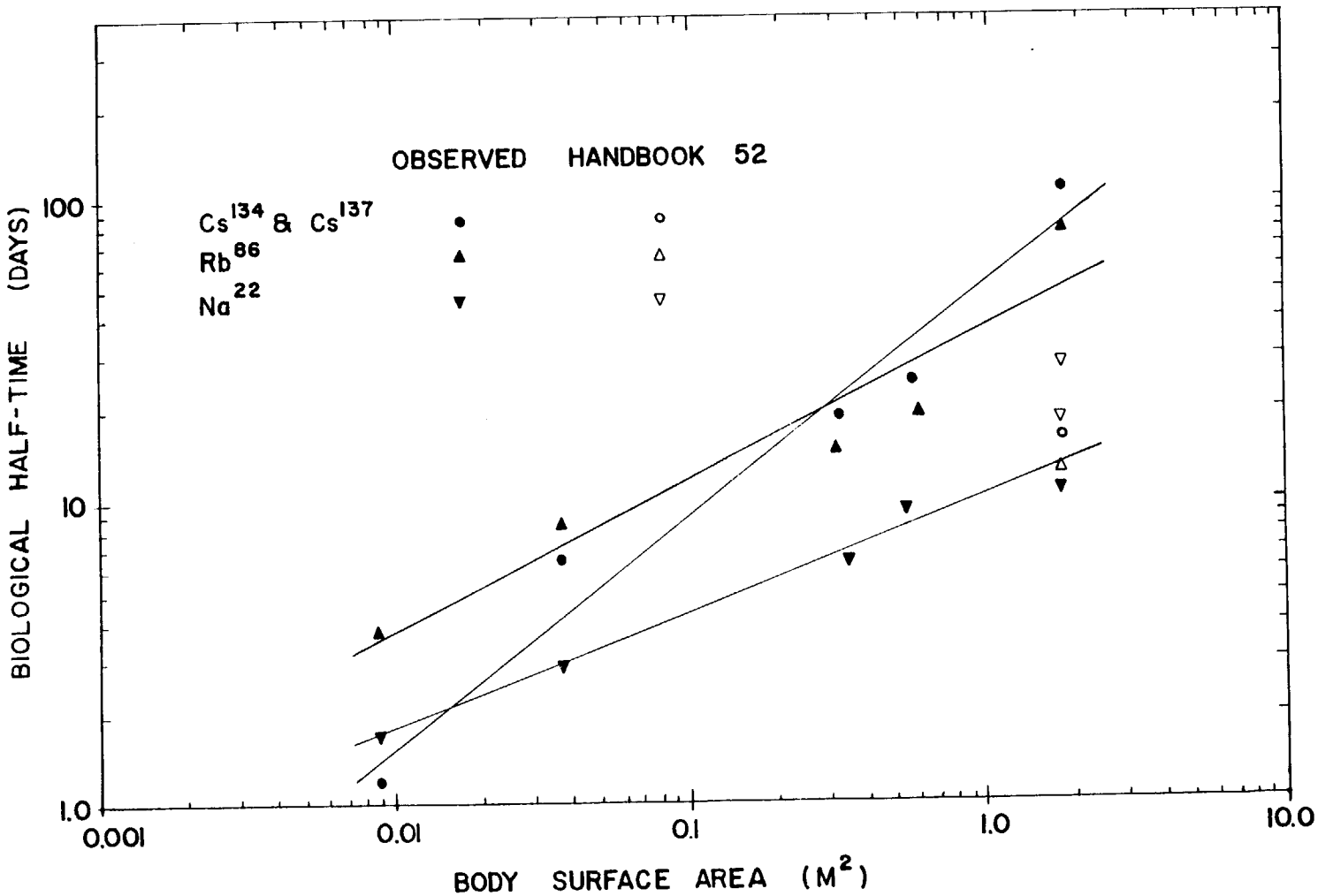


Fig. 5 Relationship between $BT_{1/2}$ and surface area for Na^{22}, Rb^{86}, Cs^{134}, and Cs^{137} in five species of animals. (Taken from LA-2207)

