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INTERNAL EMITTER LIMITS FOR IODINE, RADIUM AND RADON DAUGHTERS*

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INTRODUCTION

About four years ago, I was asked by Dr. J. N. Stannard, Chairman of SC57, the NCRP's Committee on Internal Emitter Standards, whether or not the recommendations of SC1, then available in early draft form, could serve as the basis for the derivation of internal emitter exposure limits. On reading the draft report, it quickly became clear that the answer was "Yes" and that the key question was not, "Could it be done?" but rather, "How should it be done?". In reply, I suggested some general approaches and developed detailed examples of their application in a lengthy memo prepared for a combined meeting of SC1 and the NCRP Board of Directors,* September 25-26, 1980, in Provincetown, Massachusetts.

Dr. W. J. Bair was concurrently working on the problem, and the general approaches which he and I developed independently were brought together by him in a paper presented at the Seventeenth Annual Meeting of the NCRP three years ago (1). Since then, Drs. Stannard and Bair, as members of SC1, have prepared a chapter on internal emitters with general approaches and examples of their application for a draft report of SC1. So far, the work of Drs. Bair, Stannard and myself has not gone beyond the bounds established in September, 1980, although there have been differences in detail between what each of us has done. The purpose of this paper is to extend the work and to identify some of the issues which arise as one considers the derivation of new limits on exposure to internal emitters.

To make the discussion self-contained, it opens with statements on basic and secondary radiation protection limits. The term, direct approach, used in

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*Memo dated September 22, 1980, from Robert A. Schlenker, Committee 57, on "Internal Emitter Standards Based on Committee 1 Recommendations".

the title of the oral presentation, and ones related to it, are then defined and applied to the limitation of risk from stochastic effects. Since non-stochastic effects are also important, a substantial portion of the text is devoted to non-stochastic data for specific internal emitters (^{131}I and the radium isotopes). The paper ends with a discussion of issues. Throughout, an emphasis is placed on the quantitative aspects of the limit setting problem and numerical examples are plentiful.

BASIC LIMITS

In order to develop numerical examples, a set of basic radiation protection limits is needed. Logically, these would be drawn from the recommendations of the NCRP but the new report on basic criteria has not yet been issued so the limits shown below have been arbitrarily adopted.

(a) Annual Limit on Risk \LR) of Stochastic Effects

The lifetime risk of fatal cancer plus serious genetic effects expressed in the first two generations of offspring conferred by one year of exposure may not exceed 5×10^{-4}.

(b) Annual Limit on Dose Commitment to Organs and Tissues $(ALDC)_t$ for Non-Stochastic Effects

The absorbed dose commitment for the 50 years following one year of exposure may not exceed 50 rad for negatron, positron, electron, x and gamma radiation, 5 rad for neutron, proton and heavy particle radiation with Z = 1 and 2.5 rad for alpha particles, fission fragments and other

heavy charged particles with $Z > 1$. The targets for the development of non-stochastic effects are considered to be the whole organs, except in the case of bone, where endosteal bone surface tissue and hematopoietic marrow are considered to be the targets.

These limits do not differ greatly from those which might be derived from the current recommendations of the ICRP (2). In Publication 26, paragraph 60, the risks of cancer mortality and of hereditary effects in the first two generations from uniform whole body irradiation are given as $10^{-2}\ S_v^{-1}$ and $4 \times 10^{-3}\ S_v^{-1}$, respectively. Whole body exposure at the annual limit of .05 S_v would confer a total risk of fatal cancer plus genetic effects equal to 7×10^{-4}. This is not much greater than the ALR stated above. The non-stochastic limit of 0.5 S_v per year for most organs and tissues, when applied to internal emitters, is used as a limit on dose equivalent commitment for the 50 years following exposure. The corresponding limits on absorbed dose commitment are 50 rad, 5 rad and 2.5 rad, depending on the type of radiation, when the Q values currently recommended by the ICRP (2) are used to translate from dose equivalent to absorbed dose. These three values are equal to the non-stochastic limits adopted above.

SECONDARY LIMITS

In Publication 30 (3), the ICRP replaced Maximum Permissible Concentration with Annual Limit on Intake (ALI) as the secondary limit for control of internal exposures. The basic limits adopted above and the basic criteria now being considered by the NCRP can be readily adapted either to the limitation of environmental concentration or to the limitation of bodily intake and there may be circumstances in which one type of limit is preferable

to the other because of the way in which dose-response data are reported. For example, the cancer risk for radium dial workers is reported as a function of radium intake to blood and it would therefore seem natural for the radium exposure limit to be stated in terms of intake. Alternatively, the lung cancer risk for uranium miners is expressed as a function of Working Level Months (WLM), a measure of the time integrated air concentration of radon daughters, and therefore an annual limit on WLM would be the natural one for radon daughter exposure.

When establishing a value for the secondary limit, trial values are determined from each of the basic limits and the smallest trial value is adopted as the final value because it alone guarantees that none of the basic limits will be exceeded. In order to distinguish between the various trial values of Annual Limit on Intake, the symbols $(ALI)_s$, $(ALI)_{ns,1}$, $(ALI)_{ns,2}$, $(ALI)_{ns,3}$,... will be used to denote the trial values derived from the stochastic limit and from the non-stochastic limits for tissues number 1, 2, 3, etc. The basic equations for the trial values are:

$$(ALI)_s = \frac{ALR}{LR \text{ per } \mu Ci \text{ intake}} \tag{1}$$

$$(ALI)_{ns,t} = \frac{(ALDC)_t}{(DC)_t \text{ per } \mu Ci \text{ intake}} \quad , \; t = 1,2,3... \tag{2}$$

where LR denotes lifetime risk and $(DC)_t$ denotes the absorbed dose commitment to tissue t. The final value is then:

$$ALI = \text{Min } \{(ALI)_s, (ALI)_{ns,1}, (ALI)_{ns,2}, (ALI)_{ns,3}....\} \tag{3}$$

A similar set of equations could be developed for Annual Limit on Exposure. When the exposure variable is WLM, these would be:

$$(ALE)_s = \frac{ALR}{ER \text{ per } WLM} \tag{4}$$

$$(ALE)_{ns,t} = \frac{(ALDC)_t}{(DC)_t \text{ per } WLM} \quad , \; t = 1,2,3... \tag{5}$$

and the final value would be:

$$ALE = \text{Min } \{(ALE)_s, (ALE)_{ns,1}, (ALE)_{ns,2}, (ALE)_{ns,3}...\} \tag{6}$$

DIRECT, COMBINED and INDIRECT APPROACHES

Terms such as direct approach, indirect approach, intermediate risk approach, and derived risk approach have been used to distinguish between derivations of exposure limits which utilize dose-response relationships for humans expressed as functions of radionuclide intake or exposure and derivations which utilize risk per unit absorbed dose or dose equivalent to irradiated organs and tissues, determined from various sources of information including external irradiation studies. For example, the direct approach would base exposure limits for ^{222}Rn daughters on the dose-response relationship for lung cancer induction in uranium miners while the indirect, intermediate or derived risk approaches would base the ^{222}Rn daughter limit on linear risk coefficients such as those implied by the ICRP organ weighting factors (2).

One feature of the direct approach, as it has been discussed within the NCRP, is the use of observed risk per unit observed intake or exposure for the derivation of limits. In theory, this allows the calculation of limits on

intake or exposure to be made directly from published dose-response relationships without the use of mathematical models of radionuclide uptake and metabolism to translate risk per unit organ or tissue dose into risk per unit intake or exposure. This reduces the labor required for the derivation of limits and also the uncertainty in the limits themselves by avoiding the introduction of errors associated with metabolic modeling.

In practice, the only dose-response relationship for which the observed risk is expressed in terms of the observed intake or exposure is for lung cancer in uranium miners. There would be a second one if the bone cancer induction data for ^{224}Ra were presented as a function of total injected activity rather than estimated mean skeletal dose, although, even then the requirements of radiation protection would demand the use of gastrointestinal and lung absorption models to relate ^{224}Ra injection levels to equivalent amounts of ^{224}Ra ingested or inhaled. The dose-response relationships for bone and sinus/mastoid cancer induction following the ingestion or injection of $^{226,228}Ra$ (4,5) are expressed in terms of intake to blood estimated, by the use of a retention equation, from the observed ^{226}Ra body burden and from observed and assumed values for the ratio of ^{228}Ra to ^{226}Ra. Thus, they give risk as a function of calculated intake rather than observed intake.

With the exception of the uranium miner data, it is always necessary to modify published dose-response relationships in order to derive limits on intake or exposure, and the possibility of unmodified use of a dose-response relationship should not be emphasized as a primary aspect of the direct approach.

The reliance on dose-response data for human exposure to internal emitters is another important feature of the direct approach. Because of non-uniformities in dose distribution, the risk to an organ per unit absorbed dose

or dose equivalent may be much different for internal emitter exposures than for uniform whole or partial body gamma-ray exposures such as approximated in the atomic bomb blasts. Thus, risk functions observed for specific radionuclides should give more plausible limits for those nuclides than should risk functions derived from other exposure situations.

In the present paper, the reliance on human internal emitter studies, whether or not the dose-response relationships available from them are expressed as functions of intake, exposure, or absorbed dose, will be one distinguishing feature of the direct approach. The other will be that limits are based only on the risk for effects which have been observed in statistically significant excess, e.g., lung cancer in uranium miners or bone cancer following exposure to radium isotopes.

In the typical internal emitter study, a statistically significant excess of cancer is observed in one or two organs or tissues. The failure to observe a significant excess at other sites may only mean that the natural incidence is too variable and the population observed in a particular study too small for an unequivocal observation to have been made and not that the risk is negligible. Thus, a combined approach will be introduced in which the human internal emitter data are used for the statistically significant effects, and estimates of the risk of other effects will be made using universal risk coefficients.* The indirect approach will also be used, in which total reliance will be placed on universal risk coefficients.

The equations which define the total risk per unit intake for each of these approaches are presented below:

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*This term is used to describe linear risk coefficients such as those implied by the ICRP system of weighting factors and is explained in the next section.

Direct: (Total Risk/μCi) = (Observed Risk/μCi) (7)

Combined: (Total Risk/μCi) = (Observed Risk/μCi) + (Projected Risk/μCi) (8)

Indirect: (Total Risk/μCi) = (Projected Risk/μCi) (9)

Here "Projected Risk/μCi" signifies an estimate of the risk per unit intake, based on universal risk coefficients, for organs in which no effect has been observed in statistically significant excess (combined approach) or for all organs and tissues (indirect approach). The equations for risk per unit exposure in each approach are identical except that μCi intake is replaced by an appropriate exposure variable such as WLM.

STOCHASTIC EFFECTS

The term "stochastic effects" is synonymous with "fatal cancer and fatal illness in the first two generations of offspring caused by inherited genetic damage". Genetic effects induced by internal emitters have not been observed in humans and consequently are not considered in the direct approach. Their absence underscores an important philosophical difference between this approach and the combined and indirect approaches, where risk is estimated whether or not a particular effect is known to be induced by internal emitters.

A. Universal Risk Coefficients

The "Projected Risk/μCi" which appears in the equations for the combined and indirect approaches is derived from linear risk coefficients such as those

discussed in ICRP Publication 26 (2). These coefficients give the risk of cancer or genetic effects per unit dose equivalent and are used for the estimation of radiation risk regardless of the type of radiation (α, β, γ, etc.), whether the exposure is external or internal, or which radionuclides may be involved. The coefficients are intended to be applied universally, so that, for example, the same coefficient is used to estimate the risk of lung cancer from external gamma radiation and from inhaled plutonium compounds.

The results of epidemiological dose-response analyses usually play an important role in the derivation of such universal risk coefficients. But epidemiological studies usually give the risk of a specific type of cancer from a specific type of exposure, so adjustments are necessary to obtain a risk coefficient applicable to all types of exposure. The adjustment process may involve the use of assumptions, additional human data, or data from animal or cell culture studies. The end product is an amalgamation and a universal risk coefficient is seldom traceable to a single set of epidemiological results.

Universal risk coefficients are thus obtained by a process of generalization in which the effects observed for a specific type of exposure are assumed to occur for all types. This process is necessary to fill the gaps in our knowledge created by the scarcity of human health effects data. For radionuclides, the gaps are so many that the health effects for which universal risk coefficients are available have seldom actually been observed in humans. One example is leukemia induced by ^{90}Sr. Many others could be given. Due to the preponderance of such situations, there are very few radionuclides and effects to which the direct or combined approaches can be applied. For the great majority of radiation protection calculations, the indirect approach is required.

