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# The Biological Effectiveness of Radon-Progeny Alpha Particles. III. Quality Factors

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**Domestic radon risk estimates are typically based either on data for uranium miners or on data derived from A-bomb survivors; comparison of domestic radon risk estimates derived from these two disparate sources represents an important test of their reliability. There is currently a significant discrepancy of about a factor of three between domestic radon risk estimates generated with these two independent methods. To base such risk estimates on the data for A-bomb survivors, who were exposed mainly to low-LET radiation, requires a quality factor for α particles from radon progeny; the final risk estimate is then directly proportional to this quality factor. We have used the most extensive quantitative *in vitro* data set currently available at high LET for an oncogenic end point, to make the best estimate we can that could be used as a basis for a quality factor. Our best estimates of values appropriate for the quality factor for radon progeny are significantly lower than those currently used (20–25) in estimating lung cancer mortality due to radon. Specifically, our best estimate for home dwellers is around 10. In addition, because of the different geometry in the bronchial epithelia of nonsmokers compared to smokers, our best estimate of an appropriate quality factor for home dwellers is about 18% greater than that for miners; thus our best estimate of the "effective *K* factor" to convert to effective dose/WLM in home dwellers from effective dose/WLM in miners would be increased by this factor. Based on a quality factor of ~10, the dosimetrically based estimate of radon-induced mortality would be ~35,000 per year in the U.S. rather than the value of ~70,000 obtained using a quality factor of 20. The value of 35,000, while larger than the values based on data for miners (~20,000), is much smaller than previous estimates of ~70,000 based on dosimetric methods; thus risk estimates based on the two approaches, dosimetric and epidemiological, may be partially reconciled. Finally, a quality factor of 10 would reduce the proportion of the collective effective dose caused by radon progeny from the currently accepted value of 55% down to about 38%.** 

## INTRODUCTION

There are currently two possible approaches to risk estimation for exposure to low levels of radon progeny. One is to use an epidemiological approach, in which lung cancer mortality is assessed in cohorts of underground miners who have been exposed to high levels of radon. The results for the miners are then extrapolated to the environmental situation. This approach was used, for example, in the report of the National Research Council's Committee on the Biological Effects of Ionizing Radiation assessing radon risks (BEIR IV) (*1*). There are, however, some significant drawbacks which limit the precision of the resulting risk estimates (*1*), including the following:

(a) The retrospective dosimetry of the miners involves considerable uncertainties.
(b) Most of the miners in the cohorts studied are still alive.
(c) There are few women and children in the miner cohorts studied.
(d) The conversion from effective dose per unit exposure in a mine to effective dose per unit exposure in a house is uncertain (*2*).
(e) The exposure level at which a significant effect can be detected in miners is quite high compared to an average lifetime domestic radon exposure in the U.S. of ~0.2 WLM/year (*3*).
(f) The effects of exposure rate on risk estimates are unclear (e.g. *4*, *5*).
(g) The mode of interaction of radon-induced damage with damage produced by other lung carcinogens to which many miners were exposed (particularly tobacco and arsenic) is unclear (*6–15*).

A second approach to radon risk estimates is the so-called dosimetric approach. This approach to radon risk assessment uses the following logic:

(1) Use the best physical models available to estimate a bronchio-epithelial dose per WLM cumulative exposure to radon progeny for home dwellers.



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(2) Convert this dose to the lung to an equivalent dose, using the appropriate quality factor[1] for radon-progeny α particles in the bronchial epithelium.
(3) Convert the equivalent dose to an effective dose, using the appropriate tissue weighting factor for lung.
(4) Use the best estimate for the lifetime fatality probability coefficient per unit effective dose, primarily from A-bomb survivors, to calculate the lifetime risk per unit cumulative exposure to radon progeny.

While this approach suffers from some of the same problems as the epidemiological approach, as well as some further ones (particularly extrapolation from A-bomb exposure to radon-progeny exposure), the dosimetry and the follow-up are probably significantly better for A-bomb survivors than for those exposed to radon. Thus, given the likely reliability of radiation risk estimates based on data for the A-bomb survivors, it is important, from the standpoint of credibility, that radon risk estimates derived from the epidemiological approach should be broadly consistent with risk estimates based, through the dosimetric approach, on A-bomb data.