1133894

UNCLASSIFIED
ORNL-LR-DWG 33788

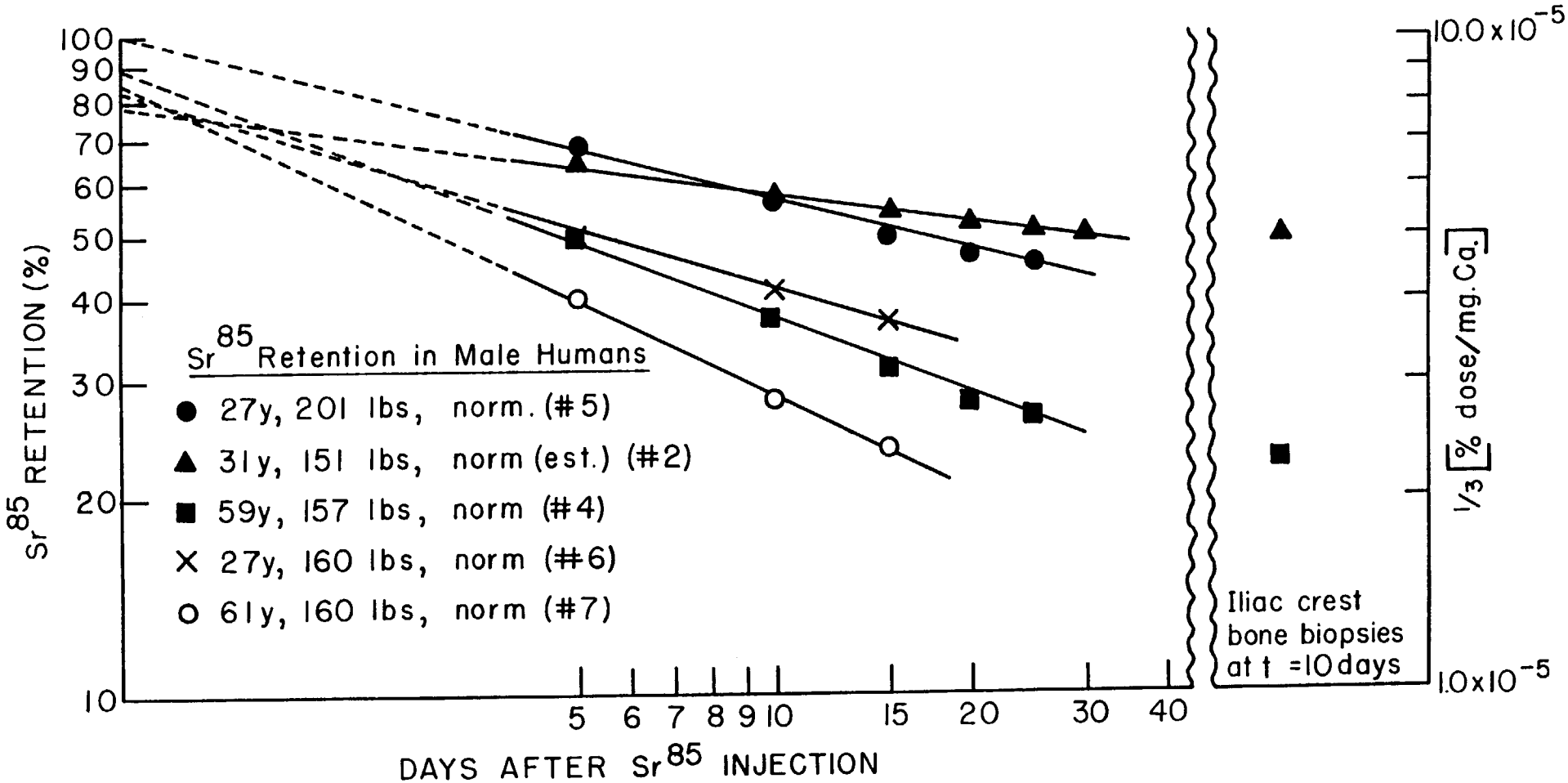
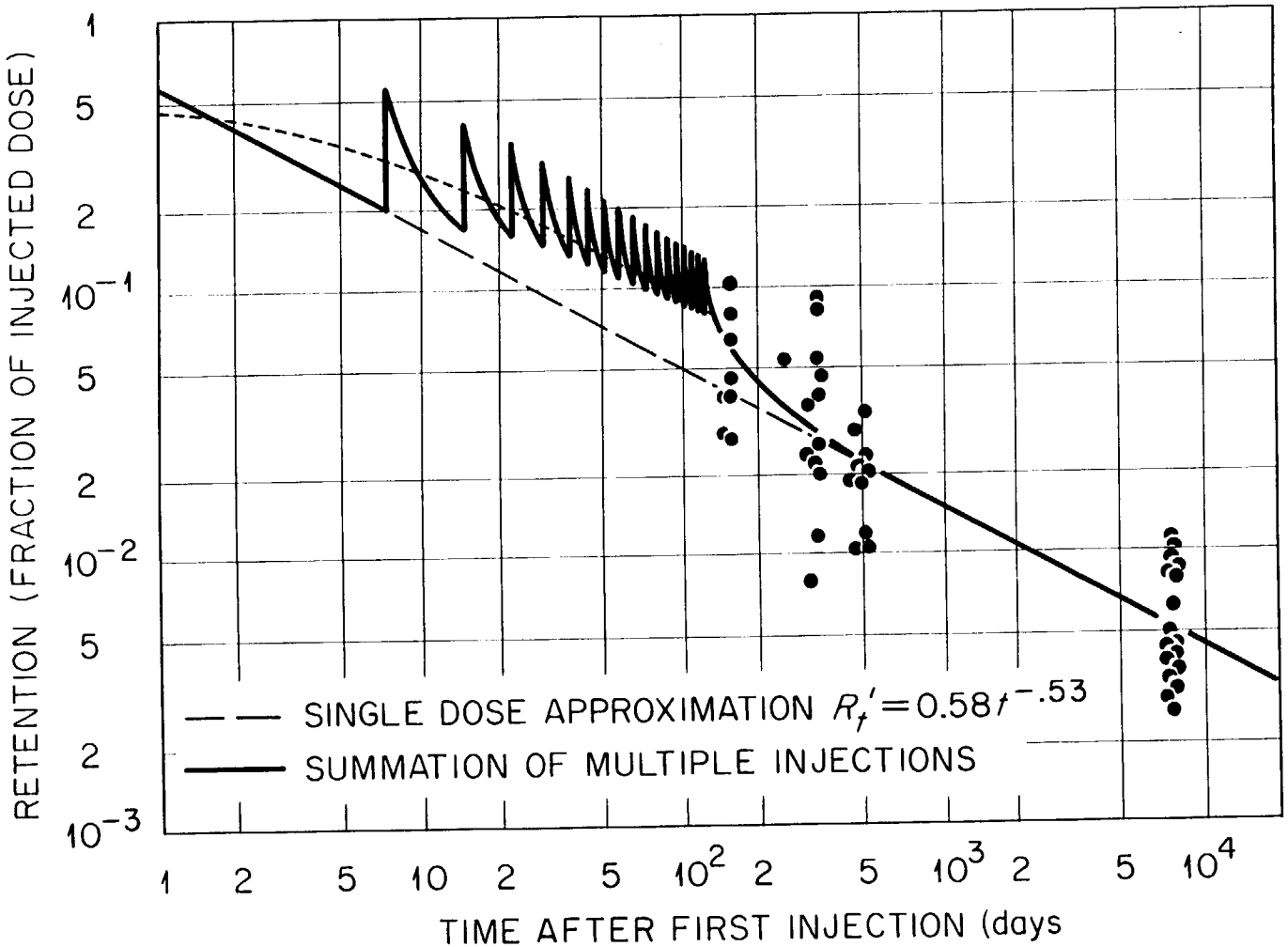


FIGURE 6

1133895

UNCLASSIFIED
ORNL-LR-DWG 33785



Retention of Radium in Elgin Hospital Patients.

FIGURE 7

1133896

so that the shape of the retention curve is not demonstrated. It is possible that further study of these patients will provide an answer. These data are roughly consistent with a retention law of

$$R(t) = .58\ t^{-.53} \tag{6}$$

The question of which model of retention to use is not an academic one. If reliable human data were available over a 50-year period, the data could be used directly to estimate the body burden and the model would be unnecessary. Any mathematical formula fitted to the data is merely a more or less convenient means of using the data. Actually the available biological data can be fitted with either of these models to within the accuracy of the data, and thus it is unimportant which model is adopted over the period of time represented by the data. However, the available data do not extend over periods of time approaching 50 years, and for this extrapolation the choice of the model is of considerable importance. For example, using equation (6) the body burden after 50 years of continuous intake is approximately 135 I, i.e., some 135 daily intakes.