The universal risk coefficients adopted for use in this paper are those implied by the ICRP weighting factors and the lifetime risk of mortality from all cancers or the lifetime risk of mutation. The weighting factor system is normally applied to the calculation of dose equivalent but is actually based on risk, as is clear from the definition (2, paragraph 104): "...w_T is a weighting factor representing the proportion of the stochastic risk resulting from tissue (T) to the total risk, when the body is irradiated uniformly...". The total stochastic risk is 1.4×10^{-4}/rem (2, paragraph 60) and the risk coefficients equal the product of 1.4×10^{-4} and the weighting factor, e.g. the risk coefficient for breast cancer is $(0.15)(1.4 \times 10^{-4}/\text{rem}) = 0.21 \times 10^{-4}/\text{rem}$. A complete set of values is given in Table 1.

B. Specific Risk Coefficients

When there are dose-response data on humans for a particular type of exposure, the best estimates of risk are obtained from them, not from universal risk coefficients. While a logical proof cannot be given for this assertion, it seems reasonable that an estimate of future health effects, based on past experience with a particular type of exposure, would be more reliable than an estimate based partly or totally on other types of exposure. To distinguish them from universal risk coefficients, risk coefficients based on effects observed in humans for a specific type of exposure will be called specific risk coefficients.

Four cases are discussed here in which cancer has been observed in humans exposed to specific radionuclides or radionuclide mixtures, namely lung cancer in miners exposed to ^{222}Rn daughters, bone cancer induced by ^{224}Ra, bone and sinus/mastoid cancer induced by ^{226,228}Ra and thyroid cancer in persons

exposed to iodine isotopes.

(1) Iodine isotopes

The risk estimates used here were developed by a task group of SC57, chaired by Dr. H. Maxon, and will appear in a forthcoming NCRP report entitled Thyroidal Carcinogenesis Following Exposure to Ionizing Radiations. The report relies heavily on data for cancer induction by external radiation exposure but predictions of the risk model compare so well with the frequency of thyroid cancer induction observed in Marshallese Islanders internally exposed to a mixture of iodine isotopes that the risk estimates are tentatively accepted as directly applicable to internal emitters. The dosimetry for the Marshallese exposures is undergoing review at Brookhaven National Laboratory and future revisions may affect the degree to which the predictions of the task group model match the data.

The lifetime risk of radiogenic cancer per unit absorbed dose to the thyroid for a North American population is

$$LR = 2.5 \times 10^{-6}\ F \cdot A \cdot S \cdot Y/\text{rad} \qquad (10)$$

where F is a dose effectiveness reduction factor which accounts for the fact that the risk per rad for ^{131}I is lower than for x rays, A accounts for the effect of age on risk, S accounts for risk differences between the sexes and Y is the number of years at risk. The values of F, S and A are: F = 1/3 for ^{131}I and 1 for x rays and the shorter lived isotopes $^{132,133,135}I$, S = 4/3 for women and 2/3 for men and A = 1 for persons 18 or less at exposure and 0.5 for persons over 18. The number of years at risk is not certain. The task group report suggests assuming 50 years as the lifetime average period of risk but

also discusses the data on time distribution of tumor appearance. It is clear that tumors can appear 20 to 30 years after childhood irradiation and may occur as long as 40 years after irradiation but cumulative incidence has been reported to approach a plateau 15 to 25 years after exposure. Selecting 10-year minimum (6, p. 367) and 40-year maximum tumor appearance times for this paper gives Y = 30. With proper diagnosis and patient care, the task group report estimates that about 10% of thyroid cancers will be fatal.

Putting these factors together, the specific risk coefficients for fatal cancer in a population of workers equally divided among the sexes and exposed in adulthood are:

$$^{131}I: \quad 1.25 \times 10^{-6}/\text{rad} \tag{11}$$

$$^{132,133,135}I: \quad 3.75 \times 10^{-6}/\text{rad} \tag{12}$$

(2) Radon-222 daughters

An association between lung cancer and the inhalation of airborne radon daugher products has been established for some groups of hard rock miners (6). The air in underground mines also contains fumes and mineral dust whose impact on lung cancer is unknown. Exposure limits will include the effect, if any, of these other agents and should probably be applied to the control of exposure only in the type of mine from which the risk data on which the exposure limits are based were drawn. The discussion here will be limited to uranium mines.

Groups of uranium miners in the United States, Czechoslovakia and Canada have been studied (6, p. 380ff). Since radiation protection limits established by the NCRP apply to U.S. workers, there is a temptation to focus

only on the U.S. results. However, to do so would imply an exactitude in the studies which does not exist. In view of the uncertainties in the health effects data (7), the accuracy of radon daughter exposure limits probably benefits from averaging the results of replicate studies even though the populations, exposure conditions and designs for the different studies are not identical.

Cohen (8) presents a useful plot of the lung cancer mortality per working level month (WLM) of radon daughter exposure drawn from many sources. The more precise uranium miner data are apparently those from the U.S. and Czech studies (9). A cursory examination of Cohen's plot shows that 10^{-5} deaths/year/WLM is an adequate estimate of the median for the U.S. and Czech data sets between 100 and 700 WLM. It should be noted that mortality among U.S. miners is less than among Czech miners at all cumulative exposure levels. The reasons are unknown but plausible ones can be offered: (a) Due to the exclusion of radon daughter measurements made by uranium mining companies after 1960 from the determination of U.S. exposures and the use of estimated values for years in which no data were collected in a particular mine, the WLM for U.S. miners tend to be biased upward (7, pp. 31,44,112); (b) the uranium miner data probably include the effects of carcinogens other than cigarette smoking and radon daughters, and the contribution of other carcinogens to the total lung cancer mortality may be greater for the Czech miners than for the U.S. miners (8, p. 279f); (c) followup periods in the two studies are comparable but the frequency of cancer induction is related to the age at first exposure and the mean age at onset of exposure was lower for the American miners than the Czech miners (10).

Assuming that deaths from radiogenic lung cancer occur over a period of 30 years at a constant rate of 10^{-5}/year/WLM, the total lifetime risk would be

$3.0\ 10^{-4}$/WLM. This statement, in effect, constitutes a simple dose-time-response model. More elaborate models with non-constant time distributions of mortality have been applied to the projection of lifetime risk for uranium miners (7,11) but it is questionable whether the additional detail produces a more accurate result given the lack of completeness in the U.S. and Czech studies.

A possible synergism between cigarette smoking and radon daughter exposure has been discussed for some years. The issue is still unresolved (12) and if there is a synergism, the multiplicative effect may be less than once thought (8). Since the issue is unresolved, the lung cancer risk derived above and any exposure limits based on it should be considered applicable only to uranium miner groups with smoking habits similar to those in the U.S. and Czech studies, i.e. to groups in which about 70% of the miners smoke (10,13,14).

In conclusion, the specific risk coefficient adopted here for the lifetime risk of radon daughter-induced lung cancer in U.S. uranium miners is 3.0×10^{-4}/WLM.

(3) Radium-224

Bone cancers are the only neoplasia known to occur in statistically significant excess following exposure to ^{224}Ra (15,16). The risk per unit skeletal dose increases with the protraction of radiation exposure and reaches an asymptotic value of 200×10^{-6}/rad (17).

Since the subjects in these studies received ^{224}Ra by injection, the potential exists to develop a dose-response relationship in terms of injected activity. The information published for individual subjects (15) is insufficient to determine the injection level for each subject but a

conversion of the risk coefficient from units of skeletal dose can be made which gives an approximate value for the risk per unit activity injected. According to Spiess and Mays (18), 0.2 rad was delivered to the skeleton for each microcurie injected into adults. Since the risk coefficient given above applies to all age groups, it can be multiplied by 0.2 to obtain a risk coefficient expressed in units of injected activity, $4.0 \times 10^{-5}/\mu Ci$.

As of 1974, the first bone cancers had occurred in subjects with one or more bone cancers, at times between 3.5 and 22 years after first injection (16,19,20). A second cancer occurred at 25 years in one patient (19). No new cancers occurred between the 1974 and the 1980 followups (19), suggesting that all radiogenic bone cancers have already appeared. The specific risk coefficient, $4.0 \times 10^{-5}/\mu Ci$, will therefore be assumed to give lifetime risk.

(4) Radium-226,228

Bone cancer and cancer arising in the mucous membranes of the sinuses and mastoid air cells are the neoplastic effects which have been causally related to the internal deposition of ^{226}Ra or ^{226}Ra and ^{228}Ra in combination. Risk for both types of cancer is given as a function of intake to blood (4) calculated from the observed body burden of ^{226}Ra and the estimated or observed ratio of ^{228}Ra to ^{226}Ra, using the Norris retention function for radium to extrapolate body content from the time of observation back to the time of intake (21, Appendix A). When the estimated initial activity of ^{228}Ra is several times greater than that of ^{226}Ra, there is an absence of sinus/mastoid tumors, leading to the supposition that ^{228}Ra is ineffective in producing the tumors (4). In contrast, each microcurie of ^{228}Ra intake is considered equivalent to 2.5 microcuries of ^{226}Ra intake in its ability to

produce bone tumors (4). In data analyses for female radium dial workers first employed before 1950, the risk functions found to provide acceptable fits to the bone cancer data depend on the definition of time at risk (5). When the latter is measured from the year of first employment, the dose-response function contains a quadratic term and exponential factor but no linear term. When time at risk is based on year of first measurement of radium body burden, a linear dose-response function provides an acceptable fit. Analyses of the sinus/mastoid tumor data are available only for risk measured from the year of first employment and for the group first employed before 1930. A linear function provides an acceptable fit to the data (4). All data analyses include an estimate of the natural tumor incidence which must be subtracted out to obtain radiogenic incidence.

The first radiogenic tumors appeared in the radium study population 5 years (bone cancer) and 19 years (sinus/mastoid cancer) after first exposure (21, Appendix B). Since then, the tumors have occurred at a fairly steady rate (20,22-24) with diagnoses made as long as 63 years (bone cancer) and 52 years (sinus/mastoid cancer) after first exposure. The continuing appearance of these tumors is attributed to the lifelong irradiation of critical cells by alpha particles from radium retained in the skeleton.

The life expectancy in the total U.S. population for persons reaching age 18, i.e. working age, is currently about 57 years (25). Subtracting 5 and 19 years from this gives 52 and 38 years as estimates of the periods of time over which workers would be at risk of radium-induced bone cancer and sinus/mastoid cancer respectively. Given that worker groups usually have a better survival experience than the general population, these figures are rounded upward to 55 and 40 years for use here.

Risk coefficients based on the linear and on the quadratic-exponential dose-response relationships for bone cancer incidence are employed here to show the differences in ALI which result from different statistically acceptable analyses of the radium data. The determination of risk coefficients from the quadratic-exponential relationship is illustrated below. D_{226} and D_{228} represent the ^{226}Ra and ^{228}Ra intake to blood respectively; the dosage variable of Rowland, Stehney and Lucas is $D = D_{226} + 2.5\ D_{228}$ (4,5). The natural incidence of bone cancer is 0.7×10^{-5}/year when time at risk is based on year of first measurement (5). The radiogenic incidence is, therefore,

$$I = [(0.7 \times 10^{-5} + 7.0 \times 10^{-8}\ D^2)e^{-0.0011D} - 0.7 \times 10^{-5}]/\text{year} \qquad (13)$$

The intake levels encountered in radiation protection are small and the exponential function can be approximated as $e^{-0.0011D} \cong 1 - 0.0011D$. The total lifetime risk, TLR, equals I multiplied by 55 years. Therefore, neglecting the cubic term,

$$TLR = 3.85 \times 10^{-6}\ D^2 - 4.24 \times 10^{-7}\ D. \qquad (14)$$

For pure ^{226}Ra, D equals D_{226} and for pure ^{228}Ra, D equals $2.5\ D_{228}$. The total lifetime risks for these two isotopes are, therefore,

$$TLR_{226} = 3.85 \times 10^{-6}\ D_{226}^2 - 4.24 \times 10^{-7}\ D_{226} \qquad (15)$$

and

$$TLR_{228} = 2.41 \times 10^{-5} D_{228}^2 - 1.06 \times 10^{-6} D_{228} \quad . \tag{16}$$

The specific risk coefficients equal TLR_{226}/D_{226} and TLR_{228}/D_{228}, and, when rounded to two significant digits are,

$$LR_{226} = (3.8 \times 10^{-6} D_{226} - 4.2 \times 10^{-7})/\mu Ci \tag{17}$$

and

$$LR_{228} = (2.4 \times 10^{-5} D_{228} - 1.1 \times 10^{-6})/\mu Ci \quad . \tag{18}$$

Specific risk coefficients based on the linear dose-response relationship for bone cancer, with time at risk based on the year of first measurement, are determined in an analogous manner. Values are presented in Table 2.

