RADIOSENSITIVITY AND DOSIMETRY OF THE TISSUES OF BONE

IMPLICATIONS FOR SETTING MAXIMUM PERMISSIBLE LEVELS OF BETA EMITTERS

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Abstract

Calculations are made of the risk to bone from incorporated β emitters, based on calculations of absorbed dose rates to bone marrow and endosteal tissues for a body burden of 1 μCi. The risk of leukaemia is based on human data and that of osteosarcoma and other bone tumours on a comparison of the incidence of these malignancies with the leukaemia incidence in animals continuously irradiated by β particles from ingested ^{90}Sr. Maximum permissible body burdens are then derived by a comparison of these risk values with a total risk estimated to correspond with an annual dose of 5 rad to the whole body.

Introduction

Although the maximum permissible levels of bone-seeking radionuclides are at present related to the human data on carcinogenesis from ^{226}Ra, there are unavoidable difficulties in this procedure. The comparison of any given radionuclide with ^{226}Ra is based on the energy absorbed per unit mass of mineral bone, but the absorbed dose delivered to the cells of bone depends on the nature of the ionizing particle and its range. In making the comparison with ^{226}Ra it is necessary therefore to adopt a quality factor for α particles relative to β particles, but there is little, if any, evidence on which to set this value for late effects in bone. It has also been necessary to include a relative damage factor for those radionuclides which differ from radium in their pattern of deposition and, in the absence of quantitative data, this has to be given an arbitrary value.

In recent years, however, there has been a measure of agreement on the identity and location of the tissues at risk in irradiated bone and this has enabled dose parameters to be chosen that are more relevant to risk calculations than the absorbed dose determined simply for the bone matrix. Calculations of the relevant absorbed doses have been published for bone-seeking radionuclides that are distributed in volume throughout bone [1,2] and, very recently, the corresponding absorbed doses for radionuclides that are deposited on bone surfaces have been determined [3].

Suggestions were made in the ICRP Report 11 that, in the case of high energy β emitters, the skeletal burden would be set by the limiting annual dose of 5 rem to bone marrow and that, for low energy β emitters, the limitation would be the dose to endosteal tissues in bone. In the intermediate energy range, however, the doses to bone marrow and bone surfaces set comparable limitations and, if the irradiation of both

marrow and endosteal tissues is regarded as undesirable, some better synthesis of the risks to both tissues should be sought.

It is worthwhile attempting to calculate the total risk in the case of bone because, although bone contains tissues that differ in their radiosensitivity, bone-seeking radionuclides irradiate only the tissues of bone, with practically no irradiation of other parts of the body. The problem of setting permissible levels of dose to organs of differing radiosensitivity, when more than one organ is irradiated, has been discussed in the Reports of two Task Groups in ICRP Publication 14[5]. A similar problem is encountered in bone because different radiosensitivities are assigned to the different tissues in bone, tissues that, under most circumstances, receive very different doses from an incorporated radionuclide. The present approach differs from that followed in the ICRP Publication 14 in that the risk of leukaemia from the irradiation of bone marrow is taken from human data as in the UNSCEAR 1972 Report [6], while risk factors for tumours of other bone tissues are derived from data on the comparative risks of these tumours and leukaemia in animals irradiated continuously by high energy β particles from incorporated $^{90}Sr+^{90}Y$. A total risk for all bone tissues is then calculated on a dosimetric basis for a body burden of 1 μCi of any given bone-seeking radionuclide and this is compared with an estimated occupational risk to give a maximum permissible body burden. The magnitude of the occupational risk is again based on UNSCEAR data and chosen to correspond approximately to an annual dose of 5 rad whole body irradiation at low LET. The maximum permissible body burdens calculated on these risk data compare interestingly with the present values of the ICRP.