If we attempt to fit a single exponential to the same two values, i.e., 3 per cent at 1 year and 2/3 per cent at 20 years, we obtain:

$$R(t) = 0.032\ e^{-\frac{0.693}{8.8}t} \tag{7}$$

where time t is in years. The half-life of 8.8 years is about three times as long as the monkey data indicate, but this does not seem inconsistent with what might be expected in extrapolating from monkey to man. The fraction absorbed seems small on the basis of the monkey data. This formula would give a body burden of about 150 daily intakes, i.e., 150 I. This result is in line with the above estimate but requires a half-life very much

1133897

shorter than the observed biological half-life of 45 years. Since this biological half-life rests on a fairly direct measurement of a chronic body burden of radium in humans, it should not be disregarded lightly. However, if the half-life of 45 years is assumed and if the retention at one year is again taken to be 3 per cent, then the body burden after 50 years of exposure will amount to about 420 I. Thus the estimated body burden would be higher by a factor of 3 if this retention formula is used. Unfortunately, the human data are not precise enough to determine which retention formula is representative of an average man. There is uncertainty here which may amount to a factor of 3. The committees concerned with internal dose decided to use the longer half-life of 45 years for Ra^{226} and of 50 years for Sr^{90} as in earlier recommendations. As further long-term studies are completed, it may be possible to resolve this difficulty.

A joint subcommittee of the ICRP and NCRP Committees on Internal Dose considered the power law for the isotopes of strontium, radium, uranium, and plutonium. The MPC values obtained in this way were submitted for consideration of the committees. In general, the use of the power function gave higher values of the MPC, and the committees decided to retain the exponential model pending further clarification of the problem and also in order to give a uniform basis for the presentation of the recommendations. The values obtained by the power function are given in an appendix of ICRP Publication 2.[17]

Only a single exponential has been used in the above discussion since for chronic exposure over 50 years the first three terms of the equation in Figure 4 would contribute a negligible amount to the body burden. Thus the coefficient .032 before the exponential in equation (7) represents only

1133898

the fraction of intake going to a single compartment. On the basis of the monkey data, the value of this coefficient should be about .27, but since the monkey data in Figure 4 were obtained from an injection study, this must be corrected for oral intake. Studies of humans by Spencer et al.[13] and animal studies have indicated a considerable spread of values for this fraction. It has been demonstrated[18] that its value depends on the amount of calcium in the diet, and recent work[19] has indicated that other elements in the diet also compete with radium and strontium. Thus the value selected can only represent an average for a certain situation. The values selected are to be considered as representative for an average individual on a typical diet. For any special diet or group of individuals, e.g., children, people with certain bone diseases, or people on certain diets, this factor would need to be adjusted, and the recommendations of ICRP and NCRP suggest that this should be done when the data are available. Some results of Spencer et al.[13] are given in Table III.

TABLE III

Excretion and Retention of Sr^{85} 12 Days Following an I.V. and Oral Tracer Dose

	Intravenous Sr^{85}, % of Administered Dose	
	Case 1	Case 3
Urine	57.2	31.6
Stool	10.4	14.2
Total Excretion	67.6	45.8
Retained	32.4	54.2
	Oral	
Urine	14.8	8.4
Stool	79.0	78.3
Total Excretion	93.8	86.7
Retained	6.2	13.3

1133899

As an indication of the variation in behavior of isotopes that are chemically similar, Table IV gives the values of the constants adopted for Ra^{226}, Sr^{90}, and Ca^{45} for the retention formula (7).

TABLE IV

Values of f_w and Biological Half-life, T_b, for the Retention Formula

$$R(t) = f_w e^{-.693t/T}$$

	Ca^{45}	Sr^{90}	Ra^{226}
f_w	0.54	0.09	0.03
T_b(days)	1.6×10^4	1.8×10^4	1.6×10^4

Iodine-131

In contrast with the foregoing, I^{131} is dispersed in many tissues of the body, but the highest concentration occurs in the thyroid gland. The biological half-life is only 138 days, and so under a constant level of intake, a state of equilibrium is attained within a few weeks. The radioactive half-life is only 8 days, and thus the total elimination due to biological processes as well as elimination due to radioactive decay gives total half-life of 7.6 days. As with strontium and calcium a deficiency of iodine in the body will result in a greatly increased uptake, but for a normal situation the fraction going to the thyroid is about 5-35 per cent, the value varying with the amount of the dose and the state of activity of the thyroid.[20] The total organ burden under equilibrium conditions is then given by

$$I \times 0.3 \times 7.7/.693 = 3.3\ I \qquad (8)$$

1133900

The MPC value so obtained is 2×10^{-5}. The range of uncertainty is here much less than in the case of Ra^{226} and Sr^{90}. This arises from the fact that the radioactive half-life is much shorter than the time for biological elimination. Thus an equilibrium condition is attained in a few weeks, and this is determined largely by the radiological half-life which is a well-determined physical quantity. The only parameter involving a large measure of uncertainty is f_w, and this is relatively easy to measure. There is a large spread of values available for f_w, depending on the individual's condition and diet. As mentioned previously, the recommendations of ICRP and NCRP point this out and state that the value of this parameter will require adjustment for special groups. In most situations such corrections are not made since the levels are generally much below the MPC, but when the question is a critical one, e.g., the Windscale incident, such corrections are made. Thus this range of variation does not represent an essential uncertainty but only an adjustment of the data that may not always be worth the making. For day-to-day use it may be easier to remain comfortably below the MPC rather than to attempt the consideration of the individual variations involved.

It may be well to clarify further the distinction referred to above in the case of iodine. The MPC values are listed in the recommendations of the NCRP and the ICRP for certain standard conditions. It is assumed the exposed person is a "standard man" and the body weight, organ weights, and intakes of air and water are carefully specified for this individual. The chemical form of the isotope is not specified, but its solubility in body fluids, e.g., the extent of absorption into the blood from the gastro-intestinal tract is specified. It is assumed the radionuclide for which

1133901

the MPC is listed is the only source of relevant exposure and that the exposure is continuous throughout the exposure period. MPC values are given for occupational exposure during 40 hours/week and also for continuous exposure during the full 168 hours/week. In actual operations, there are many adjustments which can be applied to these values. If the radionuclide is present both in air and in water, or if other radionuclides are present, the full MPC level must not be used for each type of exposure. The levels must be somewhat reduced so that the total exposure to individual organs is reduced to the recommended levels. This adjustment can be made in a variety of ways. For example, if Ra^{226} and Sr^{90} are present in water at levels of 60 per cent and 70 per cent of the MPC levels, respectively, then the level is somewhat too high. One or the other or both should be reduced. Levels of 50 per cent of the MPC values of each would be acceptable, but it would also be acceptable to merely reduce the radium to a level of 30 per cent of the MPC value for Ra^{226}. Similarly, adjustments may be made for exposure time. The recommendations of the NCRP and the ICRP are based on total exposure over 13 weeks in the case of occupational exposure, and for exposure of the population, the yearly dose has been used. Thus a concentration 10 times the MPC level does not indicate an overexposure unless the duration of the exposure is sufficiently long. Thus the level in a river might be above the $(MPC)_w$ level for population exposure in some months of the year, but if the average over the year is at or below the $(MPC)_w$, there has been no infringement of either NCRP or ICRP recommendations. Finally, adjustments may be made for solubility or chemical form. The solubility factors are listed in the ICRP Report of Committee II,[17] and the user is advised to adjust to suit particular