C. Risk Coefficients for Ingestion

In order to determine Annual Limits on Intake, the risk coefficients in the last two sections must be re-expressed in terms of the amount of radionuclide inhaled or ingested. When the risk coefficient (risk/rem, risk/rad or risk/μCi injected or absorbed into the blood) is a constant, the re-expression can be achieved by application of the following equations:

$$\left(\frac{\text{Risk}}{\text{rem}}\right)\left(\frac{\text{Dose equivalent commitment}}{\mu\text{Ci intake}}\right) \tag{19}$$

$$\text{Risk}/\mu\text{Ci intake} = \left(\frac{\text{Risk}}{\text{rad}}\right)\left(\frac{\text{Absorbed dose commitment}}{\mu\text{Ci intake}}\right) \tag{20}$$

$$\left(\frac{\text{Risk}}{\mu\text{Ci in blood}}\right)\left(\frac{\text{Activity in blood}}{\mu\text{Ci intake}}\right) \tag{21}$$

The conversion factor at the far right in each equation, e.g. Dose equivalent commitment/μCi intake, is obtained by the use of metabolic models which relate dose equivalent commitment, absorbed dose commitment or activity absorbed into blood to the number of μCi ingested or inhaled. When the risk coefficient is not constant, the same conversion factors are required, but the equations are somewhat more complicated.

Determination of the conversion factors from the metabolic models employed in contemporary radiation protection is usually difficult due to the complexity of the models; the use of computational results already available is a practical necessity. The ICRP gives values for the committed dose equivalent* per unit activity ingested or inhaled, in a supplement to Publication 30 (26). The values of absorbed dose commitment per unit activity ingested or inhaled are numerically equal to the ICRP values for radiations with $Q = 1$, the only case for which values are needed here. The activity absorbed into blood per unit activity ingested or inhaled is not presented in the ICRP publications. For long-lived radionuclides which are ingested, no significant decay occurs during transit through the GI tract. Therefore the amount absorbed into blood is simply f_1, the gastrointestinal absorption factor, multiplied by the amount ingested. For inhalation, there appears to be no simple relationship between the amount absorbed into blood and the amount inhaled. Rather than attempt to determine the relationship by carrying out the complicated series of calculations required by the ICRP lung model, this paper has been limited to a consideration of intake by ingestion.

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*This is equal to the dose equivalent commitment for the 50-year period following intake.

In order to focus attention on the organs and tissues receiving the greatest doses, ICRP Publication 30 excludes those which fail to meet the 10% criterion (3, section 4.7). Consequently, the calculation of projected risks for the combined and indirect approaches is also limited to these principal organs and tissues. Universal risk coefficients expressed in terms of intake by ingestion are given in Table 3 for these organs, with the conversion factors (dose equivalent commitment/μCi ingested).

Conversion of the specific risk coefficients for ^{226}Ra and ^{228}Ra based on the quadratic-exponential dose-response relationship (Table 2) requires multiplication by the conversion factor as indicated in Eq. (21) plus substitution of the activity ingested (Q_{226},Q_{228}) for the intake to blood (D_{226},D_{228}). The relationships between these quantities are:

$$D_{226} = f_1 \, Q_{226} \tag{22}$$

$$D_{228} = f_1 \, Q_{228} \quad . \tag{23}$$

Thus, for intake by ingestion, the specific risk coefficient for ^{228}Ra-induced bone cancer is

$$LR_{228} = [2.4 \times 10^{-5}(f_1 \, Q_{228}) - 1.1 \times 10^{-6}]f_1/\mu Ci \quad . \tag{24}$$

Analogous equations apply to ^{226}Ra-induced bone cancer and to the total risk coefficients.

The specific risk coefficients for ingestion are presented in Table 4.

D. Risk Coefficients for Inhaled Radon Daughters

The specific risk coefficient for inhalation (3.0×10^{-4}/WLM) has already been developed and attention must now be paid to the problem of re-expressing the universal risk coefficients in terms of Working Level Months. The conversion from risk/rem to risk/WLM is achieved with the following equation

$$\frac{\text{Risk}}{\text{WLM}} = \left(\frac{\text{Risk}}{\text{rem}}\right)\left(\frac{\text{Dose equivalent commitment}}{\text{WLM}}\right) \qquad (25)$$

The conversion factors (Dose equivalent commitment/WLM) and risk coefficients are discussed in this section.

(1) Lung (Observed Effects)

The lung is the only organ in which the carcinogenic effects of inhaled radon daughters have been observed. The absorbed dose and dose equivalent to various parts of the lung per WLM of exposure have been the subject of investigation for many years. An excellent brief summary of the results of these studies will be presented in tabular form in a forthcoming report by the NCRP (27).

The ICRP has developed occupational exposure limits (28) on the basis of the most recent models of lung dosimetry. Some additional background information on the ICRP limits has been presented by Jacobi (29). For simplicity and because lung dosimetry is too complex a field to review here, a value for the Dose equivalent commitment/WLM will be selected from the ICRP report. The ICRP values are based on two somewhat different approaches in which the lung is considered as a whole or as separate tracheobronchial and pulmonary regions. The former approach will be utilized here because it is consistent with the application of a single risk coefficient to the lung while

the latter is not. The ICRP presents a choice of values, 3.0 or 4.2 rem/WLM, based on two different dosimetric models. The larger and therefore more conservative value is selected for use here. The universal risk coefficient for lung cancer becomes therefore $(0.17 \times 10^{-4}/\text{rem})(4.2 \text{ rem/WLM}) = 7.1 \times 10^{-5}/\text{WLM}$.

(2) Other Organs (Unobserved Effects)

Although the lung is usually considered to be the only tissue at risk from inhaled radon daughters, there is unequivocal evidence for the absorption of daughters through the lung into the bloodstream (30). The dosimetry information for inhaled short-lived radon daughters presented in the supplements to ICRP Publication 30 is insufficient to permit estimates of the projected risk for cancers of tissues other than lung; the information is limited to ^{214}Bi although it is known that ^{214}Pb is abundantly absorbed (30) and the only organ for which committed dose equivalent is given is the kidney despite evidence that other organs receive substantial doses.

Pohl and Pohl-Rüling (31) have developed an equation for estimation of the dose, D, to individual human organs and tissues from inhaled radon and radon daughters:

$$D = A \cdot \sum_i Rn_i \cdot t_i + B \cdot \sum_i Rn_i \cdot t_i \cdot z_i \cdot \frac{\Phi_i}{\Phi_N} \qquad (26)$$

where A and B are factors, based on rodent studies, which give the dose rate in the organ per unit air concentration of inhaled radon (μrad/hr per pCi/ℓ), due to internally absorbed radon and radon daughters, respectively, t_i is the number of hours per year spent inhaling radon at the concentration Rn_i pCi/ℓ, z_i is a factor describing the relative concentrations of airborne radon

daughter products, Φ_i is the inhalation rate in ℓ/sec and Φ_N is the "normal" inhalaton rate. The summations are carried out over all environments in which a person is exposed. For example, a uranium miner would spend substantial proportions of his time in three environments: the mine, outdoors and in his home. Only the mine is considered here.

Pohl and Pohl-Rüling give values of A and B for several organs and tissues which together represent about one-half the total body mass. In the calculations which follow, weighted average values of A and B are used for the estimation of somatic risk. The computation of the average for A is presented in Table 5. The average for B, assuming that the B-value for marrow can be used for adipose tissue is 0.039 μrad/hr per pCi/ℓ inhaled radon. The equation for average dose is then

$$\bar{D} = 0.087\ (Rn)_{mine} t_{mine} + 0.039\ (Rn)_{mine} t_{mine} z_{mine} \frac{\Phi_{mine}}{\Phi_N} \quad . \qquad (27)$$

The time spent mining each year is assumed to be 2000 hours although it is clear from work statistics that most persons classified as miners spend substantially less time than this underground (32,33). The normal breathing rate, Φ_N, is given by Pohl and Pohl-Rüling as 0.23 ℓ/sec (13.8 ℓ/min). The breathing rate for mining, Φ_{mine} is taken to be 20 ℓ/min, the value adopted by the ICRP for the control of radon daughter exposures to workers (28). Thus $\Phi_{mine}/\Phi_N = 20/13.8 = 1.45$.

The value of z_{mine} depends on the concentrations of short-lived radon daughter products in mine atmospheres, relative to radon, and may be calculated with the following formula given by Pohl and Pohl-Rüling

$$z_{mine} = \frac{795a + 4640b + 1706c}{7141} \qquad (28)$$

where a, b and c are the concentrations of RaA, RaB and RaC in the mine air relative to the concentration of Rn. As often stated in the literature, the mine environment is a complex one and a, b and c vary with environmental factors such as barometric pressure and ventilation rate. Therefore, values of a, b and c reported for some U.S. mines are used here without suggesting that these values are universally applicable. The values are averages of the radon daughter ratios reported by George and Hinchliffe (34, Tables 3-8)* for sampling locations in 6 New Mexico mines and equal 0.58, 0.25 and 0.18 for a, b and c respectively; therefore, $z_{mine} = 0.27$. Under these circumstances, the radon concentration required to produce a 1 WL potential alpha energy concentration is 390 pCi/ℓ. Therefore, the dose per working level year would be

$$\bar{D} = (0.087)(390)(2000) + (0.039)(390)(2000)(0.27)(1.45)\ \mu\text{rad/WL year} \qquad (29)$$

$$= 0.080\ \text{rad/WL year} \quad .$$

With Q = 20 and 11.8 working months per year (= 2000 hours per working year/170 hours per working month), the conversion factor for somatic effects in the whole body is (0.080 rad/WL year)(20 rem/rad)/(11.8 months/year) = 0.136 rem/WLM† and the universal risk coefficient for somatic effects in the whole body, exclusive of cancer induced by daughters on the lung surface,

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*Forty-three values are listed for each radon daughter. The values for "Main drift, position #1" in Mines C and D appear to be duplicate sets. Therefore, one set was eliminated in the computation of the averages.

†Due to the short half-life of radon daughters, the dose equivalent and dose equivalent commitment are equal.

is: $(1.05 \times 10^{-4}/\text{rem})(.136\ \text{rem/WLM}) = 1.4 \times 10^{-5}/\text{WLM}$.

Pohl and Pohl-Rüling also give values of A and B for the gonads. The gonadal dose equivalent per working level month computed as above, is .032 rem and the universal risk coefficient is $(0.35 \times 10^{-4}/\text{rem})(0.032\ \text{rem/WLM}) = 1.1 \times 10^{-6}/\text{WLM}$. The total universal risk coefficient for unobserved effects is therefore $(1.4 \times 10^{-5}/\text{WLM}) + (1.1 \times 10^{-6}/\text{WLM}) = 1.51 \times 10^{-5}/\text{WLM}$.

E. The Relative Importance of Observed and Unobserved Effects in the Combined Approach

The combined approach might be described, appropriately, as the direct approach augmented by guesswork. The guesswork lies in the projection of risk for effects not known to occur. How much does this guesswork affect the final result? This question is addressed by Table 6 where the ratio of terms in the risk equation (Eq. (8)) for the combined approach is presented. It can be seen that the projected risk for unobserved effects is sometimes negligible compared to the risk for observed effects, sometimes comparable to it and sometimes much greater than it. Thus, in some cases, the projected risk can be considered a small correction to the total risk to account for the possibility that effects directly observed might not include all the effects which actually occur. But in other cases, this interpretation is not possible because the projected risks dominate. These latter cases create a serious dilemma for radiation protection philosophy. The appeal of the direct approach lies in the fact that it is tied as closely as possible to actual observation. The combined approach augments this with proforma guesses made in the spirit of conservatism. Should radiation protection adhere as closely as possible to direct observations when they are available or should it say

that the direct observations are too insensitive to be of value?

F. Stochastic Annual Limit on Intake or Exposure

The Annual Limit on Intake, $(ALI)_s$, defined by stochastic effects, is computed from Eq. (1) using the total risk coefficients for the direct, combined and indirect approaches presented in Table 7. The application of Eq. (1), when the risk coefficient is a constant, requires no comment since only simple division is involved. In order to apply Eq. (1) with the nonconstant risk coefficients for ^{226}Ra and ^{228}Ra, the variables Q_{226} and Q_{228} must be replaced by $(ALI)_s$. Using the ^{228}Ra risk coefficient for the direct approach, $(.0096\ Q_{228} - .0022) \times 10^{-4}/\mu Ci$, as an example, Eq. (1) becomes

$$(ALI)_s = \frac{5 \times 10^{-4}}{(.0096(ALI)_s - .0022) \times 10^{-4}} \tag{30}$$

This equation reduces to the following quadratic,

$$.0096(ALI)_s^2 - .0022(ALI)_s - 5 = 0 \tag{31}$$

whose solution is,

$$(ALI)_s = 22.937\ \mu Ci \quad . \tag{32}$$

The Annual Limit on Exposure, $(ALE)_s$, for radon daughters is computed from Eq. (4). Values of $(ALI)_s$ and $(ALE)_s$ for all nuclides considered here are presented in Table 8. The Q and L forms of the risk coefficient for ^{228}Ra yield substantially different values and, in some cases, the three approaches do also. The final choice of form or approach is largely a matter of

philosophy since there are no unequivocal guidelines based on scientific data to tell which give the most accurate results.