Tissues at Risk and Late Effects in Bone

It was concluded in the ICRP Report 11[4] that the tissues at risk in irradiated bone were the active bone marrow with respect to leukaemia, the osteoprogenitive tissues of the endosteum with respect to osteosarcoma, and certain epithelial tissues adherent to bone in cranial air sinuses with respect to carcinoma. Considerations put forward more recently by Loutit and Vaughan[7] suggest that tumours may also arise from the reticulo-endothelial and supporting tissues in the marrow spaces in trabecular bone. With regard to the location of osteoprogenitive cells near endosteal surfaces, Sissons[8] and Vaughan[9] have concluded that the majority lie within a zone extending from the endosteal surface out to a distance of not more than 10 μm. Osteoprogenitive cells must also be present near endosteal surfaces in cortical bone but, because proliferative activity is so much less on these surfaces than on trabecular surfaces, it is assumed in this paper that the radiosensitivity of cortical endosteum is less than that of trabecular endosteum.

The late effects taken into account in the risk calculations, together with the corresponding tissues and their location and the relevant dose parameters, are summarized in Table 1. The associated risk factors are also designated for later reference.

Principles of the Calculation of Total Risk to Bone

The risk factors in Table 1 are defined as the probability of tumour occurrence per year for "continuous" irradiation and are expressed conveniently as cases /10^6/ yr for an absorbed dose rate of 1 rad/yr to the relevant tissues. Numerically the value for a given risk rate is the same as the total number of cases per million occurring in the years following a single dose of 1 rad, - as given for example in the conclusions of the UNSCEAR Report[6]. Assuming that the risk factors in Table 1 are known, the total risk R_1 to bone for a body burden of 1 μCi can be written:

$$R_1 = (r_m + r_a)\bar{D}_M + r_o\bar{D}_S + r'_o\bar{D}'_S$$

Table 1

Late Effect	Tissue and Location	Relevant Dose	Risk Factor
Leukaemias	Haemapoietic bone marrow in trabecular spaces	Average dose to red marrow, $\bar{D}_M$	r_m
Osteogenic sarcomas	Endosteal tissue layer, 10 μm thick, on:	Average dose to endosteal layer:	
	(1) trabecular surfaces	(1) trabecular, $\bar{D}_S$	r_o
	(2) cortical surfaces	(2) cortical, $\bar{D}'_S$	r'_o
Angiosarcomas reticulum-cell tumours, some fibrosarcomas	Reticulo-endothelial and supporting tissues in trabecular spaces	Average dose to tissues in trabecular spaces, $\bar{D}_M$	r_a

where the absorbed dose rates $\bar{D}_M$, $\bar{D}_S$ and $\bar{D}'_S$ are calculated from the corresponding dose factors $\bar{D}_M/D_o$ etc. The parameter D_o is the absorbed dose rate to a very small soft-tissue inclusion in bone such that the irradiation is under conditions of particle equilibrium. The value of D_o is calculated in rad/yr for a body burden of 1 μCi, taking values of f_2, for the fraction of the body burden in the skeleton, from the Report of Committee II of ICRP, Publication 2[10]. The mass of bone matrix in which the radionuclide is distributed is taken as 5000 g.

If now some level of personal occupational risk, R_{MPL}, is assumed, the corresponding maximum permissible body burden, q, will be given by the equation:

$$qR_1 = R_{MPL} \qquad (2)$$

where it is assumed that only the tissues of bone are irradiated and that the risk to the person is that to bone alone.

The dosimetric data on which the calculations are made are shown in Fig. 1 for volume-seeking radionuclides and in Fig. 2 for those that are deposited on surfaces. The dose factors are skeletal averages in the case of trabecular bone; for cortical bone the dose factors refer to the resorption cavities and Haversian canals of a section of a human femur, the only bone for which calculations are so far available. The calculations for surface-seeking radionuclides are based on the assumption that the retained radionuclide is distributed uniformly in a layer of very small thickness on the endosteal surfaces. Integration of the dose over the 10 μm zone containing the cells at risk results, of course, in a finite average dose factor. It is convenient also to adopt the convention of expressing the dose factors for the surface seekers in terms of the parameter D_o. To do this, the retained radionuclide is considered to be distributed either over the total endosteal surface area A, or distributed through a bone volume V, and for numerical convenience the ordinate in Fig. 2 is given as $\bar{D}(V/A \times 10^2 \times D_o)^{-1}$. In this paper V is taken as approximately 2500 cm^3 and A as 10 m^2; $V/A \times 10^2$ then has the value 2.5.