1133902

compounds or characteristics of the material. In general, the forms given in the recommendations correspond to the more insoluble and the more soluble forms that have been tested. Corrections for individual differences, or group differences, could also be made and should be made in applying these values to special situations or groups of individuals, e.g., children, pregnant women, etc. The diet of the standard man has not been as carefully specified as many of his other metabolic characteristics, and this would be a factor in adjusting the MPC values for particular applications. These adjustments to correct for specific characteristics of the exposure situation probably should not be considered as "uncertainties" in the MPC values. They are factors which can be introduced whenever the necessary data are available, and the situation seems to warrant the effort. Thus corrections for increased uptake of iodine or strontium by children are usually made if the situation is critical enough to warrant the effort as was done in determining permissible levels following the Windscale incident. In routine operations the concentration level may be so far below the MPC level that these corrections may be neglected. Often the resulting levels are assumed to produce the body burdens or dose limits specified in the recommendations, and this may involve considerable inaccuracy. However, this is not directly an inaccuracy in the MPC as listed but rather in applying it to other conditions of exposure without appropriate corrections. Such neglect of corrections may be warranted when the operational level is so low as to effectively make some allowance for these modifications.

Cesium-137

Cs^{137} is an example of a radionuclide of long half-life which deposits quite generally in the soft tissues of the body. Since the radiation

emitted is largely gamma radiation, the dose is not particularly high in any one organ. Rather the body tissues as a whole are irradiated. In such a case the ICRP and the NCRP have recommended that the occupational dose should not exceed 5(N-18) rem where N is the individual's age in years and 18 years is the age at which employment begins. The recommendations do permit exposure above 5 rem in any one year up to 12 rem per year provided the above age proration formula is not exceeded. The MPC value listed in NBS Handbook 69 is based on this life-time average of 5 rem/year. Higher yearly doses are permitted by the recommendations under certain conditions, i.e., up to 12 rem/year if the age proration formula is not exceeded, but this amounts to another adjustment which the health physicist can make in applying the value to specific cases. The work of Langham and Richmond referred to above provides better data than is available for most radionuclides, but this study was only partially completed at the time of preparation of Handbook 69. The biological half-life in muscle and in some other tissues is about 140 days, while the body as a whole was assumed to have a half-life of about 70 days. As will be seen from Figure 5, their completed study would indicate a value of slightly more than 100 days. Using a value of f_w of 1 and T_b = 70 days, and f_2 = 1, the equilibrium body burden is found from equation (2) to be about 100 I, i.e., 100 daily intakes. From formula (4) using R = 0.1 rem/week, m = 7 x 10^4 g, and = 0.59 MeV, qf_2 is found to be 34 μc. Since the daily intake of water is 2200, the $(MPC)_w$ is determined by 2.2 x 10^5 $(MPC)_w$ = 34 or $(MPC)_w$ = 1.5 x 10^{-4} μc/cc, or in round numbers 2 x 10^{-4} μc/cc. It will be seen that the estimate would be lower if a biological half-life of 100 days had been used. However, the decision of both the ICRP and NCRP committees to

round off the values to a single significant digit reflects the judgment that the values may be uncertain by a factor of 2 or more, and this is illustrated by the present example.

Radon

Radon may serve as an example of the special problems encountered in attempting to estimate the dose delivered to a certain tissue. The high incidence of carcinoma of the bronchial epithelium and other respiratory diseases among the miners of Schneeberg and Joachimstal attracted attention to the difficult problem of estimating the dose to this tissue from inspired radon. The cancers found are of squamous cell type and seem definitely associated with the epithelium layer of the bronchus.[21] Many calculations of the dose to lungs and bronchus have been attempted, but in 1956 Chamberlain and Dyson[22] published an account of an experimental determination of this dose. They demonstrated, as had been noticed by Shapiro,[23] that the dose was due largely to the inhaled daughter products of Rn^{222} rather than to daughter elements produced in the respiratory tract and also found that the dose was primarily due to the free ions of RaA, the first daughter of Rn^{222}, in the air. Thus, with a fixed concentration of Rn^{222} in air, the dose varied greatly, depending on the number of dust particles or condensation nuclei in the air, and this dose correlated well with the number of unattached ions. The ions of RaA attached to dust particles or other nuclei for the most part are retained in the upper respiratory tract or are exhaled before they disintegrate. Chamberlain and Dyson measured the retention of RaA ions on the bronchus under various conditions and calculated that the dose to the surface layer of the epithelium would be 30 mrads/hr if the concentration of radon in unfiltered atmospheric air was

1133905

10^{-9} c/l. Using an RBE of 10 for the alpha radiation, this amounts to 0.3 rem/week for a 40-hour work week if the air level of Rn^{222} is 2.5×10^{-8} μc/cc of air. The uncertainty inherent in this estimate is rather large. The mucus of the bronchus undoubtedly provides some protection, but this may not be as great as has sometimes been supposed. The Rn^{222} and daughters will be in the mucus to some extent, and thus the mucus is not a mere layer of shielding material. Moreover, the mucus is in motion and transports radon and daughter products from the lungs and alveoli upward over the surface of the bronchus. The RBE of 10 used here is that recommended by both NCRP and ICRP for chronic exposure, but it has not been demonstrated to be correct for carcinoma of the bronchial epithelium. However, this layer of tissue does seem to be the tissue primarily involved in the carcinomas that have appeared and seems at least as radiosensitive as other tissues of the respiratory tract.

Uranium

Natural uranium is a mixture of three isotopes of uranium. The specific activity, i.e., disintegrations per second per gram, is quite low so that the primary hazard from soluble inhaled uranium is the toxic effect on the kidney. However, for isotopes or mixtures of uranium isotopes of greater specific activity, the dose to the bone becomes the controlling limit. Thus the critical organ and the type of effect considered change according to the specific activity of the uranium considered. As an example of the use of toxicity as a criterion and in order to point out a major uncertainty, the $(MPC)_w$ of natural uranium will be estimated. The critical parameters needed to determine the $(MPC)_w$ for natural uranium are thus the permissible concentration in kidney, the fraction f_w of