NON-STOCHASTIC EFFECTS

Radiation protection limits were first established to avoid skin erythema, a non-stochastic effect, and only later did the emphasis shift to the avoidance of cancer and genetic effects when it became clear that these might be the most sensitive indicators of undue radiation exposure. Since 1977, when the ICRP adopted the terminology "non-stochastic" and "stochastic", attention has been drawn again to the importance of non-stochastic effects. This is evidenced by the latest report from the United Nations Scientific Committee on the Effects of Atomic Radiation in which an entire annex is devoted to the subject (35), where there was none previously.

The excellent treatment in the United Nations report does not present in detail internal emitter information relevant to the present paper. The purpose of the sections which follow is to discuss some of the data for ^{131}I and the radium isotopes and to identify problems and issues associated with their application to radiation protection.

Non-stochastic effects are generally assumed to arise from radiation-induced cell death, inactivation or alteration in function. The observable manifestations of the cellular changes are expected to vary with the number of cells affected and therefore as a function of radiation dose. As the dose increases, different effects will gradually become apparent. The dose-incidence curve for a particular effect should therefore exhibit an approximate threshold below which the effect is not observed. In addition, the severity of an effect is expected to vary with dose. If a level of severity exists below which the injury is deemed acceptable, the level can be

used to establish a practical threshold on the dose-severity curve. This threshold and the threshold on the dose-incidence curve can be used to establish radiation protection limits. Thus the analysis of non-stochastic data is essentially a search for thresholds.

In the studies discussed here, radiation insult was expressed as absorbed dose to the organ or tissue at risk or as the amount of radioisotope injected or initially taken into the blood. The latter units can be easily translated into an equivalent amount ingested, by use of the gastrointestinal absorption factor, f_1. The thresholds and limits derived from the data will therefore be expressed in terms of absorbed dose or directly in terms of ingestion level.

A. Iodine-131

An excellent review of the literature on radiogenic effects in the thyroid gland has appeared in the American Journal of Medicine (36) and, with slightly different content, in the Reactor Safety Study (37). The present discussion draws frequently on that review. Since this section is concerned with ^{131}I, information from external irradiation studies will be largely ignored. Not only is this justified by the choice of topic but data on the incidence of thyroid effects is much less abundant for external radiation than for ^{131}I. Five sources of information will be utilized: (a) a follow-up study of children who received radioiodine diagnostically, (b) a report on children exposed to ^{131}I in fallout, (c) a report on the follow-up of Marshallese Islanders exposed to fallout from the Bikini weapons test, (d) studies of the after-effects of radioiodine therapy for thyrotoxicosis and (e) studies of people given radioiodine therapy for intractable angina pectoris. Radiation induces two clinically observable non-stochastic endpoints, acute thyroiditis and hypothyroidism. The former appears not to occur at the low

doses of concern in routine radiation protection and only the latter will be considered here.

Before proceeding with discussion of the radioiodine data, a comment on external irradiation is warranted. From the data reviewed by Maxon et al. (36), one might conclude that external irradiation of the normal thyroid at low dose rates over periods of several weeks or longer would not lead to clinical hypothyroidism for total doses below several thousand rad. Due to the scarcity of the data, the evidence for a threshold is not unequivocal, but it is noteworthy and it supports the notion that a threshold exists for radiation-induced hypofunction.

A follow-up study of persons whose thyroids were normal at the time of ^{131}I exposure was underway in the mid-1970's and preliminary data, published in WASH-1400, indicate that 8 persons among 443, exposed at ages less than 16 years, had developed hypothyroidism. The average follow-up time was 14 years and when the data were sorted according to dosage group, the frequency of occurrence increased with dose equivalent, as one would expect for a radiogenic effect. The observed incidence was about 0.2%/yr which is significantly greater than the natural incidence of 0.02%/yr estimated by

Maxon et al. (36).*

In apparent agreement with these results are the findings, attributed to Rallison (37), of 2 cases of overt hypothyroidism among 1378 children exposed in southern Utah and Nevada during infancy and early childhood to ^{131}I from nuclear weapons fallout (38) and none among 3453 controls. The best estimate of thyroid dose in the exposed group was 120 rad, with a possible range of 30 to 240 rad (39, p. 19).

The frequencies of occurrence reported for the fallout study give the prevalence of hypothyroidism while those for the diagnostic test study give the cumulative incidence. Since the clinical signs of hypothyroidism are usually reversed by the first few months of treatment, a non-zero prevalence suggests the existence of untreated cases within the population. Assuming that childhood hypothyroidism would be treated if detected, a comparison between the studies can be based on the amount of time that would elapse between the appearance of symptoms and their reversal. The chain of events leading to proper treatment would begin with parental recognition that a health problem exists, proceed to a search for causes and end with correct

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*The conclusion that a significant difference exists is based on the following analysis developed for this paper: Among the three dose equivalent groups (Nu75), 10-30 rem (mean 18 rem), 31-80 rem (mean 52 rem) and 81-1900 rem (mean 233 rem), the relative frequencies of hypothyroidism were 0/146, 3/146 and 5/151, respectively, while the incidences were 0%/yr, 0.15%/yr and 0.23%/yr. Using the method of Wilks (40) for the binomial distribution, the 95% confidence interval estimates for the relative frequencies are calculated to be (1/146, 8.6/146) for the 31-80 rem group and (2.1/151, 11.4/151) for the 81-1900 rem group. These confidence limits can be used in conjunction with the mean relative frequency in each group to scale the incidence values, e.g., for the 31-80 rem group the scaled incidences are (1/146) ÷ (3/146) x 0.15%/yr = 0.05%/yr and (8.6/146) ÷ (3/146) x 0.15%/yr = 0.43%/yr. For the 81-1900 rem group, they are 0.099%/yr and 0.52%/yr. The lower limits of the confidence intervals, 0.05%/yr and 0.099%/yr, both exceed 0.02%/yr, leading to the conclusion that the observed incidence in both dose equivalent groups is significantly greater than the natural incidence with better than 95% confidence.

diagnosis and treatment. This process could require several months to more than a year depending on the rate of progression of the disease, the physical and behavioral clues from the child and the accuracy of diagnosis. For the present discussion, let us assume that a minimum of 0 and a maximum of 12 months are required and that symptoms would be prevalent for three months longer than this, i.e., for a minimum of 3 months and a maximum of 15 months. The incidence of about 0.2%/year observed in the diagnostic test study would imply a minimum prevalence of (.002)(3/12)(1378) = 0.7 and a maximum prevalence of (.002)(15/12)(1378) = 3.4 among the 1378 children in the group exposed to fallout; 2 were observed. By analogous computations using the natural incidence of 0.02%/year (36), the prevalence among the 3453 controls would be 0.2 to 0.9; none were observed. The agreement between predicted and observed values is good enough to conclude that the results of the two studies are consistent with one another.

Frank hypothyroidism has also been observed following exposure to fallout from the Bikini weapons test in March, 1954 (41). Two of 19 Marshallese less than 10 years of age at the time of the test developed hypothyroidism several years after exposure on Rongelap atoll. The total body gamma-ray dose was estimated at 175 rad and the total doses to the thyroids of the 19 children lay in the range 810 to 1150 rad. Besides gamma rays, thyroid dose was delivered by $^{131,132,133,135}I$ with dose from the short-lived isotopes $^{132,133,135}I$ estimated at two to three times the dose from ^{131}I. The complex mixture of radiations precludes classification of these cases of hypothyroidism as ^{131}I induced. However, 80% or more of the dose was delivered by radiations from iodine isotopes and the induction was no doubt heavily influenced by internal radiation.

Thus, there are three studies which appear to confirm the induction of hypothyroidism following the delivery of relatively low doses by iodine in childhood. Unfortunately, the diagnostic test study has never been reported in a form sufficiently detailed to allow the merit of the results to be judged by the scientific community. Although support for the results is given by the comparison made with the fallout study, the comparison rests on an unverified estimate of the amount of time that symptoms would be prevalent and thus the comparison must be considered speculative. However, the results of the diagnostic test study cannot be dismissed as irrelevant to radiation protection. If correct, the results indicate that the threshold for hypothyroidism lies at a lifetime dose of no more than a few tens of rad, at least in people irradiated at an average age of about 11 years. This would be a very important conclusion for environmental radiation protection and although the result would not be directly applicable to occupational radiation protection, it suggests that the threshold for ^{131}I-induced hypothyroidism in adult workers may be well below the apparent threshold for induction by external radiation.

The most abundant information on the incidence of radiogenic hypothyroidism in adults comes from the follow-up of persons given ^{131}I for the treatment of thyroid hyperfunction. In this procedure, radioiodine is administered in order to inactivate some of the glandular tissue and reduce the level of thyroid secretion to the normal range. One of the undesirable sequelae is the onset, in many subjects, of hypothyroidism at times post treatment which may vary from a few months to many years. Dose-response data from three studies, corrected for the spontaneous incidence of hypothyroidism among persons treated for thyrotoxic conditions, are presented in Fig. 1. Following a suggestion of Maxon et al. (36), the spontaneous incidence was

taken equal to 0.7%/year, which is the incidence observed, two or more years after surgery, among persons given partial thyroidectomy for thyrotoxicosis (42) or Graves' disease (43).

Before commenting on the data, the assignment of dose values requires discussion. The data of Smith et al. (44) were collected at a treatment center with a well documented history of careful dosimetric studies (45-47). The estimates, by the authors, of 3500 rad and 7000 rad as average values for the two treatment groups, are probably quite accurate although there is a substantial variation of individual doses about the average, due to differences between diagnostic and therapeutic uptake (47). In the study by Blair et al. (48), standard treatments of 1.25 mCi and 2.5 mCi were given but there is no prescription in the paper for associating absorbed dose values with the treatment levels and no estimates of thyroid dose are presented by the authors. Because the treatment levels and thyroid weights are almost identical to those in a second trial of Smith et al. (44) (Blair: 1.25 and 2.5 mCi, 32 g vs. Smith: 1.3 and 2.4 mCi, 34 g) and both study populations were drawn from residents of the United Kingdom, the doses of 1750 rad and 3500 rad in the second trial of Smith et al. have been assigned to the Blair et al. treatment groups. The absorbed doses assigned to the Becker et al. dosage groups (43) are numerically equal to the dose equivalents estimated in WASH-1400 (37).

The term "probability" in Fig. 1 is synonymous with "cumulative incidence" (44,48) or with the probability determined by life table methods (43). The data plotted for Becker et al. are those given in WASH-1400 (37, Table VI H-2) with the probability for 12,600 rem corrected to 0.28. Since the induction of hypothyroidism continues to occur for many years after treatment, the probability will vary with the time period chosen. Five years

was adopted here because it was long enough for effects to have appeared at all dose levels but shorter than the maximum follow-up time in the three studies quoted. The length of follow-up chosen is unimportant for determining a threshold for non-stochastic effects provided the time is not so short that effects are missed altogether.

The lowest dose for which a datum is plotted in Fig. 1, 1750 rad, is the lowest dose for which data appear to be available in the literature. Since the probability of hypothyroidism is non-zero, 1750 rad must lie above the threshold for induction. The implication for radiation protection is that the lifetime dose should never reach this value. Therefore, the maximum annual dose permitted during a working lifetime of 50 years should be less than 1750 rad/50 years = 35 rad/year. Since the threshold lies at an unknown dose less than 1750 rad, a conservative approach would be to include a safety factor in the derivation of the annual dose limit. A factor of 3 would lead to an annual limit of 12 rad and a factor of 10 would lead to an annual limit of 3.5 rad.