The value of the quality factor used for radon-progeny α particles in almost all current models is 20 (*3*, *16–21*). These reports refer back to the ICRP Report 26 (*22*), which in turn can be traced back to Handbook 59 published in 1954 by the National Bureau of Standards (*23*). In fact, an interagency review of data available with regard to uranium mining[2] suggested a quality factor of 3, while a more recent analysis of epidemiological data on lung cancer in humans (*24*) suggested a value of 4.

In summary, radon-progeny quality factors are needed for point (2) above to quantify the dosimetric estimate of radon risks. In addition, the *ratio* of quality factors for radon progeny for miners and for home dwellers is also needed for point (d) above. It is the purpose of this work to contribute to credible estimates for these quantities, and to discuss their significance in terms of comparisons of radon risks obtained using the epidemiological and dosimetric techniques.

[1]The quality factor, $Q$, is implicitly defined at a given point in a radiation field by the relation $H = Q \cdot D$, where $D$ is the dose at that point and $H$ the equivalent dose. A more recent formalism introduced in ICRP Report 60 (*53*) refers to averages over an organ or tissue, $T$, through the relation $H_T = w_R \cdot D_{T,R}$: here $D_{T,R}$ is the dose from radiation $R$ averaged over tissue $T$, and $w_R$, the "radiation weighting factor," is defined at a depth of $10^4$ μm in a tissue-equivalent sphere; this latter "organ-averaged" formalism is not appropriate for the very short-ranged α particles emitted by radon progeny, and so the terminology of quality factor will be maintained in this work.

[2]Environmental Protection Agency. Final Report of Subgroups 1B. Interagency Uranium Mining Radiation Review Group, Environmental Protection Agency, Washington, DC, 1971.

## METHODS

For a heterogeneous radiation field, the overall quality factor, $Q$, has usually been estimated in terms of LET ($L$) as

$$Q = (1/D)\int Q(L)D(L)dL, \quad (1)$$

where $D(L)dL/D$ is the proportion of dose delivered with LET values between $L$ and $L + dL$, and $Q(L)$ is an empirically determined weighting function. The microdosimetric correlate of this equation is (*25*, *26*)

$$Q = (1/y_F)\int Q(y)d(y)dy, \quad (2)$$

where $d(y)$ is the normalized probability density of dose in lineal energy ($y$), and $y_F$ is the track-averaged lineal energy. Lineal energy, $y$, is the energy deposited in a given target by the passage of a single track of radiation through the nucleus divided by the mean path length through the target. Again, $Q(y)$ is an empirically determined weighting factor.

In the following we shall use Eq. (2) as the basis of our estimates of values appropriate for the radon quality factor, though the analysis could be carried out using Eq. (1) with similar conclusions. Our rationale for preferring Eq. (2) (i.e. the use of lineal energy rather than LET) is that the energy *deposited* in a cell nucleus ($y$) is more likely to correlate with biological effect than energy *lost* (LET) by a passing particle (*26*). We reiterate, however, that the analysis could be carried out equally well using Eq. (1).

It can be seen from Eq. (2) that the estimation of the quality factor has two separate aspects—evaluation of the physical quantities, $d(y)$, and estimation of the biological weighting factor, $Q(y)$. Some general features are described briefly here:

The function $d(y)$ refers to the energy deposition distribution produced by the radon-progeny α particles. It depends on the location and shape of the target nuclei in the bronchial epithelium, as well as the initial ratio of disintegrations of $^{214}$Po (7.7 MeV α particles, range in tissue ~72 μm) and $^{218}$Po (6 MeV α particles, range in tissue ~46 μm).

The function $Q(y)$ refers to the weight that any given value of $y$ contributes to the total quality factor (see Eq. 2). As such, it does not relate specifically to any particular radiation, but it is applicable to any radiation once the energy deposition function, $d(y)$, for that radiation is known. $Q(y)$ is designed to be a consensus derived from $Q$ functions obtained with many relevant biological end points. Each such $Q$ function can be unfolded from the biological response of the system to a variety of radiations, as discussed below. The result for a particular end point is then usually denoted as $Q_\varepsilon(y)$—i.e. $Q$ for a specific end point (*25*).