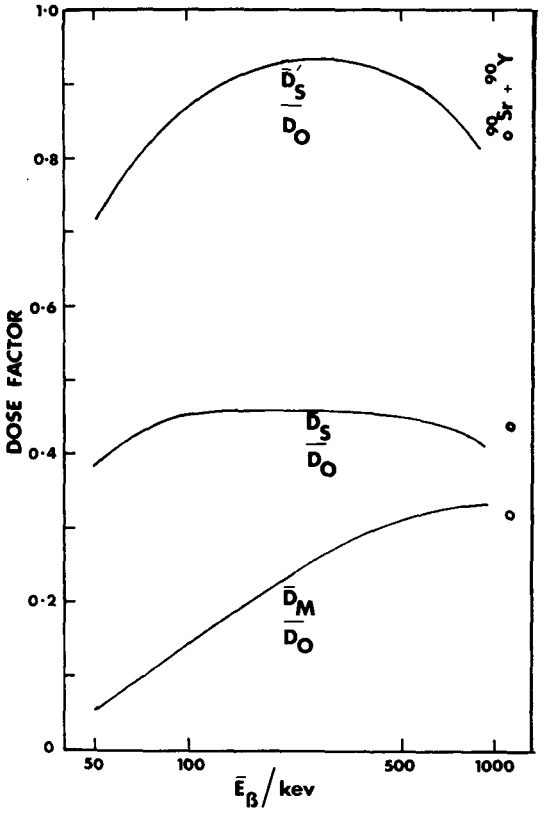

Fig. 1 Dose factors for volume-seeking β emitters.

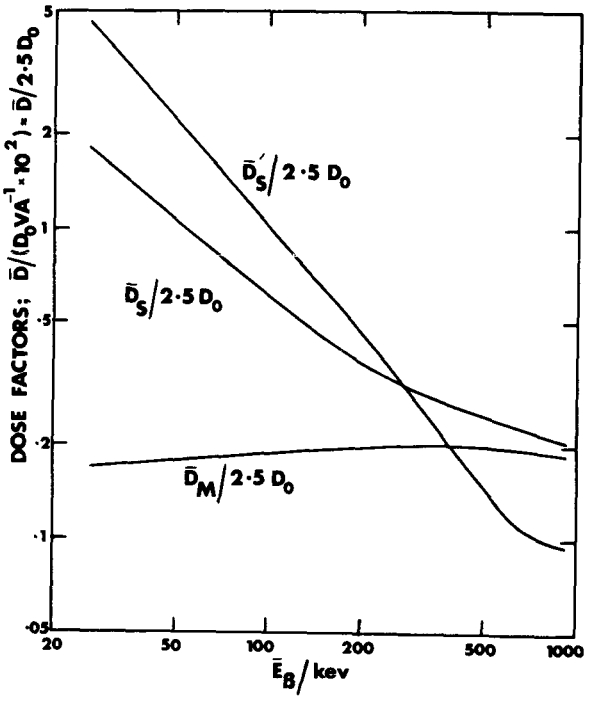

Fig. 2 Dose factors for surface-seeking β emitters;
curve for $\bar{D}'_S$ only approximate.