It is often said that the hyperfunctioning thyroid is more radiosensitive than the normal thyroid due to the fact that much higher doses of radioiodine are necessary for the treatment of intractable angina pectoris in persons with normal thyroids than for the treatment of thyrotoxicosis. The difference is not surprising. With angina, the usual objective is complete destruction of the thyroid (49) while, with thyrotoxicosis, the objective is to reduce thyroid secretion to the normal range. One would expect complete destruction to require doses which were higher, perhaps many times higher, than those required for a reduction in function. Therefore the difference in doses required by the two therapy regimens cannot be taken, by itself, as evidence for a difference in radiosensitivities. Maxon et al. (36) have addressed the

issue by showing that the probability of hypothyroidism following radioiodine treatment for angina is roughly consistent with the probability observed following the treatment of Graves' disease, when corrections to the latter data are made for the spontaneous incidence of hypothyroidism. Thus it appears that the data from treatment of thyrotoxic conditions are applicable to normals, when the data have been properly adjusted.

The delivery of 1750 rad in a single treatment leads to a maximum dose rate of (0.693)(1750 rad)/(6 days) = 200 rad/day assuming a 6-day effective half-life for radioiodine in the thyrotoxic gland and to an average dose rate which is considerably lower. Compared with external radiation therapy, these dose rates are quite low. Whether they are low enough to avoid the dependence on dose fractionation and protraction commonly encountered in radiation therapy is not certain. Data of Blair et al. (48) indicate that the cumulative incidence following multiple treatments of 1.25 mCi is not much different than that following single treatment, and that it is substantially lower than the cumulative incidence following single treatment with 2.5 mCi. The lower incidence could be interpreted as a dose fractionation effect. The problem is that a thyroid gland requiring multiple treatments of ^{131}I to cure thyrotoxicosis is, by definition, more resistant than one requiring single treatments. Thus, the fact that the cumulative incidence for persons multiply treated with 1.25 mCi is not much different than for persons singly treated may simply reflect the greater radioresistance of the multiply-treated glands. The lower incidence compared to single treatment with 2.5 mCi may also be a reflection of radioresistance and not of dose fractionation effects. Thus the data are not sufficiently conclusive to establish the existence of fractionation effects and the data cannot be used to determine whether or not the threshold for, or the incidence of, hypothyroidism would be

affected by a reduction of dose rate from the levels encountered in radioiodine therapy to those common in radiation protection.

From the discussions in this section, it is clear that no unequivocal interpretation of the data exists and that the establishment of a non-stochastic limit for ^{131}I in the thyroid will be a matter of judgment. It would seem though that the evidence from internal emitter studies is sufficiently strong to raise serious doubts about the 50 rad annual limit adopted at the beginning of this paper, and about the 50 rem annual limit currently employed by the ICRP (2).

B. Radium-224

A number of non-stochastic effects including diseases of the kidney and liver, cataract, tooth breakage and growth retardation have been observed in persons injected with ^{224}Ra (15,16). Of these, the last three seem definitely to be radiation induced, for some age groups at least. This conclusion is based on the available dose-response data, a comparison of observed with expected relative frequencies of occurrence and the specific characteristics of some lesions. Persons exposed as juveniles 15-20 or 16-20 years of age are at much higher risk than persons exposed as adults age 21 or older. Since the late juvenile (16-20 years) and occupational age ranges (18-70 years) overlap, it may be necessary to give special consideration to the 16-20-year age group when developing limits for protection against the effects of ^{224}Ra.

Data on the relative frequencies of occurrence for tooth breakage, growth retardation and cataract are collected in Table 9. Since the radiogenic origin of these effects may not be obvious, some comments are required. For tooth breakage, the nature of the lesion distinguishes radiation-induced tooth loss from loss due to periodontal disease (16) and therefore all cases of

breakage are probably radiation induced. The ability of bone seeking radionuclides to slow or arrest the development of bone is so well known that a radiogenic origin for the retardation effect is the most likely explanation. The prevalence of naturally occurring cataract (50) among persons with ages similar to those who developed cataract in the adult exposure group (15, Table 10) is not much different than the observed value and there is no statistical justification for assuming that cataracts in the latter group are radiation induced. In contrast, the four persons with cataracts in the juvenile group developed them at 36, 44, 45 and 46 years of age. This is young for naturally occurring cataract and the relative frequency of 4/59 appears to be too high to justify an assumption of natural origin. Therefore, cataract in the 16-20-year exposure group is assumed to be radiation induced.

(1) Juvenile Workers

Because of the high radiosensitivity of juveniles compared with adults, juvenile workers 18-20 years of age constitute a special exposure group within the worker population. Sufficient dosage information is available for growth retardation and cataract, to permit an estimation of limits for the protection of juvenile workers: The smallest injected activities associated with growth retardation and cataract among all persons exposed between 1 and 20 years of age, are 175 μCi (51, p. 239) and 329 μCi respectively (15, Table 10, patient FeB and 51, Table 6, patient B. Fe.). The risk of growth retardation diminishes rapidly with age and it is quite likely to be near zero by the time persons in the 16-20-year age range reach 18. Therefore, it is assumed that juvenile workers could sustain an injection of 175 μCi without risk. This is equivalent to 875 μCi taken in by ingestion (f_1 = 0.2) and the objective for

the protection of these workers would be to keep the total intake during the three years between ages 18 and 20 below this level. This leads to an annual limit of 275 μCi/3 years or about 300 μCi/year. When the same procedure is applied to the derivation of a limit for cataract, 550 μCi/year is obtained. Since the dependence of cataract risk on age at exposure is unknown, it would seem prudent to apply a safety factor to this estimate. Factors of 3 and 10 lead to annual limits of 180 and 55 μCi for the work period between 18 and 20 years of age.

The ALI for ^{224}Ra ingestion currently recommended by the ICRP, 8.1 μCi, is determined by the non-stochastic annual limit of 50 rem on the committed dose equivalent to bone surface tissues. Therefore the ALI constitutes a non-stochastic limit for ingestion which can be compared with the above estimates based on internal emitter data. It appears that the ICRP limit is unduly conservative and could be increased substantially without placing young workers at risk of developing bone damage leading to growth retardation or of cataract. How this would affect the risk of tooth breakage is unknown since dose-response data have not yet been published for this effect.

(2) Adult Workers

Adults appear not to be at risk of cataract or growth retardation, and therefore tooth breakage is the endpoint on which a non-stochastic limit should be based, but the lack of dose-response data makes this impossible.

If the limit were based on cataract, a value could be established as follows: Adults were injected with a maximum of about 60 μCi/kg (15, Appendix) or about (60 μCi/kg)(70 kg) = 4200 μCi total, apparently without the induction of cataract. Had the ^{224}Ra been delivered by ingestion, about five times this amount, i.e., 21,000 μCi, would have been necessary to produce a

blood uptake of 4200 μCi. This represents a minimum estimate of the threshold for cataract induction by ingestion. Delivered at a constant rate for 50 years, a 21,000 μCi total would imply a minimum annual limit on ingestion of 420 μCi. The current ICRP limit again seems conservative in comparison.

C. Radium-226,228

The first health effects associated with occupational exposure to radium were non-stochastic. They consisted of mandibular bone necrosis with osteomyelitis and a failure of the jaw to heal after tooth extraction (52). Bone necrosis is now recognized as an effect which occurs throughout the skeleton, accompanied by a variety of gross and microscopic lesions (53-55). The former are visible in x-ray films, especially of the appendages, and a system has been developed for scoring the severity of damage (53). The data which have been obtained are notable for their abundance and, when severity is plotted against dose, accurate determinations of thresholds can be made. Though fewer in number, dose-severity data are also available for plugged Haversian canals, a type of microscopic damage whose presence signifies the partial or complete interruption of bone blood flow near the site of examination. Interestingly, the thresholds obtained for this effect are similar in value to the thresholds for gross lesions.

The other endpoint discussed here is cataract. The data give frequency of occurrence rather than severity of effect and, though not very abundant, do suggest an association between the induction of early cataract and radium intake which provides the basis for the estimation of an ingestion limit for protection against cataract induction.

(1) Bone Necrosis

The section on Basic Limits and also the Recommendations of the ICRP (2) identify bone surface tissues as the tissues in which dose should be limited to protect against health effects in bone. However, the gross lesions seen in skeletal radiographs of ^{226,228}Ra patients (53) often appear in the diaphyses of long bones where there is little endosteal tissue. No such lesions have appeared in ^{224}Ra patients (56) although many received endosteal doses comparable to those associated with lesions in ^{226,228}Ra patients. Because the ^{224}Ra decayed mostly on bone surfaces, the average dose to bone was an order of magnitude less than in ^{226,228}Ra patients when endosteal doses were equal. This suggests that bone dose rather than endosteal dose has been the principal determinant of gross lesions. Histological examination indicates that damage to non-endosteal tissues, and possibly to all of the cells in bone, plays a role in the etiology of necrosis caused by internal emitters (57). The weight of the foregoing evidence suggests that the whole bone volume would be a better choice of target tissue for bone necrosis than surface tissues. This choice would lead to the use of different target tissues for stochastic and non-stochastic effects in bone and would require relaxation of the assumption, now implicit in radiation protection recommendations, that the target tissue for both types of effect be the same.

The scoring system for gross lesions has been used in two forms, one in which all lesions are scored and one in which malignancies and fractures are ignored (58). Since we are dealing with non-stochastic effects, data obtained by the latter usage will be quoted. The lesions which are scored consist of osteolytic areas of various sizes, areas of increased mineral density, found most frequently in the ends of long bones, and coarsening of trabeculation (53). The score obtained is called the reduced x-ray score and has a maximum

value of 60 for the whole skeleton. Fig. 2 is a dose-severity plot adapted from one presented by Evans et al. (59) in terms of the combined ^{226}Ra and ^{228}Ra dose to the marrow-free skeleton. The dose scale based on 5 and 7 kg marrow-free masses for females and males is the original one. The second scale is added to conform to ICRP Publication 23 (60) which recommends 3.4 and 5 kg as the total bone mass for females and males respectively. The latter scale is inexact since the factor, 5/3.4, which transforms the original doses for females into the new values is greater than the factor, 7/5, which transforms the values for males. Correctly applying these factors to each point would cause the points for females to shift relative to the points for males and the appearance of the correct plot for the new doses would be slightly different than the one shown. Because most of the points in the figure represent women, the discrepancy is small.

The three values of (new) dose indicated on the graph identify different possible thresholds derived from the data. Six hundred rad corresponds to the intersection of the lines representing the minimum clinically significant score* and the outer envelope of the data points. Fifteen hundred rad is the dose at which there is a clear downward break in the pattern of points, and 300 rad is just below the lowest dose at which a clinically significant score is observed.

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*The level of significance was set at the highest score, 8, included in the range for minimal radiation effects. Scores of 9 and above indicate mild, moderate and advanced radiation effects, depending on the value. Normal elderly people show scores in the range 0-4 (53). Evans states that scores of 5 or less are not considered clinically significant. Finkel et al. concluded that minimal changes were of no clinical importance and that the boundary of clinical significance lay between the mild and moderate changes, i.e., at scores of about 16-17 (61).

Stated differently, a threshold of 300 rad would protect everyone, 600 rad would protect all but one person and 1500 rad would protect all but two. The fraction of the population not protected by 600 or 1500 rad is less than 1%.

Many subjects in Fig. 1 were alive and data points for them would be expected to move upward and to the right with increasing time. The increases in the threshold values brought about by this would be small because most points on the graph represent persons exposed in late adolescence for whom the follow-up time exceeded four decades and for whom the dose rates had consequently fallen to low levels.

To compare the threshold doses with the non-stochastic annual limit adopted earlier in this paper, imagine that a worker is constantly exposed at the limiting annual rate. During an occupational lifetime of 50 years, he would accumulate a dose commitment of 125 rad to bone surface tissues from alpha radiation. Assuming this to be equally divided between ^{226}Ra and ^{228}Ra,

the dose commitment to bone would be 125 rad/0.83* = 150 rad. The actual dose delivered during the worker's life would probably be less than this since the dose commitment would not be fully expressed during a life of normal length. The dose to bone, under this assumption, would be substantially less than any of the thresholds. The safety factor implied by the difference seems

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*This factor is derived as follows: Following a single intake, the total energy released in bone is directly proportional to the integral of the retention function. For ^{226}Ra, the 50-year retention integrals for cortical and trabecular bone are 73.3 and 25.4 days respectively (62, Table 36). Bone dose is proportional to the retention integrals divided by the bone mass, i.e., to 73.3 days/4000 g = 0.01832 days/g for cortical bone and to 25.4 days/1000 g = 0.02540 days/g for trabecular bone. The average dose for all bone is proportional to the sum of the retention integrals divided by the sum of the bone masses, i.e., to 98.7 days/5000 g = 0.01974 days/g. The ratio of cortical to average bone dose is 0.01832/0.01974 = 0.9281, and of trabecular to average bone dose is 0.02540/0.01974 = 1.287. Therefore, when the average dose is 1 rad, the cortical dose is .9281 rad and the trabecular dose is 1.287 rad.