1133906

ingested material depositing in the kidney, and the biological half-life or retention function by which it accumulates there. The NCRP and ICRP Committees on Internal Dose selected the level at 3 μg of U per gram of kidney and a biological half-life of 15 days for uranium in the kidney. The evidence for these is summarized in Reference 24. At the level of 3 μg of U per gram of kidney, the experimental animals did show detectable effects, but these were mild, and it has been demonstrated that the kidney develops some resistance to uranium with low-level exposure. The evidence in man is scanty and inconclusive. The most accurate and detailed data in man are those obtained from injection studies of terminal brain tumor patients.[25] These studies were all at relatively high levels because of the therapeutic objectives of the study. Consequently the concentration of uranium in the kidney was higher than the above-mentioned value, and all showed some evidence of kidney damage. Industrial experience to date has not resulted in any known cases of kidney damage from exposure at the present MPC level. The biological half-life in kidney seems to vary from about 4-5 days in small mammals to 10-15 days in man.[24] The dose level seems to have an important effect on the uptake and retention of uranium by the kidney. The human studies referred to above and later animal studies have confirmed that at high dose levels the kidney damage results in greatly increased burdens of uranium in the kidney.[26] These dose-level effects emphasize the importance of experimental studies at or near the MPC levels. While such experiments may not reveal any biological effects of the intake, they are a check on the accuracy of the metabolic model that is assumed. When this model is obtained by extrapolation from a study at a high dose level, it is desirable that it be checked at a level near the MPC.

1133907

The very low value of $f_w = 1.1 \times 10^{-5}$ as used in the Internal Dose Handbooks is open to some question. It rests upon early short-term studies. Studies reported since the completion of NCRP Handbook 69 have indicated it might be considerably in error.[27] In addition to the dose effect mentioned above, the fraction absorbed into the blood is very small and therefore difficult to determine accurately. It is relatively easy to control the contamination of drinking water in most uranium operations, and ingestion has not been a major problem for the industry. Nevertheless, further studies are needed to give a more accurate estimate of the intake and retention of uranium.

If the value of 3 μg of U per gram of kidney is accepted as a permissible level, then the permissible organ burden is 900 μg of U since the kidney has a mass of 300 g. From formula (3) the organ burden will be 2.3×10^{-4} I if I is the daily intake by ingestion, and

$$R(t) = 1.1 \times 10^{-5} e^{-\frac{0.693}{15} t}$$

Hence, I = 3.9 g and $(MPC)_w = 3.9/2200 = 1.8 \times 10^{-3}$ g. Since the effect is a chemical one, it might be preferable to express the amount in grams, but for the sake of uniformity it is given in μc in NBS Handbook 69 as in the case of all other radionuclides. It is conventional to consider one μc of natural uranium as consisting of 1 μc of U^{238}, 1 μc of U^{234}, and 0.046 μc of U^{235}.

Thorium

The MPC of natural thorium is one which is currently very much in doubt. For industrial applications the maximum permissible concentration in air $(MPC)_a$ is of primary interest. The greatest uncertainty is

1133908

probably that involved in the retention model adopted for inhalation. The deposition and retention in lung is known to depend on particle size, chemical form, and perhaps also on certain physical parameters such as the shape of the particle or crystal. For retention in lung tissue, a biological half-life of 120 days is assumed, but it is not known what range of particle size would have this long a half-life. There is considerable uncertainty also concerning the pattern of elimination from the lung. In NCRP and ICRP recommendations it is assumed 25 per cent of the inhaled material is exhaled and that 50 per cent of the inhaled material is deposited in the upper respiratory passages and subsequently swallowed. If the compound is soluble, the remaining 25 per cent is assumed to pass into solution in the body fluids. If the compound is very poorly soluble, it is assumed that 12.5 per cent will be swallowed within a day, while the remaining 12.5 per cent remains in the lung with a biological half-life of 120 days or longer. In the case of thorium, experiments have indicated a longer biological half-life of about 4 years. The distribution of this final 12.5 per cent represents the second major source of uncertainty for these insoluble compounds. Perhaps no compound is completely insoluble, and some portion must reach the blood. There is also the possibility that there is some translocation of material into the blood stream without going into solution. Some fraction may be carried up by the mucus and swallowed. Within the last few years, increasing evidence has been found that the lymph nodes are a major site of deposition of the heavy metals. It appears that after a few months of chronic exposure the concentration in lymph nodes surpasses the concentration in lung, and the rate of elimination from the lymph nodes is very slow and in many cases could not be

measured. A summary of recent work is given in Reference 27. Although very high concentrations of particulates have been produced in lymph nodes of animals, the lymph nodes have not shown evidence of serious damage. The dose calculation is difficult, because the high concentrations make it possible that a considerable part of the energy is absorbed in the particulate material and does not reach the tissue. Also, it may be that the lymph nodes form a layer of inert scar tissue about such deposits and that the alpha radiation does not penetrate to the mitotic layers of tissues of the lymph nodes. Certainly the lymph nodes of experimental animals seem to show astonishing resistance to large doses of radiation over periods of months or a few years. Whether there might be more serious late effects following many years of exposure is not known.

Thus the $(MPC)_a$ values based on lung are doubtful, because the response of one of the tissues where the concentration is highest is not accurately assessed and also because the amount deposited in the lung and lymph nodes depends on many parameters whose influence has not been adequately determined. It is possible that studies now under way or in the planning stage will provide answers to some of these questions. These uncertainties are largely present in the retention model and thus are not peculiar to thorium. Therefore, similar uncertainties are inherent in the case of all the $(MPC)_a$ values for insoluble compounds of the heavy metals.

In the case of a soluble compound, some fraction of the 25 per cent of the thorium leaving the lung will deposit in bone. The present $(MPC)_a$ values for soluble thorium based on bone assume 70 per cent of this 25 per cent reaches the bone. The biological half-life of Th^{232} in bone is of the order of 200 years, so that elimination is almost negligible over

1133910

a period of 50 years. Using formula (3), the bone would accumulate about 3150 daily intakes. The energy per disintegration of an atom of Th^{232} is found to be about 270 effective MeV per disintegration in bone. The calculation of this energy is quite involved since much of the energy comes from the daughter atoms, and of these some appear to recirculate to the blood upon formation and do not all remain in bone. This is somewhat analogous to the behavior of the Rn^{222} atoms formed by the decay of Ra^{226} in bone. From formula (1), $(qf_2) = 0.041$ μc, and thus for Th^{232} $(MPC)_a = 6.5 \times 10^{-13}$ μc/cc since the daily intake of air is 2×10^7 cc. In this case the bone burden does not reach equilibrium and so increases throughout the exposure period. Only at the end of the period would it reach the value of essentially 0.041 μc indicated above.

In the case of Th^{228} the radiological half-life in bone is only 700 days, and thus the bone burden of Th^{228} will reach essential equilibrium long before 50 years of exposure. Using the total half-life in bone as 693 days and $f_w = 0.18$, formula (3) gives $(qf_2) = 180$ I, i.e., 180 daily intakes. The effective energy in bone is 970 effective MeV, and thus by formula (1) $qf_2 = 0.011$ μc. Hence $(MPC)_a = 3.1 \times 10^{-12}$ μc/cc.