Choice of Risk Factors

Bone Marrow Risk

The bone marrow risk is considered to be leukaemia and the risk factor is taken from the upper limit of the range of 15-40 cases per rad per million persons exposed as given in the UNSCEAR REPORT[6]. The value of r_m, for a dose rate of 1 rad/yr, is therefore assumed to be:

$$r_m = 40/10^6/\text{yr} \qquad (3)$$

Osteogenic Sarcoma Risk

There is not much evidence of the induction of bone tumours in humans by low LET external radiation and, in the ICRP Report 14[5], bone tumour risk is classed as an order of magnitude less than leukaemia. On the other hand, where beagles [11] and miniature swine[12] have been subjected to continuous irradiation of bone and bone marrow from ingested ^{90}Sr, both osteogenic sarcoma and myeloid and lymphoid leukaemias have occurred. It is therefore probably more relevant to the radiation protection situation to

take into account this evidence from continuous irradiation by a bone-seeker and to estimate a ratio of osteogenic sarcoma incidence to leukaemia incidence from animal data. Only data relating to irradiation by the energetic β particles of $^{90}Sr+^{90}Y$ have been considered because it is only in this case that the bone marrow and the surfaces of trabecular bone receive comparable doses - see Fig. 1. The evidence from the beagles and swine is numerically not very concordant; in the beagles 19 osteogenic sarcomas have been recorded against 14 myeloid leukaemias whereas in the swine only 7 sarcomas have occurred, compared with 23 myeloid and 17 lymphoid leukaemias. In both cases, however, bone tumours show a greater prevalence in relation to myeloid leukaemia than suggested by the human data for external irradiation, received instantaneously or over a short period of time. It is therefore prudent for the present purpose to assume that, for the continuous internal irradiation of bone, osteogenic sarcomas are about half as prevalent as leukaemia and hence to assume a risk rate of $20/10^6$/yr for a dose rate of 1 rad/yr. We then have:

$$r_o + r'_o = 20/10^6/yr \qquad (4)$$

The division of the risk between trabecular surfaces (r_o) and cortical surfaces (r'_o) can only be conjectured at present, but at least a clue is given by data from the radium poisoning cases. Here only two mid-shaft tumours have been recorded in a total of 30 sarcomas of the six long bones[13]. Considerations of the relative cortical and trabecular surface areas in the mid and outer thirds of these bones indicates that, despite some differences in dosimetry and isotope retention, the probability of tumour occurrence per unit area of cortical bone is unlikely to be more than one half of that of trabecular bone. Since the total surface areas of cortical and trabecular bone in the skeleton are roughly equal the following values of r_o and r'_o have been assumed:-

$$r_o = 13/10^6/yr \text{ and } r'_o = 7/10^6/yr \qquad (5)$$

Angiosarcoma and other Bone Tumour Risk

Only animal data are available to suggest what magnitude should be attached to the risk of angiosarcoma, reticulum-celled tumours and other tumours that might arise in tissues of the marrow spaces. In the beagles continuously irradiated[11], tumours of this class were only about one tenth as frequent as osteogenic sarcomas; similarly low ratios were shown in beagles given multiple injections of ^{90}Sr at high dose[14] and in mice given high dose ^{90}Sr injections[15]. On the other hand in beagles given low dose injections[14], in beagles given single injections[16] and in mice given low dose injections, the ratio of angio and other tumours to osteogenic sarcomas ranged from 0.5 to 0.8. The low dose data have therefore been given the greater weight and the angio-group tumours have been taken to be half as prevalent as the osteosarcomas. The value of r_a has been assumed to be:

$$r_a = 10/10^6/yr \qquad (6)$$

The overall result of these choices of risk factors is to make the bone tumour risk approach more nearly to the leukaemia risk than the human data for external irradiation suggests. It is probably better to make these assumptions, both on grounds of caution and because the animal data represent all that is available for the internal irradiation of bone by incorporated β emitters.