In each type of bone, part of the alpha particle energy is released from a volume deposit and part is released from a surface deposit. The amount released is proportional to the retention integral for the deposit. The integrals are 72.7 and 0.6 days for the volume and surface deposits in cortical bone and 24.8 and 0.6 days for the volume and surface deposits in trabecular bone (62, Table 36). Therefore, of the dose to cortical bone, a fraction 72.7/(72.7 + 0.6) = 0.9918 is delivered by the volume deposit and a fraction 1 - 0.9918 = 0.0082 is delivered by the surface deposit. The corresponding fractions for trabecular bone are 0.9764 and 0.0236. Thus, when the average dose is 1 rad, the dose delivered by a volume deposit in cortical bone is (.9281 rad)(.9918) = 0.9205 rad, the dose from a surface deposit is 0.0076 rad, and the doses from volume and surface deposits in trabecular bone are (1.287 rad)(.9764) = 1.257 rad and 0.0304 rad.

According to ICRP Publication 30 (3, Chapter 7) 0.01 of the energy released in cortical bone volume is deposited in the endosteum. Therefore, a 0.9205 rad contribution to cortical bone dose leads to an endosteal energy absorption of (0.9205 rad)(4000 g)(0.01) = 36.82 g-rad. Using the same logic and ICRP absorbed fractions, the endosteal energy absorption from a cortical bone surface source delivering 0.0076 rad, would be 7.6 g-rad, the absorption from a trabecular volume source would be 31.42 g-rad and the absorption from a trabecular surface source would be 7.60 g-rad. The total endosteal energy absorption, when the average bone dose was 1 rad, would therefore be 83.4 g-rad. The mass of endosteal tissue is 120 g and the dose is therefore 83.4 g-rad/120 g = 0.695 rad, i.e., the ratio of endosteal dose to average bone dose is 0.695. Calculations for ^{228}Ra give 0.966 rad to the endosteal tissue per rad average dose to bone. The mean of the values for ^{226}Ra and ^{228}Ra is 0.83, which constitutes a best estimate of the factor which should be used with mixed exposures to ^{226}Ra and ^{228}Ra.

unnecessary because the threshold doses are based on a substantial amount of data, and do not contain the large uncertainties found in thresholds derived from lesser amounts. Therefore, the annual limit of 2.5 rad to endosteal tissues seems overly conservative and could be increased without jeopardizing members of the work force. This conclusion also applies to the limit used by the ICRP. Raising the non-stochastic limit would increase the ALI's for ingestion of ^{226}Ra and ^{228}Ra (3) because they are now determined by the non-stochastic limit. If the limit were raised enough so that maximum permissible lifetime exposure led to a dose commitment of 600 rad, the ALI's for both nuclides would become determined by the stochastic limits and would increase from their current values of 1.9 μCi (^{226}Ra) and 2.4 μCi (^{228}Ra) to 5.4 and 2.7 μCi respectively (3).

In order to derive non-stochastic limits directly from the thresholds, it would be necessary to determine the dose commitment which, if accumulated annually for 50 years, would lead to a dose during the average lifetime equal to the threshold. The dose commitment computed in this way would become the non-stochastic annual limit for bone, which could be converted if necessary to a limit for bone surface tissues. Simple approximations which underestimate the limit are obtained by dividing each threshold value by 50 years. This gives 300 rad/50 years = 6 rad/year, 600 rad/50 years = 12 rad/year and 1500 rad/500 years = 30 rad/year.

The calculations on which the dose values of Fig. 2 were based (63) utilize the Norris retention function for radium (64) rather than the alkaline earth model employed by the ICRP (62). The experimental data consist of a body burden measurement; the initial intake to blood which would be necessary to yield this body burden is calculated with the Norris function, taking the duration of exposure and the time since exposure into account. The dose is

then calculated from the initial intake, again using the Norris function to describe the retention and including the buildup and decay of daughter products. The net effect of the calculations described is to multiply the body burden by a scaling factor which for single intake is proportional to the retention integral to a time t divided by the retention at time t. When t is short to moderate in length, say up to 25 years, the scaling factors for ^{226}Ra obtained from the Norris function and from the ICRP alkaline earth model have similar values. But as t increases the scaling factor obtained from the ICRP model becomes increasingly greater than that obtained from the Norris function. For ^{228}Ra, the scaling factors are more or less the same for all times. Therefore, had the dose calculations for Fig. 2 been based on the ICRP model, the dose values probably would, on the average, have been no less that than the ones shown and possibly would have been higher. For the present purposes, the differences are not of great significance, but, should non-stochastic data such as these eventually be used to establish official radiation protection limits, it would be important to recalculate the doses using the ICRP model, to avoid inadvertent use of two different and sometimes conflicting retention models for radium.

When setting limits for a particular organ, one must choose not only the endpoint on which the limit is to be based but also the measure of severity. For bone necrosis, there are at least three measures available, the reduced x-ray score discussed above and two measures based on the microscopic examination of bone tissue: the percentage of Haversian canals found to be plugged when microradiographs of bone sections are examined (65) and the frequency of abnormalities identified in histological slides (55). Whenever different measures of severity are available, the possibility exists that the thresholds based on those measures will differ.

The threshold dose, based on Haversian canal plugs is similar to that based on x-ray score. To quote from Simmons et al. (55, p. 774): "Due to uncertainty in normal incidence, significant increases in plugging due to radium probably cannot be detected below an average skeletal dose of about 1000 cumulative rads...". This threshold dose, based on 5 and 7 kg masses for the marrow-free skeleton, is equivalent to about 1500 rad based on the 3.4 and 5 kg bone masses of ICRP Publication 23. The microradiographic survey data are not sufficiently abundant to permit derivation of threshold values based on subjects of high apparent radiosensitivity for comparison with the 300 rad threshold from the x-ray score data.

For histological abnormalities, the threshold appears to be lower than for x-ray score. Sharpe (55) reports osteonecrosis for persons with skeletal doses well below 1000 rad (5/7 kg basis, equivalent to 1500 rad, 3.4/5 kg basis) and nearly every case examined with a dose of 20 rad or more showed osteonecrosis.*

The difference in thresholds for bone necrosis based on x-ray score and histological damage emphasizes the fact that the threshold dose depends on the measure of damage employed. Because cellular change is expected from any level of radiation exposure, sensitive measures should yield low thresholds.

(2) Cataract

Adams et al. (50) have shown that the cumulative latency for the development of early cataract is significantly less for subjects in whom the combined intake to blood of ^{226}Ra and ^{228}Ra was greater than 50 μCi than for

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*The ^{226}Ra body burdens in Sharpe's Table 2 for cases 5043 and 5204 are erroneous. The correct values are zero (21, Table A1, Cases 05-043 and 05-204).

subjects in whom it was less. This suggests 50 μCi as a first approximation to the threshold for intake to blood or 250 μCi for intake by ingestion. The non-stochastic limits for the lens of the eye, based on the latter value, would be 5 μCi/year, or 1.7 μCi/year with a safety factor of 3 and 0.5 μCi/year with a safety factor of 10. Assuming the effectiveness for cataract induction to be the same for 1 μCi ^{226}Ra and 1 μCi ^{228}Ra, these limits would apply to either isotope.

It is not clear that safety factors are warranted. For ^{131}I and ^{224}Ra, they were employed when the minimum amount associated with the effect was known. For the $^{226,228}Ra$ data, 50 μCi intake to blood is not the minimum amount associated with early cataract, it is simply a value used to divide the intake data into different classes. It is therefore less than the minimum associated with cataract, but how much less is unknown.

D. Non-stochastic Annual Limit on Dose Commitment and Ingestion

Non-stochastic annual limits on dose commitment and ingestion drawn from the preceding sections are presented in Table 10. ICRP values for the committed dose equivalent per unit activity ingested can be used in Eq. (2) to convert the dose commitment limits into annual limits on ingestion if the ICRP values are first divided by the quality factor. For example, the committed dose equivalent to the thyroid per unit ^{131}I activity ingested, is 4.8×10^{-7} S_v/Bq = 1.78 rem/μCi (26, p. 205). When divided by a quality factor of 1, this gives 1.78 rad as the absorbed dose commitment per μCi ingested, which, when applied to the 12 rad limit, yields a limit on ingestion of (12 rad/year)/(1.78 rad/μCi) = 6.7 μCi/year.

Values for committed dose equivalent to bone per unit activity ingested are not given by the ICRP but may be scaled from the corresponding values for

bone surface tissue (26, pp. 289,300) using the factors 0.695 (^{226}Ra) and 0.966 (^{228}Ra) given previously in a footnote. This yields 36.2 rem/μCi (^{226}Ra) and 22.2 rem/μCi (^{228}Ra), which, upon division by a quality factor of 20, give 1.81 rad/μCi (^{226}Ra) and 1.11 rad/μCi (^{228}Ra). The annual ingestion limits, obtained by dividing these conversion factors into 30 rad, are 17 μCi (^{226}Ra) and 27 μCi (^{228}Ra). As mentioned, the data from which the 30 rad/year limit was determined utilize dose calculations which employ the Norris retention function. Consequently, the 30 rad annual dose commitment limit and the ingestion limits derived from it may be biased toward the low side.

The non-stochastic Annual Limits on Intake by ingestion presented in Table 10 or obtained from the preceding calculations are collected in Table 11 for comparison with values determined from the basic limits on dose commitment given at the beginning of the paper. Conversion of the basic dose commitment limits to ingestion limits was accomplished with the aid of the ICRP values of committed dose equivalent, as described above. For ^{224}Ra, the dose commitment to bone surface tissues is 0.296 rad/μCi based on the ICRP value of committed dose equivalent per unit intake (26, p. 281). Since bone is not a target tissue for the basic limits, the entries for ^{226}Ra and ^{228}Ra were obtained by determining the dose commitment to bone which would give a dose commitment of 2.5 rad to bone surface tissues. This was accomplished by dividing 2.5 rad by 0.695 or 0.966 to obtain 3.60 rad (^{226}Ra) and 2.59 rad (^{228}Ra). Then the conversion factors of 1.81 rad/μCi and 1.11 rad/μCi were applied to obtain ingestion limits of 2.0 μCi (^{226}Ra) and 2.3 μCi (^{228}Ra).

It is clear that the values for the radium isotopes derived from the basic limits are lower than the values based on the analyses of internal emitter data in this paper but for ^{131}I, the opposite is true. This again underscores the fact that conclusions based on the direct analysis of internal

emitter data may be different than those drawn from proforma application of basic radiation protection limits.

ANNUAL LIMIT ON INTAKE

The values of $(ALI)_s$ and $(ALI)_{ns,t}$ in Tables 8 and 11 can be used to determine ALI's for ^{131}I, ^{224}Ra, ^{226}Ra and ^{228}Ra. The results, given in Table 12, depend on which values are used in the minimization procedure described by Eq. (3). The ALI's obtained from the direct approach and thresholds are more closely tied to factual information on internal emitters than are any others. Those obtained from the indirect approach and basic limits depend on a chain of reasoning and numerical factors which parallel those used by the ICRP.

The method used to obtain the ALI clearly has a strong influence on its value. The indirect approach and basic limits offer simplicity because the same risk coefficients and non-stochastic limits are applied to all organs and tissues, with rare exception. The direct approach and non-stochastic thresholds have appeal because of their close connection with human health effects data for internal emitters. Which method is adopted ultimately will be a matter of judgment.

ISSUES

A number of issues, which may merit further consideration by the NCRP, have been raised or are implied by the discussions in this paper. Some of these issues are listed here with comments.

A. Stochastic Effects

1. Which approach should be used?
2. Should limits be based on risk estimates for unobserved effects?
3. Is complexity a problem?

The direct approach makes the most direct use of epidemiological data on internal emitters, the data which are presumably the most relevant ones for the establishment of internal emitter limits. It does so by excluding any consideration of risk estimation for genetic effects or for types of cancer whose induction by a particular nuclide has never been proven. There may be a virtue in this. The risk-based system for radiation protection is already troubled by the large quantitative uncertainty associated with extrapolation of risk data from high to low dose levels. Should its troubles be compounded by using the highly uncertain risk coefficients obtained by extrapolation to estimate the risk of effects whose existence is highly uncertain?