Natural thorium is considered to consist of a mixture of Th^{232} and Th^{228}, and it is customary to consider 1 μc of natural thorium as consisting of 1 μc of each of these isotopes. Thus a level in air of 1 μc of natural thorium would eventually produce a dose of $0.56/(MPC)_a^{Th-232}$ rem/week from 1 μc of Th^{232} and also $0.56/(MPC)_a^{Th-228}$ rem/week from 1 μc of Th^{228}. Consequently $(MPC)_a = 5.7 \times 10^{-13}$ μc/cc for natural thorium.

The value of $(MPC)_a$ given above is quite low but is not out of line with animal experiments on the relative hazard of thorium and plutonium

which has very similar chemistry and essentially the same $(MPC)_a$. The comparative studies of Ra^{226}, Th^{228}, Pu^{239}, and Sr^{90} reported in Reference 28 indicate that Th^{228} is indeed as toxic as Pu^{239} on the basis of the injection studies reported there. It should be observed that Th^{228} has a far higher specific activity than natural thorium so that the gram amounts injected in the case of the dog studies are much less than the gram amounts of the same number of μc of natural thorium. There is considerable evidence that this influences the amount retained by bone and that natural thorium would not be absorbed to the same extent as Th^{228}. This mass effect on retention, although not completely explored at the present time, was largely conjectural several years ago, and even now it is difficult to estimate this effect for man. Thus the metabolic model is again in doubt, and further research will be needed to clarify and quantitate this effect.

The value of $(MPC)_a = 6 \times 10^{-13}$ for natural thorium is 1/50 of the value given in the previous recommendations. This former value had never been calculated on the basis of a limiting dose rate but was listed by comparison of industrial experience with uranium and thorium. It may be that the industrial situations usually encountered in mills, mines, and factories would be such that this, the higher value, is appropriate, but this has never been demonstrated. No really careful and statistically valid survey of thorium industrial experience has been made, though some persons with a fairly long history of exposure have been located. No observable effects have been found, though they are believed to have been exposed to high concentrations of thorium. Whether the concentration was consistently high throughout their period of employment, whether the

1133912

particle size or some other factor prevented the retention of 12 per cent, and whether there may have been a mass effect on retention because of the presence of "carrier" material is not known. The ICRP and the NCRP have, therefore, listed both the high and the low value of $(MPC)_a$ for natural thorium. It is recognized that a change of this order involves a period of adjustment, and both NCRP and ICRP have recognized that a period of 5 years might be reasonable. Before the expiration of that time, it is hoped more definitive data will be available.

Undoubtedly the measure of uncertainty in the MPC for thorium and perhaps for uranium may be somewhere between 10 to 100. This uncertainty is largely associated with the metabolic parameters used to estimate the MPC and emphasizes the need for research on these aspects of the problem.

In summary, there are three categories of uncertainty:

(1) The uncertainty of the basic standard, whether expressed in terms of a limiting dose rate or as a permissible body burden. One cannot attach a numerical value to this aspect of uncertainty until the type of biological effect to be expected and the rate of incidence to be permitted are specified. The specification of these truly basic standards involves the weighing of the benefits and risks to be expected at the given level of incidence. The appropriate body burden or dose rate that would give a selected incidence rate is not well established.

(2) The uncertainty of the metabolic model used to estimate the body burden varies greatly with the isotope and type of intake in question. In some cases, such as ingested I^{131}, the estimate is probably correct within 20-50 per cent and for others, such

1133913

as inhaled natural thorium, uncertainty may be by a factor of 10-100. The judgment that the value for iodine is this accurate is to be understood in the sense that the estimate applies to a "standard man," i.e., this does not allow for individual departures from the average.

(3) The changes in the MPC that will be necessary if individual characteristics and habits are to be taken into account will be large, perhaps by a factor between 0.1 and 10. This would include differences due to age, sex, body size, diet, personal habits, etc. As indicated above, these may be considered as adjustments that should be made in applying the MPC to a particular individual or group. They become uncertainties when their influence is neglected or when the relevant corrections are not known.

It is clear that the margin of uncertainty is rather large in all cases. However, it is to be remarked that only a very few sciences have attained the precision of, say, the astronomy of the solar system. In a case where no adequate theoretical basis is available and where controlled experiments are largely impossible, the situation is not surprising. The number of cases where some of these estimates can be checked quantitatively is not very large, but on the whole the results are encouraging. In several cases where victims of accidents have been studied the estimates of body burden obtained by the use of the metabolic model have been checked by use of the whole body counter or in some cases upon autopsy. Agreement within a factor of two has been the rule rather than the exception.[29] The dose to the gastrointestinal tract from radioactivity present in the contents has been calculated.[17] This has been checked in dogs by

implantation of dosimeters with very good agreement.[30] The same studies also indicated that a state of constipation or of diarrhea could change the answer greatly, thus again emphasizing that the dose estimates involved are always for a precisely defined individual and situation and that category (3) mentioned above must be taken into account in assessing the uncertainty of the estimates.

It would be misleading to leave the impression that these checks are extensive enough to cover the field or that they are all favorable. The changes that occur in the MPC values from one revision to the next are ample evidence that new information often points up the inadequacy of the former values, and we may expect more changes as better data become available. That changes in these estimates should occur is not surprising, but to be expected. The more surprising element in the situation is rather that amid all the concern expressed for more or less of control there is relatively so little concern with obtaining the accurate information which is essential for intelligent control.

1133915

SUPPLEMENTARY QUESTIONS ON STRONTIUM-90

(1) Discuss the Radium-226 Standard for bone-seekers. What is assumed about RBE, non-uniform distribution, retention, etc.?

This question has been discussed above (paragraphs 3-10).

(2) To what extent is the Radium-226 Standard (0.1 microgram) compatible with present recommendations of MPD? Does the Radium-226 Standard represent a departure in concept from a concept of increasing hazard with increasing dose?