Risk Factor for Occupational Dose Level

The maximum permissible annual occupational dose is 5 rem for whole-body irradiation and this presumably represents a maximum permissible occupational risk. The conclusions of

the UNSCEAR Report[6] are that an absorbed dose of 1 rad may result (on the linear dose-effect hypothesis) in from 30 to 140 cases of certain specified cancers per 10^6 persons irradiated; there is a further estimate of some possible 40 cases of thyroid cancer but no figure is given for bone cancer. Great uncertainty necessarily attaches to these estimates and for the purpose of the present calculations the risk level is taken in round figures as 100 cases/10^6 persons and hence an "acceptable" maximum risk corresponding to 5 rad/yr is :

$$R_{MPL} = 5 \times 100 \times 10^{-6} = 5/10^4/\text{yr} \qquad (7)$$

Total Risk to Bone and Calculation of the MPBB

Using the values of the risk factors given in Eqs. (3) (5) and (6), the total risk for a body burden of 1 μCi is:-

$$R_1 = (50\bar{D}_M + 13\bar{D}_S + 7\bar{D}'_S)/10^6/\text{yr} \qquad (8)$$

and the value of the MPBB, q, is:-

$$q = R_{MPL}/R_1 = \frac{500}{50\bar{D}_M + 13\bar{D}_S + 7\bar{D}'_S} \ \mu\text{Ci} \qquad (9)$$

This formula can be applied to both volume-seeking and surface-seeking β emitters if the values of the dose rates are calculated from the data in figs. 1 and 2.

Results for Volume-Seeking Beta Emitters

The risks calculated for six volume-seeking radionuclides are set out in Table 2 which gives the separate contributions from the trabecular spaces, the trabecular surfaces and the cortical surfaces. The total risk is then given, followed by the resulting value of the MPBB according to Eq. 9. The ICRP value quoted in the last column (from ICRP Publication 2[10]) is either that for bone as the critical organ (^{45}Ca, ^{89}Sr, ^{32}P and ^{90}Sr + ^{90}Y) or bone as a reference organ (^{14}C and ^{18}F). In the case of ^{14}C there is a large contribution to the dose to the trabecular spaces from the radionuclide present in marrow fat, because red marrow has been estimated to contain 53% fat[16]. In the case of ^{18}F the contribution to the total risk from the annihilation radiation is almost as great as that from the β radiation. If only β radiation from the radionuclides incorporated in the bone matrix were considered, the risk values for ^{18}F and ^{14}C would be lower and the calculated MPBB values much higher. The ratio of the present calculations of MPBB to those given by the ICRP would then range from 2 for high energy β emitters to about 4 for the low energy β emitter ^{14}C. This increase towards low energies is to be expected from the data in Fig. 1 where $\bar{D}_M/D_o$ falls as the β-particle energy decreases. The dose factor $\bar{D}'_S/D_o$ also falls at low energies but to a less marked extent.

Results for Surface-Seeking Beta Emitters

The risks and values of the MPBB calculated for five surface-seeking radionuclides are presented in Table 3 in the same form as in Table 1. These radionuclides have been considered to be surface-seekers either because they are known to deposit on endosteal surfaces or because they belong to the same chemical groups as known surface-seeking elements. Thus the three group IIIA radionuclides, ^{171}Tm, ^{143}Pr and ^{90}Y, are taken to deposit on resorbing and quiescent surfaces as does the lanthanide element yttrium[17]. The two group IIIB radionuclides, ^{115}In and ^{204}Tl, are considered to behave like the element gallium which deposits in regions of osteogenic activity[17]. As with the volume-seeking radionuclides the ratio of the present calculation of the MPBB to

Table 2: Volume-Seeking Beta Emitters

Radionuclide	Energy $\bar{E}_\beta$/MeV	Risks as cases/10^6/yr for 1 μCi: Trabecular spaces	Trabecular surfaces	Cortical surfaces	BB Total risk	MPBB μCi	ICRP μCi
^{14}C	0.050 β^-	1.58	0.35	0.10	2.03	250	300(fat) 400(bone)
^{45}Ca	0.077 β^-	1.51	1.59	1.63	4.73	110	30
^{18}F	0.25 β^+	6.60	3.08	3.43	13.11)	20	20
	0.51 γ	8.00	2.08	1.12	11.20)		
^{89}Sr	0.55 β^-	33.90	12.61	14.03	60.54	8	4
^{32}P	0.70 β^-	24.65	8.39	8.30	41.34	12	6
$^{90}Sr+^{90}Y$	1.13 β^-	71.65	25.62	26.05	123.3	4	2
^{226}Ra	5.65 α	317	2077	1229	3623)	0.14	0.1
	0.42 $\bar{\beta}$	21	8	8	37)		