The direct approach is, in a sense, complex. It requires a large catalog of risk coefficients. If all the risk information required by the direct approach were available, this catalog would contain a different coefficient for each nuclide and each organ or tissue. Some of these would be constants, others would be functions of intake. Use of the latter to derive ALI's would require more than simple arithmetic. On the other hand, there would be relatively little metabolic information required and the complexity of metabolic modeling would be greatly reduced. What makes the direct approach seem complex now is that it utilizes specific risk coefficients but is not free of the burdens of metabolic modeling, except with ^{222}Rn daughters. In contrast, the indirect approach seems simple. The catalog of risk

coefficients is very limited and the complexities of metabolic models have already been dealt with, at least in the ICRP system of radiation protection. Presumably, we would like to work toward the direct approach but is this the right time to begin? On the other hand, would it be better not to begin at all? What is to be gained by substituting one type of complexity for another?

B. Non-Stochastic Effects

1. What is the role of internal emitter data?
2. Which endpoints are important and which are not?
3. Should especially radiosensitive people be protected?
4. How should limits be estimated from minimal data?
5. Should the non-stochastic limit for bone surface tissues be increased?
6. When and by whom should the minimum significant level of severity be established?

It would seem that the best source of information on internal emitter effects is internal emitter experience. The data on necrotic lesions induced by $^{226,228}Ra$ allow thresholds to be determined with as much precision as ever will be required for radiation protection. There may be a similar abundance of data for other radionuclides. A thorough review of the literature is needed to determine what information is available and how it is to be used.

Protection against non-stochastic effects assumes the existence of thresholds and therefore opens the possibility that complete protection can be achieved. However, data such as reported by Sharpe (55) make it clear that the observable manifestations of cell damage cannot be completely avoided

unless the non-stochastic limit is placed very close to zero. Thus, it appears necessary to devise explicit criteria to determine when the health consequences of any effect are important enough for the effect to be included in the limit setting process and when they are sufficiently unimportant for the effect to be ignored. Such criteria might be thought of as defining a reasonable level of harm, comparable to the reasonable level of risk, which has been discussed within the NCRP.

Non-stochastic effects are presumably deterministic, i.e., an effect will occur in an individual whenever the threshold is exceeded. Thresholds differ among individuals and protection of the whole work force can be achieved only when the protection limit is set below the threshold for the most sensitive person. There are no problems when individual thresholds are distributed over a narrow range of values, but when the distribution is broad, the protection limit may be forced to a very low level in order to protect everyone. This leads to the question of whether or not everyone should be protected. An alternative would be to protect a portion of the work force. For example, the limit could be set at the median threshold for the population in order to protect half the workers or at a value designed to protect a higher proportion such as 68% or 95% of the work force.

The decision made on the handling of radiosensitive workers will influence the method for estimation of limits from minimal data such as the data on cataract induction for the radium isotopes. If the objective becomes to protect even the most radiosensitive worker, large safety factors will be required and the use of a point of division in a data set, without application of a safety factor, as the basis for a limit, such as the 50 μCi point in the cataract data for ^{226,228}Ra patients, will be unacceptable. If the objective becomes to protect the majority of people, then safety factors will be

unnecessary in some cases. This will be true when limits are derived from studies, such as those for the radium isotopes, in which the dosage range extends well below the dosage on which the limit is based,* since the proportion of individuals in the population with thresholds below this dosage is presumably small. Safety factors will still be necessary when limits are based on studies, such as those of hypothyroidism following radioiodine therapy for thyrotoxic conditions, in which effects are observed at the lowest dosages studied.

The Annual Limit on Intake by ingestion for most alpha emitters is determined by the non-stochastic limit in bone surface tissues (3). The data on gross necrotic lesions for $^{226,228}Ra$ indicate that even the most radiosensitive persons do not develop clinically significant effects when the absorbed dose commitment to bone surface tissues is about twice the value allowed by the non-stochastic limit, and that, less than 1% of persons develop clinically significant lesions when the dose commitment is about 10 times the allowed value. The ^{224}Ra data on growth retardation show an even greater disparity between the tolerable annual level of ingestion (about 300 μCi) and the allowed value (8.1 μCi). Thus, it appears that the current limit for bone surface tissues could be increased substantially without placing workers at risk of developing clinically significant effects. Raising the non-stochastic limit sufficiently, would lead to ALI's which were determined by the stochastic limit. Since the historical trend in radiation protection has been toward lower and lower limits, it is not clear that an increase would meet with acceptance. Nevertheless, radiation protection is based on scientific

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*The lowest dosage observed to produce an effect in any member of the study group or a point of division in the dosage range, known to be less than this lowest dosage.

data, and the best data available for bone seekers support an increase.

Thresholds derived from dose-severity data depend on the minimum significant level of severity used in the data analysis. The level may be chosen after the data have been collected and examined and it may be varied to determine the effect on thresholds without requiring the collection of new data. This flexibility can be an advantage but carries the disadvantage that levels set a posteriori may be unduly influenced by the data. Ideally, the level should be established before data collection begins, using independent sources of information. This is impossible when the data are unique and conclusions about the significance of damage can only be drawn after the data first become available. When the threshold is a strong function of the level of significance, the choice of level will exert a strong influence on the radiation protection limit derived from the threshold. Thus, the choice of level may become a matter of controversy. In such cases, and perhaps in all cases, it would seem prudent to establish the minimum significant level of severity by consensus.

For dose-incidence data, the minimum significant level of severity is defined, implicitly, by the criteria used to establish whether an effect is present or absent. Since these criteria are laid down before the data are assembled, the minimum significant level of severity becomes an implicit and unchangeable part of the final data set. The only way the level could be changed would be through a change or the criteria and the assemblage of a new data set. Such an effort lies outside the normal scope of activities of radiation protection committees and therefore, the issues raised by changing the minimum significant level of severity following examinaion of the data would not, as a practical matter, exist for limits based on dose-incidence data. From this standpoint, the latter type of data is preferable to dose-

severity data, provided, of course, that the criteria defining the presence or absence of an effect are acceptable.

C. Concluding Remarks

This list of issues is not all inclusive. It, and the paper as a whole, are provided to stimulate discussion within the NCRP. There has been a temptation to draw hard and fast conclusions and to make specific recommendations or proposals, but this has been avoided. The NCRP operates by consensus and recommendations on matters related to the objectives of the Council should be established in that way. It is hoped that this paper will contribute to that process.

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FIGURE LEGENDS

Figure 1. The probability of developing radiogenic hypothyroidism within 5 years following single treatment with ^{131}I. The names Becker, Blair and Smith in the legend designate data from Becker et al. (43) on Graves' disease, and from Blair et al. (48) and Smith et al. (44) on throtoxicosis. Only the data from Smith's first trial are shown.

Figure 2. Reduced x-ray score for persons with combined exposures to ^{226}Ra and ^{228}Ra. Two dose scales are given, one based on 5 and 7 kg masses for the marrow-free skeleton in females and males and the other based on 3.4 and 5 kg total bone mass for the respective sexes. The horizontal line which intersects the y-axis at 8 represents the minimum clinically significant score. The doses of 300, 600 and 1500 rad are thresholds derived from the data as described in the text.

Table 1

Universal Risk Coefficients

A. Cancer

Tissue	ICRP Weighting Factor	Coefficient (10^{-4}/rem)
Breast	0.15	0.21
Red marrow	0.12	0.17
Lung	0.12	0.17
Thyroid	0.03	0.042
Bone surface tissues(1)	0.03	0.042
Remainder(2)	0.30	0.42
Whole body(3)	--	1.05

B. Genetic effects: 0.35×10^{-4}/rem

(1) The ICRP weighting factor and hence the risk coefficient, includes two types of cancer (2, paragraph 47 and 3, p. 36, last paragraph), bone sarcoma and carcinoma of the paranasal sinuses and mastoid air cells.

(2) To be divided equally between the 5 remaining organs with the highest dose equivalents (2, paragraph 105).

(3) The risk coefficient is the sum of the risk coefficients for all organs and tissues.

Table 2

Specific Risk Coefficients for Radium-226,-228

Isotope[1]	Coefficient (10^{-4}/μCi in blood)		
	Bone	Sinus/Mastoid[2]	Total
^{226}Ra - Q	.038 D_{226} - .0042	6.4	.038 D_{226} + 6.4
- L	11.0	6.4	17.4
^{228}Ra - Q	.24 D_{228} - .011	0	.24 D_{228} - .011
- L	27.5	0	27.5

(1) The letters Q and L distinguish between risk coefficients based on the quadratic-exponential and the linear dose-response relationships for bone cancer discussed in the text.

(2) Based on the best-fit linear function of Rowland, Stehney and Lucas (4). Entries are duplicated so that total risk coefficients can be determined for both forms of the bone cancer risk coefficient.

Table 3

Universal Risk Coefficients for Ingestion

A. Observed Effects

Nuclide	Organ	Coefficient (10^{-4}/rem)	Conversion factor (rem/μCi)	Coefficient (10^{-4}/μCi)
^{131}I	Thyroid	.042	1.78	.075
^{132}I	Thyroid	.042	.0144	.0006
^{133}I	Thyroid	.042	.336	.014
^{135}I	Thyroid	.042	.0666	.0028
^{224}Ra	Bone surfaces	.042	5.92	.25
^{226}Ra	Bone surfaces	.042	25.2	1.1
^{228}Ra	Bone surfaces	.042	21.5	.9

B. Unobserved Effects

Nuclide	Organ	Coefficient (10^{-4}/rem)	Conversion factor (rem/μCi)		Coefficient (10^{-4}/μCi)
^{131}I	None	---	---		---
^{132}I	Stomach wall	.084	.00233		.0002
^{133}I	None	---	---		---
^{135}I	None	---	---		---
^{224}Ra	Gonads	.35	.0777		.0272
	Red marrow	.17	.555		.0944
	ULI wall	.084	.307		.0258
	LLI wall	.084	.740		.0622
				Σ	.21
^{226}Ra	Gonads	.35	.340		.11
	Red marrow	.17	2.22		.377
				Σ	.50
^{228}Ra	Gonads	.35	.592		.207
	Breast	.21	.592		.124
	Red marrow	.17	2.41		.410
	Lungs	.17	.592		.101
				Σ	.84

Table 4

Specific Risk Coefficients for Ingestion

A. Iodine

Nuclide	Coefficient (10^{-4}/rad)	Conversion factor (rad/μCi)	Coefficient (10^{-4}/μCi)
^{131}I	.0125	1.78	.022
^{132}I	.0375	.0144	.00054
^{133}I	.0375	.337	.013
^{135}I	.0375	.0666	.0025

B. Radium

Nuclide	Coefficient (10^{-4}/μCi in blood)	Conversion factor	Coefficient (10^{-4}/μCi ingested)
^{224}Ra	.4	.2	.08
^{226}Ra - Q	.038 D_{226} + 6.4	.2	.0015 Q_{226} + 1.3
- L	17.4	.2	3.5
^{228}Ra - Q	.24 D_{228} - .011	.2	.0096 Q_{228} - .0022
- L	27.5	.2	5.5

Table 5

Calculation of Weighted Average for A

Tissue	Weight, g[1]	A, μrad/hr / pCi/ℓ [2]	Weight x A
Adipose	15000	.30	4500
Blood	5500	.015	82
Bone	5000	.0034	17
Kidney	310	.015	5
Liver	1800	.013	23
Muscle[3]	29830	.013	388
Total	57440		5015

Weighted average = 5015/57440 = 0.087 μrad/hr per pCi/ℓ inhaled radon.

(1) Reference 60, Table 108.

(2) From Pohl, Pohl-Rüling (31); values for the adrenals and gonads are excluded because the weights for these organs constitute a negligible fraction of total body weight; the value for adipose tissue is twenty times the value given for marrow, to reflect the difference between radon concentrations in stomach fat and marrow recorded by Pohl, Pohl-Rüling (30).

(3) Includes skeletal muscle, GI tract, heart, aorta and dissectable blood vessels.

Table 6

Ratio of Risks for Unobserved and Observed Effects in the Combined Approach

Nuclide	Proj/Obs
$^{131,133,135}I$	---
^{132}I	.37
^{222}Rn daughters	.054
^{224}Ra	2.6
^{226}Ra - Q	.38[1]
- L	.14
^{228}Ra - Q	40[1]
- L	.15

[1] Evaluated for Q_{226} = 1.89 μCi and Q_{228} = 2.41 μCi, the ALI values for ^{226}Ra and ^{228}Ra currently recommended by the ICRP (3).