It is not currently possible to estimate $Q_\varepsilon$ functions directly in any realistic quantitative sense for relevant *in vivo* end points. Consequently, the rationale adopted is to estimate $Q_\varepsilon(y)$ for an *in vitro* end point which we consider to be (a) relevant to cancer induction and (b) adequately quantifiable. The use of *in vitro* data for oncogenic transformation as a basis for risk estimates for more complex end points such as carcinogenesis in humans has been discussed elsewhere (*26*). Essentially the rationale, other than the pragmatic issue of quantifiability, is that the quality factor is used for predicting only *relative risks* (compared to photons) of one radiation relative to another, rather than absolute risks. Given that the differences in the spatial pattern of energy deposition between different types of radiations last for only microseconds within cells (*27*), the assumption is that the biological processes that subsequently occur within the cell or organ will not themselves show further strong dependence on radiation quality. This is the general framework in which it is assumed that a single quality factor or radiation weighting factor can be appropriate for the diverse phenomena leading to radiation-induced carcinogenesis in humans.

The weighting factor, $Q(y)$, that was recommended for use in ICRU Report 40 (*26*) was derived (*25*) from an analysis of data for dicentric chromosomal aberrations in human lymphocytes. In fact, the standard errors quoted (*25*) for the unfolded $Q(y)$ are such that the function is