According to our best estimates, a bone burden of 0.1 μg of Ra^{226} results in an average dose to bone of 0.06 rad/week. This is nearly all α radiation and, if an RBE of 10 is assumed, gives an average dose of about 0.56 rem/week to the bone. This is of the same order as the dose of 0.6 rem/week permitted to the thyroid and skin, but it is nearly double the dose permitted to most soft tissue. The ICRP in its 1958 Recommendations justified the somewhat lower rate of 0.3 rem/week in most soft tissues as follows:(31) "Whereas in the case of the blood-forming organs, the gonads, the lenses of the eyes and the skin, the objective of protection is to prevent or minimize definitely known types of injury, in the case of other organs the type of injury is not known. (Bone constitutes the only exception, in which case the relevant injury is cancer and permissible limits may be set on the basis of data furnished by human subjects who accumulated radium in their skeletons.) Possibly, radiation in sufficient dosage may increase the incidence of cancer in one of these organs (e.g., the thyroid gland) or it may accelerate aging of the organ. In the absence of

1133916

factual data, it was deemed prudent in earlier recommendations of the commission to set the maximum permissible limit for these organs, when irradiated by internal sources, as low as that for the more sensitive organs such as the gonads, that is, 0.3 rem/week." In my judgment the different limits on dose reflect (1) judgment concerning the seriousness of the effect, (2) some knowledge of relative sensitivity of tissues to radiation, and (3) in some cases a considerable lack of knowledge of what the effects and rates may be. It is not a departure from a concept of increasing hazard with increasing dose since the limits apply to different tissues.

(3) To what extent is the Strontium-90 body burden (1.0 microcurie) compatible with present recommendations of MPD?

According to the best estimates available, a body burden of 1 μc of Sr^{90} would deliver an average dose to bone of 0.056 rem/week. According to Hindmarsh et al.,[10] the peak dose may be some three times this value, or about 0.17 rem/week. The dose in marrow would range from 0.17 rem/week down to perhaps 0.006 rem/week, depending on the size of marrow deposit that is assumed. An average in marrow would probably not be more than 0.02 rem/week and the average to the entire blood-producing organs would be even less according to these estimates.

(4) What are the arguments for switching Strontium-90 over to an MPD-based standard? What are the principal unknowns (or uncertainties) in the present Radium-226 comparison method?

The arguments in favor of basing the body burden on a MPD can only have the validity ascribed to the MPD that is used. As the

statement quoted above from ICRP Recommendations of 1958[31] indicates the MPD of 0.3 rem/week is taken somewhat lower than in the case of skin, thyroid, etc., because of uncertainty concerning effects and incidence rates. The radium standard is indirectly used in arriving at the rate of 0.3 rem/week, and thus the use of this dose rate indirectly refers to the radium standard. The principal uncertainties in the use of the radium standard are:

(a) The effect of nonhomogeneity in the dose distribution.

(b) The effect of the distribution of dose in time.

The radium dial painters and medical patients had a high initial body burden and dose rate which decreased thereafter. The occupational worker will experience the reverse of this situation.

(c) The proper value of the RBE.

This last uncertainty does not apply to α emitters but does apply to β emitters and hence to Sr^{90}.

(5) Why was the Strontium-90 body burden doubled? Was the corresponding dose doubled? How is this reconciled with the Radium-226 Standard?

As the above discussion has indicated, there are a number of possible ways of using the radium standard to define a body burden of some other bone-seeker. The members of NCRP and ICRP vote as individuals and do not always indicate which reasons determined their vote. From the discussions and correspondence the following

reasons seemed most influential:

(a) The dose values indicated under (3) when doubled are still within NCRP and ICRP dose limits from radium in bone, or for other organs, and this is true whether average dose or maximum dose is considered.

(b) The comparison with radium by direct experiment has only been carried out in small mammals at rather high dose levels and for times much shorter than the latent period for bone cancers from radium in man. Thus it is not at all clear that the direct application to man is valid.

(c) The two methods give essentially the same value. The difference of 1 μc and 2 μc can hardly be regarded as significant in the light of present knowledge. To have adopted the value of 1 μc would have required a rationalization of why this bone-seeker was given a different treatment than that accorded the others. The Committees insisted on giving values to only one digit which implies that differences of 0.5-1.5 or 1.5-2.5 are not regarded as significant.

It is evident that the dose to bone will be doubled if the body burden of Sr^{90} is doubled. The previously recommended body burden of 1 μc of Sr^{90} was not based primarily upon a dose rate, but was based upon a comparison of carcinogenic effects of Sr^{89} and Ra^{226} in experimental animals. It appeared that Sr^{89} was about 5 times as potent a carcinogen as Ra^{226} on the basis of equal dose to the skeletons of these animals. What the corresponding equivalent doses would be in man at a much lower

dose rate is difficult to determine. The greater fraction of Rn^{222} escaping from the bones of the mouse is one example of a correction that must be made. Whether this equivalent dose from Sr^{90} in man averages 0.11 rem/week (the average dose from a body burden of 2 μc of Sr^{90}) or is more nearly half of this is not demonstrated on either basis. In the one case, the comparison is based on the relative biological effects but requires corrections for differences in species, dose rate, exposure period, etc. In the other case, the long-term biological effect of Ra^{226} is taken as the starting point and the comparison is made through dose rates and dose effectiveness.

This does not conflict with any evidence from the radium dial painters or the cases of medical exposure that have been observed to produce bone cancer. It should be noted that in man, the body burden would only approach the value of 2 μc after some 50 years of exposure. Throughout most of this period his body burden would be expected to be less than this. There is no conflict here with the radium standard since the observed cases of bone cancer due to radium had a much higher dose rate early in the period of their exposure.

(6) Is Strontium-90 level for food as worked out from NCRP Handbook 69 independent of the water content? Of the Calcium content?

In adjusting the $(MPC)_w$ of NCRP Handbook 69 to apply to food, the total intake must be considered, and this includes the intake of other radionuclides as well as Sr^{90}. The calcium content needs to be considered also since this has been shown to influence the fraction taken up by the bone. These are adjustments which ICRP and NCRP have indicated as appropriate to adjust the MPC to a particular individual or situation.

1133920

(7) How does the philosophy of limiting intake limit Strontium-90 in bone for a low Calcium diet?

For an individual on a low calcium diet, the value of f_w, the fraction of intake going to bone, would have to be increased. Without such correction the individual on a low calcium diet would retain a greater fraction of his intake. If it is assumed he ingests the same amount as a "standard man" on a normal diet, he would attain a larger body burden than the "standard" individual.

(8) How is the MPL applied to drinking water of known Strontium-90 content but unknown content of other activities?

If drinking water contains Sr^{90} and other unknown radionuclides, one can, in the absence of all other information, assume the worst, i.e., that the other radionuclides were among those with the lowest MPC known and calculate accordingly. Frequently it is possible to make a partial elimination, e.g., no α emitters present, and then use the lowest MPC for the radionuclides not eliminated. Handbook 69 gives detailed tables and examples of such an approach.

(9) If child or adult drinks milk having 25% MPC of Strontium-90, will bone be 25% of MPBB?

If the adult drinks the milk during 50 years, his body burden would be expected to reach this level. The child would take up a larger fraction during his early years and would eventually surpass the 25 percent level of the MPBB according to the model.

(10) Can all of the MPL's for bone-seekers be wrong?