Table 7

Total Risk Coefficients for the Direct, Combined and Indirect Approaches

A. Ingestion

Nuclide	Direct (10^{-4}/μCi)	Combined (10^{-4}/μCi)	Indirect (10^{-4}/μCi)
^{131}I	.022	.022	.075
^{132}I	.00054	.00074	.0008
^{133}I	.013	.013	.014
^{135}I	.0025	.0025	.0028
^{224}Ra	.08	.29	.46
^{226}Ra - Q	.0015 Q_{226} + 1.3	.0015 Q_{226} + 1.8	---
- L	3.5	4.0	1.6
^{228}Ra - Q	.0096 Q_{228} - .0022	.0096 Q_{228} + .84	---
- L	5.5	6.3	1.7

B. ^{222}Rn Daughter Inhalation

Direct:	3.0×10^{-4}/WLM
Combined:	3.2×10^{-4}/WLM
Indirect:	8.6×10^{-5}/WLM

Table 8

Stochastic Annual Limit on Intake or Exposure for the Direct, Combined and Indirect Approaches

A. Ingestion

Nuclide	$(ALI)_s$, μCi Direct	Combined	Indirect
^{131}I	230	230	70
^{132}I	9300	6800	6200
^{133}I	380	380	360
^{135}I	2000	2000	180
^{224}Ra	62	17	11
^{226}Ra - Q	3.8	2.8	---
- L	1.4	1.2	3.1
^{228}Ra - Q	23	5.6	---
- L	.9	.8	2.9

B. ^{222}Rn Daughter Inhalation, $(ALE)_s$

Direct:	1.7 WLM
Combined:	1.6 WLM
Indirect:	5.7 WLM

Table 9

Relative Frequency of Non-Stochastic Effects Among Persons Injected with ^{224}Ra at 16-20 Years of Age or as Adults

	Exposure Group	
Effect	16-20	Adult[1]
Tooth breakage	9/59[2]	13/680
Growth retardation	3/24[3]	0/680
Cataract	4/59[4]	25/680

(1) Reference 19.

(2) Reference 16.

(3) Reference 51. The age range in the exposure group for growth retardation was 15-20 rather than 16-20.

(4) Reference 15.

Table 10

Non-stochastic Annual Limit on
Dose Commitment and Ingestion

Nuclide	Health Effect	Target Tissue	Limit(1) Dose Commitment (rad)	Limit(1) Ingestion (μCi)
^{131}I	Hypothyroidism	Thyroid	12(3x)	--
^{224}Ra - juv.	Growth retardation	Bone surface	--	300
	Cataract	Lens	--	180 (3x)
- adult	Cataract	Lens	--	420
^{226}Ra	Bone necrosis	Bone	30	--
	Cataract	Lens	--	5
^{228}Ra	Bone necrosis	Bone	30	--
	Cataract	Lens	--	5

(1) Numbers in parenthesis are the safety factors included in the limit.

Table 11

Non-stochastic Annual Limit on
Intake by Ingestion

Nuclide	Tissue	$(ALI)_{ns,t}$, μCi	
		Threshold(1)	Basic(2)
^{131}I	Thyroid	6.7	28
^{224}Ra - juv.	Bone surface	300	8.4
	Lens	180	--
- adult	Lens	420	--
^{226}Ra	Bone	17	2.0
	Lens	5	--
^{228}Ra	Bone	27	2.3
	Lens	5	--

(1) Determined from the thresholds for non-stochastic effects presented in this paper.

(2) Determined from the basic limits given at the beginning of this paper.

Table 12

Annual Limit on Intake by Ingestion Obtained by Different Methods

Nuclide	ALI, μCi[1]			
	Direct,[2] Threshold	Combined,[3] Threshold	Indirect,[4] Basic	ICRP[5]
^{131}I	6.7 (NS)	6.7 (NS)	28 (NS)	27 (NS)
^{224}Ra	62	17	8.4 (NS)	8.1 (NS)
^{226}Ra[6]	3.8	2.8	2.0 (NS)	1.9 (NS)
^{228}Ra[6]	5 (NS)	5 (NS)	2.3 (NS)	2.4 (NS)

(1) The letters NS in parenthesis indicate that the ALI is determined by the non-stochastic limit.

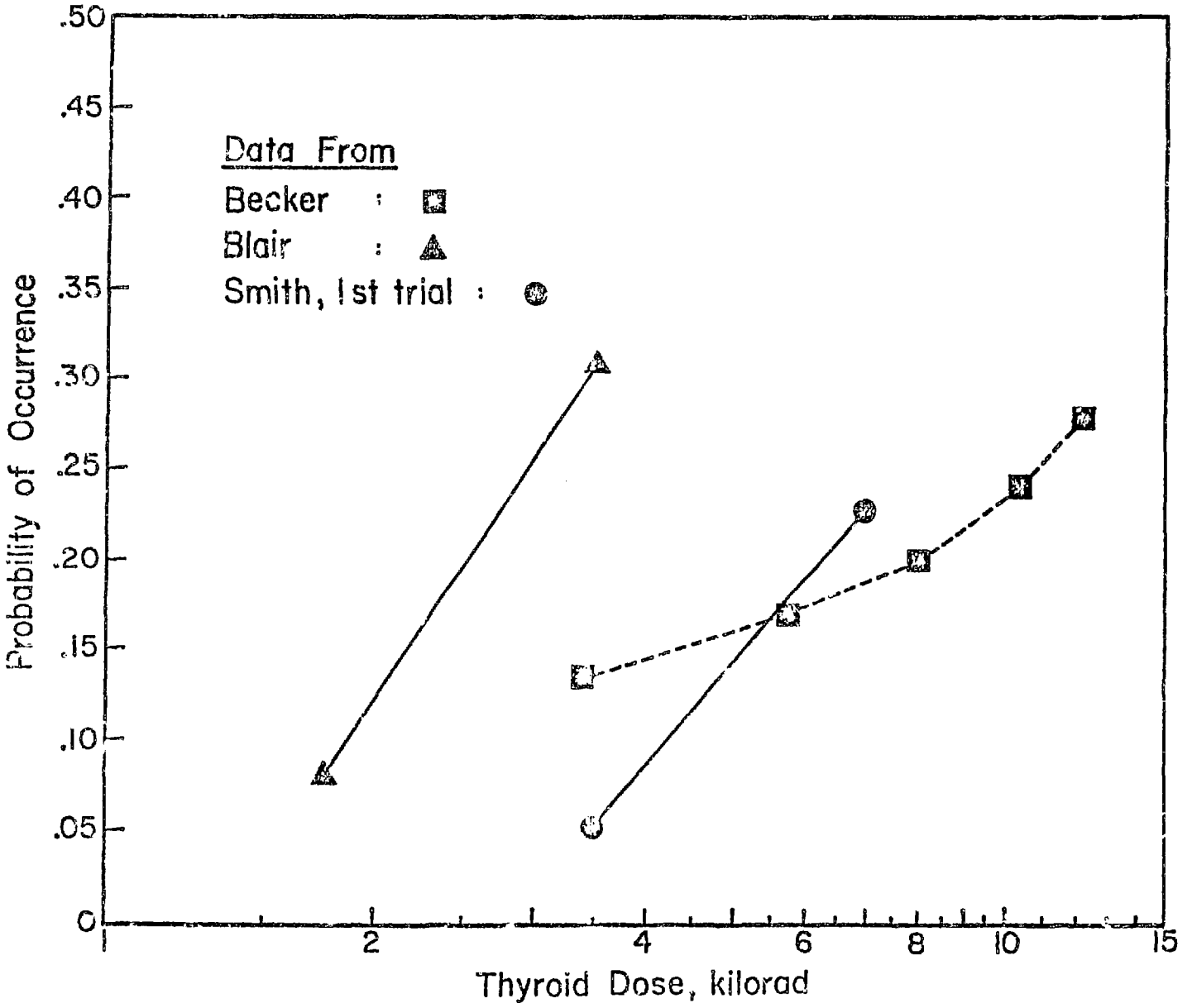
(2) Based on $(ALI)_s$ for the direct approach and $(ALI)_{ns,t}$ obtained from internal emitter effects thresholds.

(3) "Combined" designates combined approach.

(4) Based on $(ALI)_s$ for the indirect approach and $(ALI)_{ns,t}$ obtained from the basic radiation protection limits.

(5) Reference 3.

(6) The entries under "Direct, Threshold" and "Combined, Threshold" are based on the $(ALI)_s$ for the quadratic-exponential risk coefficient (Table 8).


.50
.45
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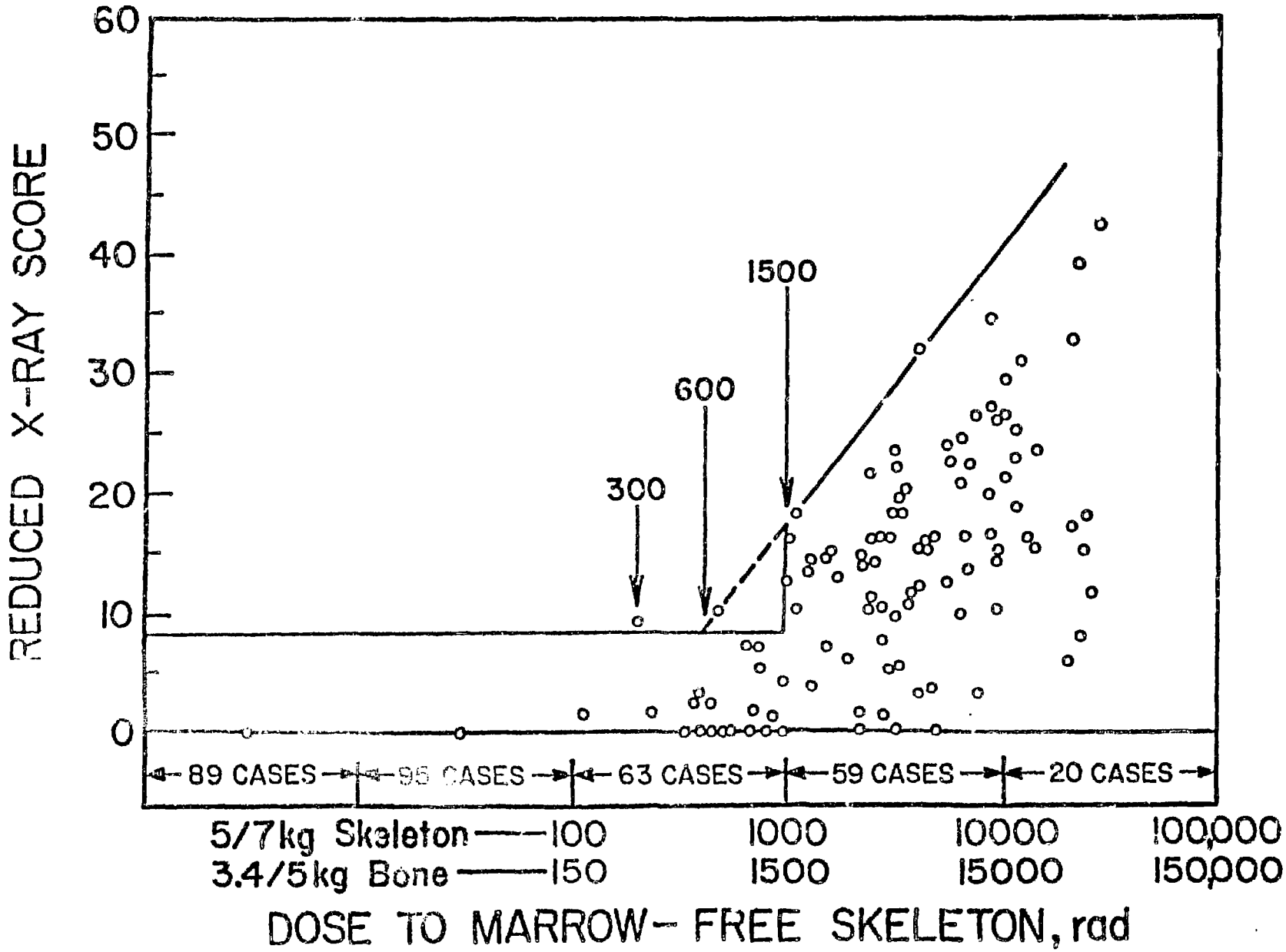
0
Probability of Occurrence
Data From
Becker :
Blair :
Smith, 1st trial :
2
4
6
8
10
15
Thyroid Dose, kilorad

Internal Emitter Limits for Iodine, Radium and Radon Daughters: Different Approaches to Stochastic Risk Limitation and Consideration of Non-Stochastic Effects

Robert A. Schlenker

Figure 1


REDUCED X-RAY SCORE
60
50
40
30
20
10
0
1500
600
300
89 CASES
95 CASES
63 CASES
59 CASES
20 CASES
5/7kg Skeleton——100 1000 10000 100,000
3.4/5kg Bone——150 1500 15000 150,000
DOSE TO MARROW- FREE SKELETON, rad

Internal Emitter Limits for Iodine, Radium and Radon Daughters: Different Approaches to Stochastic Risk Limitation and Consideration of Non-Stochastic Effects

Robert A. Schlenker

Figure 2