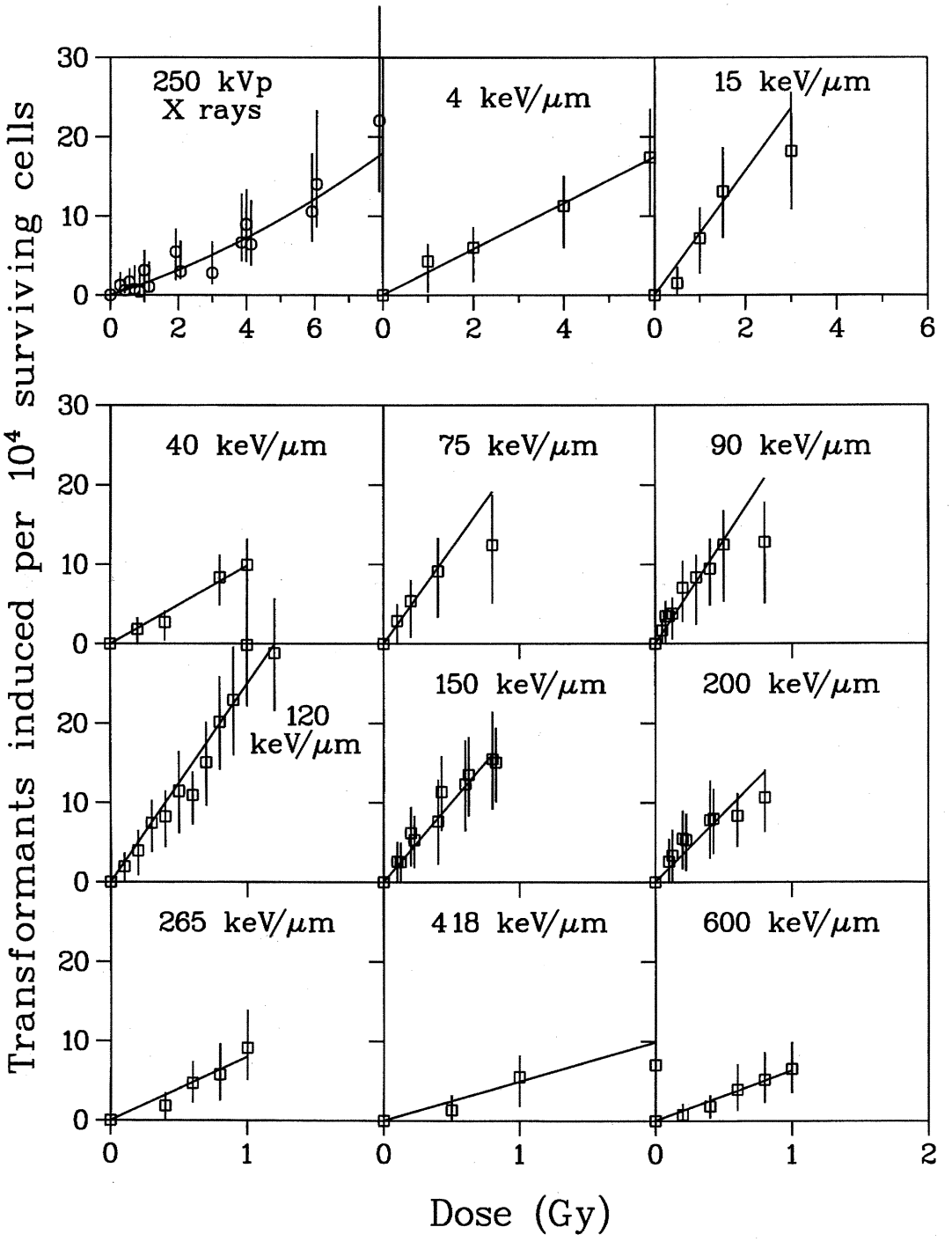


**FIG. 1.** Yield of oncogenically transformed cells per 10,000 surviving C3H 10T1/2 cells exposed to X rays and monoenergetic charged particles of various LETs (*28*). Curves are fits to Eq. (3).

almost completely unknown above ~150 keV/μm—the area of particular interest for radon. It is the purpose of this work to use recent comprehensive data published in a companion paper to this report (*28*) to obtain a realistic estimate of $Q_e(y)$ (for the C3H 10T1/2 oncogenic transformation system) which covers the LET range of interest for radon-progeny α particles adequately (~50 to 250 keV/μm).

The new data set used here (*28*), using the C3H 10T1/2 oncogenic transformation system, is the most complete quantitative data set for an oncogenic transformation end point, as a function of LET and dose, currently available. The data (see Fig. 1) consist of results at 12 LETs varying from 4 to 600 keV/μm, with an average of nine low-dose points per LET, as well as data for 250 kVp X rays.

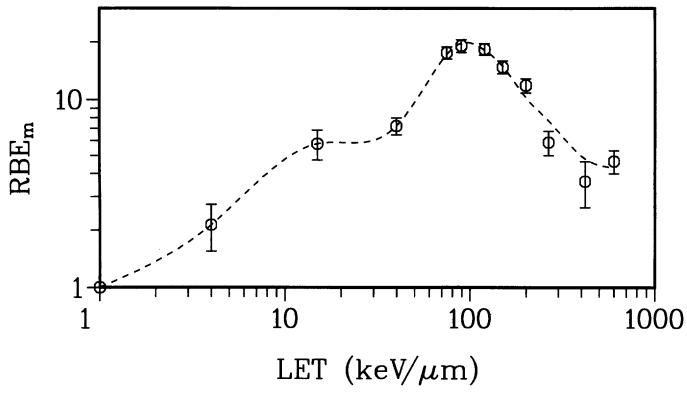


**FIG. 2.** $RBE_m$ values for oncogenic transformation in C3H 10T1/2 cells, based on fits (Eq. 3) to the data in Fig. 1. The dashed curve represents the predicted relationship between $RBE_m$ and LET based on the unfolded $Q_T(y)$ function (see text). For visual clarity, the X-ray point is shown at 1 keV/μm, though it is not assigned a single LET value in the calculation.

The curves in Fig. 1 consist of fits of the yield, $Y_i$, of transformed cells per surviving cell at dose $D$ to the equation

$$Y_i(D) = \alpha_i D + \beta D^2 \quad (3)$$

for radiation types $i$, where $\alpha_i$ represents the initial slope of the dose–response curve for radiation $i$. Figure 2 shows the maximum low-dose RBEs (based on these initial slopes) as a function of LET, relative to that for X rays.

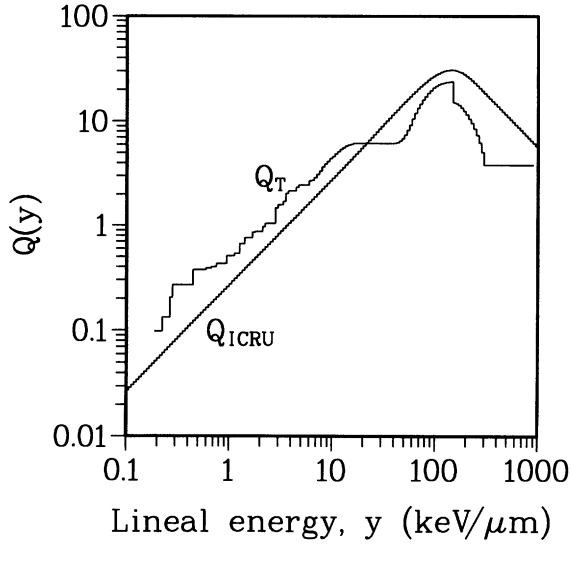


**FIG. 3.** Estimated $Q_\varepsilon(y)$ weighting functions. The $Q_T$ histogram is based on an analysis of the data in Fig. 2 for oncogenic transformation in C3H 10T1/2 cells. The $Q_{ICRU}$ curve is from ICRU Report 40 (*26*) and is based on chromosomal aberration yields in human lymphocytes.