The question can be interpreted in several ways. If the MPL refers to the basic standard, then this reflects a value-judgment. Whether

1133921

0.1 μg of Ra^{226} is a proper standard for permissible body burden depends partly on what incidence rate of cancer or other effects society will tolerate in order to have the applications that occasioned these body burdens. At present these incidence rates are not known precisely but seem of an order that has escaped detection during a half-century or more of the use of radium. Thus they seem to be not more than the levels of risk commonly accepted. The same can be said of the basic dose rates. If too high, the higher incidence rate has not manifested itself thus far, but since experience with these is not so extensive, more caution is indicated. The basic limits can only be judged as too high or too low when weighed against the benefits obtained from the application.

If the MPL refer to the MPC values, then it is likely that all are wrong to some degree in the sense that they may not produce the body burdens they are now expected to produce, even under the standard conditions assumed in deriving them. We may expect that as better data accumulate these values will be changed from time-to-time.

1133922

References:

1. Looney, William B., "The initial medical and industrial use of radioactive materials (1915-1940)," Am. J. Roentg., Radium Therapy and Nuclear Med. 72, 838-848 (1954).

2. Furth, Jacob, and J. L. Tullis, "Carcinogenesis by radioactive substances," Cancer Research 16, 3-21 (1956).

3. Norris, William P., T. W. Speckman and P. F. Gustafson, "Studies of the metabolism of radium in man," Am. J. Roentg., Radium Therapy and Nuclear Med. 73, 785-802 (1955).

4. Massachusetts Institute of Technology, "Radium and mesothorium toxicity in human beings," Radium and Mesothorium Poisoning and Dosimetry and Instrumentation Techniques in Applied Radioactivity, Annual Progress Report, AECU-3774 (May 1958).

5. Aub, J. C., R. D. Evans, L. H. Hempelmann, and H. S. Martland, "The effects of internally deposited radioactive materials in man," Medicine 31, 221-239 (1952).

6. Evans, R. D., "Radium Poisoning: II. The quantitative determination of the radium content and radium elimination rate of living persons," Am. J. Roentg. and Radium Therapy 37, 368-378 (1937).

7. Mays, C. W., "Escape of radon and thoron when produced in bone," COO-216 (March 1958), Radiobiology Laboratory, College of Medicine, University of Utah.

8. Finkel, M. P., "Internal emitters and tumor induction," Proc. Int. Conf. Peaceful Uses of Atomic Energy 11, 160-146 (August 1955).

9. Brues, A. M., H. Lisco and M. P. Finkel, "Carcinogenic action of some substances which may be a problem in certain future industries," MDDC-145 (1946).

10. Hindmarsh, Margaret, Maureen Owen, Janet Vaughan, L. F. Lamerton and F. W. Spiers, "The relative hazards of Sr^{90} and Ra^{226}," Brit. J. Radiol. 31, 518-533 (1958).

11. Cook, M. J., K. Z. Morgan, and A. G. Barkow, "An experiment designed to test the validity of the current practice of using single exposure data to calculate maximum permissible concentration in water for continuous exposure to radioisotopes," Am. J. Roentg., Radium Therapy and Nuclear Med. 75, 1177-1187 (1956).

12. Evans, R. D., "Radium Poisoning. A review of present knowledge," Am. J. Public Health 23, 1017-1023 (1933).

1133923

13. Spencer, H., D. Laszlo, and M. Brothers, "Strontium-85 and calcium-45 metabolism in man," J. Clinical Investigation 36, 680-688 (May 1957).

14. Durbin, P. W., C. W. Asling, et al., "Retention of calcium-45 and strontium-90 in the Rhesus monkey," Biology and Medicine Semiannual Report, UCRL-8513 (1958).

15. Richmond, C. R., "Retention and excretion of radionuclides of the alkali metals by five mammalian species," LA-2207 (1958).

16. Van Dilla, M. A., S. Wallach and J. S. Arnold, "Sr-85 tracer studies in humans," Semiannual Progress Report, University of Utah (September 30, 1956).

17. Recommendations of the International Commission on Radiological Protection, Report of Committee II, "Permissible Dose for Internal Radiation - 1959 Revision," ICRP Publication No. 2 (Pergamon Press, London, April 1960).

18. Comar, C. L., R. H. Wasserman, Sven Ullberg and G. A. Andrews, "Strontium metabolism and strontium-calcium discrimination in man," Proc. Soc. Exptl. Biol. Med. 95, 386-391 (1957).

19. MacDonald, N. S., P. C. Spain, F. Ezmirlian and D. E. Rounds, "The effects of phosphate in foods on radiostrontium accumulation," UCLA-317 (1954).

20. Duffy, B. J., Jr., and J. W. Howland, "Radioiodine (I^{131}) principles of diagnosis and treatment of thyroid disease," UR-138 (October 25, 1950).

21. Lorenz, Egon, "Radioactivity and Lung Cancer. A critical review of lung cancer in the miners of Schneeberg and Joachimsthal," J. National Cancer Inst. 5, 1-15 (1944).

22. Chamberlain, A. C., and E. D. Dyson, "The dose to the trachea and bronchi from the decay products of radon and thoron," Brit. J. Radiol. 29, 317 (1956).

23. Shapiro, Jacob, "Radiation dosage from breathing radon and its daughter products," A.M.A. Arch. Ind. Health 14, 169-177 (August 1956).

24. Snyder, W. S., "Interspecies correlations," Symposium on Occupational Health Experience and Practices in the Uranium Industry, New York City, October 15-17, 1958, HASL-58, pp. 95-97.

25. Bernard, S. R., "Maximum permissible amounts of natural uranium in the body, air and drinking water based on human experimental data," Health Physics 1, No. 3, 288 (December 1958).

1133924

26. Fish, B. R., "Distribution and excretion of uranium," Health Physics Division Annual Progress Report, ORNL-2806 (July 1959), pp 191.

27. Fish, B. R., "Inhalation of uranium by mouse, rat, dog, and man," Proc. Symposium on Inhaled Particles and Vapors, British Occupational Hygiene Society, Oxford (In press).

28. Stover, C. N., Jr., Annual Progress Report, Radiobiology Laboratory, College of Medicine, University of Utah, COO-218 (March 1959).

29. Foreman, H., W. Moss and W. Langham, "Plutonium accumulated from long-term occupational exposure," Health Physics 2, No. 4 (In press).

30. Hayes, R. L., M. M. Nold, C. L. Comar, H. Kakehi, "Internal radiation dose measurements in live experimental animals," (Parts 1 and 2 to be published in Health Physics, 1960).

31. Recommendations of the International Commission on Radiological Protection (adopted September 9, 1958), ICRP Publication No. 1 (Pergamon Press, London, 1958), pp 6.

1133925