Table 3: Surface-Seeking Beta Emitters

Radionuclide	Energy $\bar{E}_\beta$/MeV	Risks as cases/10^6/yr for 1 μCi: Trabecular spaces	Trabecular surfaces	Cortical surfaces	BB Total risk	MPBB μCi	ICRP μCi
^{171}Tm	0.026 β^-	1.70	4.80	6.68	13.18	40	90
^{115}In	0.147 β^-	2.88	1.76	1.37	6.01	80	60
^{204}Tl	0.242 β^-	1.95	0.85	0.50	3.30	150	100
^{143}Pr	0.307 β^-	12.40	4.86	2.38	19.64	25	20
^{90}Y	0.927 β^-	65.90	18.50	4.59	88.99	6	3

that given by the ICRP is 2 for the high energy β emitter ^{90}Y, but the ratio falls towards lower energies and is about 0.5 for ^{171}Tm. This trend is also in line with the data of Fig.2 because, whereas the curve for $\bar{D}_M$ is now almost independent of β-particle energy, the curves for the surface dose parameters rise steeply at low energies.

Results for ^{226}Ra

Dosimetric data are also available for ^{226}Ra uniformly distributed in bone[18] and risk values have also been calculated for this radionuclide and its retained daughter products. The results are given in the last section of Table 2. Risk factors appropriate to ^{226}Ra have been derived from the linear extrapolation given in the report of the U.S. Advisory Committee on the Biological Effects of Ionizing Radiations (BEIR Report 1972)[19].

In this Report, 48 cases of osteogenic sarcoma are recorded in a group of 775 persons subjected to a mean dose of 1700 rad, i.e. a tumour rate of 36 cases/10^6 for a dose of 1 rad to the bone mass. Because the dose to trabecular endosteal tissues is about one third of the dose to bone (and only a few tumours have been identified as originating in the cortical mid-thirds of long bones[13]) the risk rate for osteogenic sarcomas can be put at $105/10^6$/yr for a dose rate of 1 rad/yr. The value of r_o can then be taken as $70/10^6$/yr and r'_o as $35/10^6$/yr. The radium case data, reviewed in the BEIR Report, also include a further 20 cases of carcinoma of air sinuses for which the risk rate can be similarly deduced as $40/10^6$/yr for a dose rate of 1 rad/yr to a layer of tissue adjacent to bone of the air sinus cavities. The dose factor for this situation will be approximately the same as for the trabecular surfaces and so this risk can be added to the value of r_o for calculation purposes. No data are available for the incidence rate of angiosarcoma etc., except that these tumours seem to have occurred very rarely in radium cases; no value has been given therefore to the factor r_a. Only a nominal value of 200 has been given to the bone marrow risk factor r_m because, as can be seen from Table 2 the very low dose to bone marrow makes the total bone risk insensitive to this factor. The nominal value of 200 was taken as 5 times the value used for β emitters because the risk factor for osteogenic sarcoma, $105/10^6$/yr, was about 5 times greater than the value of $20/10^6$/yr chosen for β emitters in Eq. (4). The value of the total risk for a volume-seeking α emitter is then given by:

$$R_1 = (200\bar{D}_M + 110\bar{D}_S + 35\bar{D}'_S)/10^6/\text{yr} \qquad (10)$$

In calculating the value q for the MPBB, the same value of R_{MPL} is used and a small contribution is added for the ^{226}Ra β particles, according to Eq. 8. The result, q = 0.14 μCi is surprisingly close to the ICRP value, based on quite other considerations.