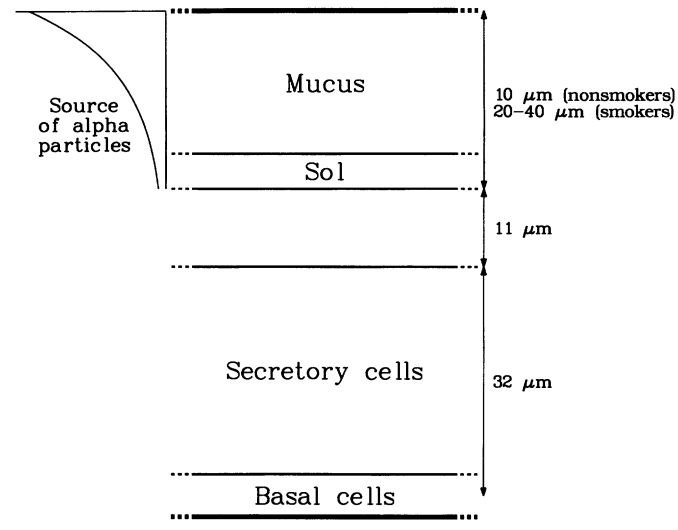


**FIG. 4.** Geometries used in this work. $^{214}Po$ and $^{218}Po$ α particles are emitted isotropically from the mucus/"sol" layer of the segmental bronchial epithelium, with an exponentially decreasing source distribution (half-value layer 6 μm), and are transported by Monte Carlo simulation through the epithelium until the end of their range. Energy deposition is scored in spherical targets (6 μm and 1 μm), as a function of depth.

## RESULTS

Using the techniques described by Zaider and Brenner (*25*), we have numerically unfolded the specific quality-factor weighting function, $Q_T(y)$, from the data shown in Fig. 1, using as input the fitted low-dose (maximum) RBEs ($RBE_i = \alpha_i/\alpha_X$, as shown in Fig. 2) of radiation type $i$. This involves numerically unfolding $Q_T(y)$ from

$$RBE_i = (1/y_{F_i}) \int Q_T(y) d_i(y) dy. \quad (4)$$

As discussed above, the subscript $\varepsilon = T$ on $Q_T(y)$ distinguishes it from $Q(y)$ of Eq. (2), which is designed (*26*) to be a generic function relating to all relevant end points; $Q_T(y)$, on the other hand, specifically relates to oncogenic transformation in C3H 10T1/2 cells. The microdosimetric spectra, $d_i(y)$, needed in Eq. (4) were calculated using the techniques described earlier (*25*, *29*). The function, $Q_T(y)$, which was numerically unfolded from Eq. (3), is shown in Fig. 3, and the fitted curve for RBE as a function of LET is compared to the original data in Fig. 2.

The function $Q_T(y)$, shown in Fig. 3, exhibits the same general features as the function recommended in ICRU Report 40 (*26*), $Q_{ICRU}(y)$ (also shown in Fig. 3). Specifically, they both show a monotonic increase followed by a decrease at high $y$ values—a saturation phenomenon. As we discuss below, however, the differences between the curves at high $y$ values turn out to be highly significant for the radon problem.

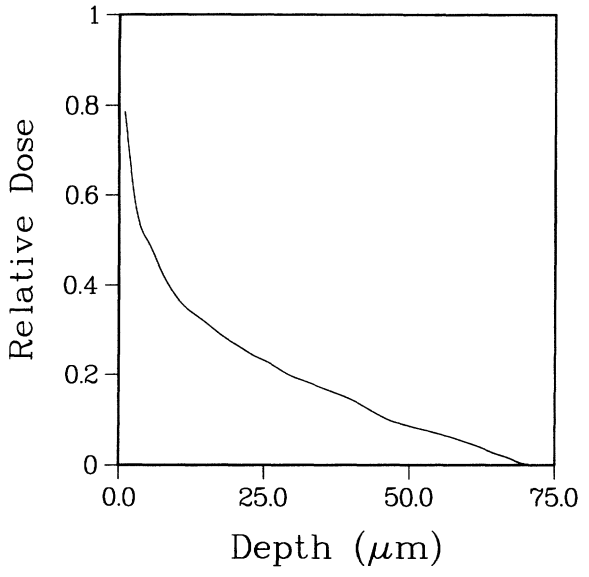


FIG. 5. Calculated variation in dose with depth, for a nonsmoker source geometry (see Fig. 4).