Conclusions

This paper attempts to calculate maximum permissible body burdens for a number of β emitters that are deposited in bone either throughout the bone matrix as volume-seekers or on bone surfaces as surface-seekers. The principles are different from those used hitherto, in that the dose parameters are the absorbed doses in rad to the relevant tissues and risk parameters are derived from the commonly accepted linear extrapolations of available human data on tumour incidence, combined with incidence ratios for other tumours from animal investigations. The values of MPBB so obtained are higher than present ICRP values, but not so much higher as to rule the method out of court. Concordance with ICRP values for high energy β emitters could be obtained by altering the choice of risk corresponding to that for occupational exposure. If this were done then at low β-particle energies, the new calculations would generally give higher values for the MPBB for the volume-seekers and lower values for the surface-seekers, compared with present ICRP values. A more formal approach to the problem would be to use the dosimetric data in a similar manner, but simply choose the risk factors to follow ICRP dose levels, i.e. put the total risk for bone tumours at one third of that adopted for the bone marrow risk, - in accordance with a dose of 5 rem to bone marrow and 15 rem to a single organ. It is suggested, however, that the method used in this paper is preferable and the concordance obtained when the method is applied to ^{226}Ra gives encouragement that eventually all the bone-seeking radionuclides may be treated in this way, without recourse either to a relative damage factor or to an overt specification of a quality factor.

References

1. Joan R. Whitwell and F. W. Spiers, in Proceedings of the Fifth Congress of the French Society for Radioprotection, Grenoble, (1971).
2. F. W. Spiers, G. D. Zanelli, P. J. Darley, J. R. Whitwell and M. Goldman, in Biomedical Implications of Radiostrontium Exposure, Eds. M. Goldman and L. K. Bustad, AEC Symposium Series 25, CONF-710201, 130, (1972).
3. Joan R. Whitwell and F. W. Spiers, unpublished data.
4. International Commission on Radiological Protection, ICRP Publication 11, Pergamon Press, Oxford, England, (1968).
5. International Commission on Radiological Protection, ICRP Publication 14, Pergamon Press, Oxford, England, (1969).
6. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), Official Records of the General Assembly, Supplement 25 (A/8725), United Nations, New York, (1972).
7. J. F. Loutit and Janet M. Vaughan, Brit. J. Radiol., 44, 815, (1971).
8. H. Sissons, Medical Research Council, London, Sub-Committee on Permissible Levels, PIRC/PL/70/4, (1970).
9. J. Vaughan, Medical Research Council, London, Sub-Committee on Permissible Levels, PIRC/PL/70/4, (1970).
10. International Commission on Radiological Protection, ICRP Publication 2, Pergamon Press, New York, USA, (1959).
11. R. R. Pool, R. J. R. Williams and M. Goldman, in Biomedical Implications of Radiostrontium Exposure, Eds. M. Goldman and L. K. Bustad, AEC Symposium Series, CONF-710201, 277, (1972), and D. L. Dungworth, M. Goldman, J. W. Switzer and D. H. McKelvie, Blood, 34, 610, (1969).
12. W. J. Clarke, R. H. Busch, P. L. Hackett, E. B. Howard, M. E. Frazier, B. J. McClanahan, H. A. Rogan and G. S. Vogt, in Biomedical Implications of Radiostrontium Exposure, Eds. M. Goldman and L. K. Bustad, AEC Symposium Series, CONF-710201, 242, (1972).
13. C. W. Mays, personal communication.
14. M. P. Finkel, B. O. Biskis, I. Greco and R. W. Camden in Biomedical Implications of Radiostrontium Exposure, Eds. M. Goldman and L. K. Bustad, AEC Symposium Series, CONF-710201, 285, (1972).
15. A. Nilsson, Acta Radiol., 9, 155, (1970).
16. B. E. Roberts, D. W. Miles and C. G. Woods, Brit. J. Haemat., 16, 75, (1969).
17. F. C. McLean and A. M. Budy, Radiation, Isotopes and Bone, Academic Press, New York, USA, 34-35, (1964).
18. Joan R. Whitwell and F. W. Spiers, unpublished data.
19. Report of the Advisory Committee on the Biological Effects of Ionizing Radiations, National Academy of Sciences, National Research Council, Washington, D.C., 128, (1972).