To use our estimated $Q_T(y)$ function to calculate weighting factors appropriate for radon progeny, the corresponding lineal energy distributions $d(y)$ (see Eq. 2) need to be calculated as a function of depth in the bronchial epithelium. Although analytical techniques are available for calculating lineal energy distributions due to α particles (*30*), we have preferred to use the Monte Carlo technique to facilitate the extension of this work to more complex geometries. The geometry we have used is illustrated in Fig. 4, and we describe its rationale briefly here.

Measurements by Kirichenko *et al.* (*31*) in rabbit and canine trachea and bronchial tubes indicate that the radon progeny are located throughout the mucus and "sol" layers of the epithelium in exponentially decreasing concentrations with increasing depth. The half-value layer (where the concentration is reduced by 50%) is about 6 μm in the canine bronchial tube.

The thickness of the mucus layer in the human segmental bronchus has not been measured directly. The overall volume of mucus in the normal lung is about 1 ml (*32*). Assuming that the thickness of the mucus layer in a given bronchial-generation airway is proportional to the diameter of that airway, its thickness in the segmental bronchial epithelium would be about 5 μm. For smokers with bronchitis or emphysema, the volume of mucus is considerably larger than in a normal lung (*32*), corresponding, in the segmental bronchial epithelium, to a mucus thickness of 15 to 35 μm. Below this mucus layer, it is reasonable to assume that a 5-μm-thick "sol" layer (*33*) surrounds the cilia.

Having established a source geometry, the technique involves transporting α particles [$^{214}$Po and $^{218}$Po, with activity ratio 3:1 (*2*, *17*)] from an extended volume source, representing the distribution of aerosols in the mucus and "sol" layers in the epithelium. The extended source consists of a radially decreasing exponentially distributed distribution (half-value layer 6 μm) in the cylindrical shell volume of the mucus layer surrounding the epithelium. The thickness of the mucus/"sol" source shell (see above) was 10 μm for a nonsmoker and ranged from 20 to 40 μm for smokers. The transport and energy deposition calculations were carried out using the techniques and stopping powers described by Brenner (*34*). Lineal energy deposition distributions were calculated as a function of depth in the epithelium for 6-μm-diameter cellular targets, taken to represent the mean diameter of basal cells[3] (*35*, *36*). A calculated depth–dose curve produced by the radon-progeny α particles with a nonsmoker source geometry is shown in Fig. 5, and corresponding representative lineal energy spectra are shown in Fig. 6 for various depths.

Having calculated the lineal energy distribution $d(y,x;G)$ as a function of depth, $x$, and source geometry, $G$, we may now fold it with the estimated quality function, $Q_T(y)$, to produce estimated weighting factors at any depth for a given source geometry:

$$Q_T(x;G) = \frac{1}{y_F(x)} \int Q_T(y)\, d(y,x;G)\, dy, \qquad (5)$$

or

$$Q_{ICRU}(x;G) = \frac{1}{y_F(x)} \int Q_{ICRU}(y)\, d(y,x;G)\, dy. \qquad (6)$$

If the target cells are assumed to be located over a range of depth $a$ to $b$, then, for example,

$$Q_T(G) = \int_a^b Q_T(x;G)\, D(x;G)\, dx, \qquad (7)$$

where $D(x;G)$ is the normalized distribution of dose with depth for source geometry $G$.

The calculated function $Q_T(x;G)$, for a nonsmoker geometry, is shown in Fig. 7. Also shown in this figure is the calculated function $Q_{ICRU}(x;G)$, also for a nonsmoker geometry, based on the ICRU (*26*) quality function $Q_{ICRU}(y)$, shown in Fig. 3. The results, using the $Q_T(y)$ function derived here, show more variation with depth than those obtained using the $Q_{ICRU}(y)$ function, because the

[3]C. R. Geard, J. Jones and D. J. Brenner, Human lung cellular morphometry and radon-progeny alpha particles. In Center for Radiological Research, Columbia University, Annual Report, pp. 107–114, 1990.

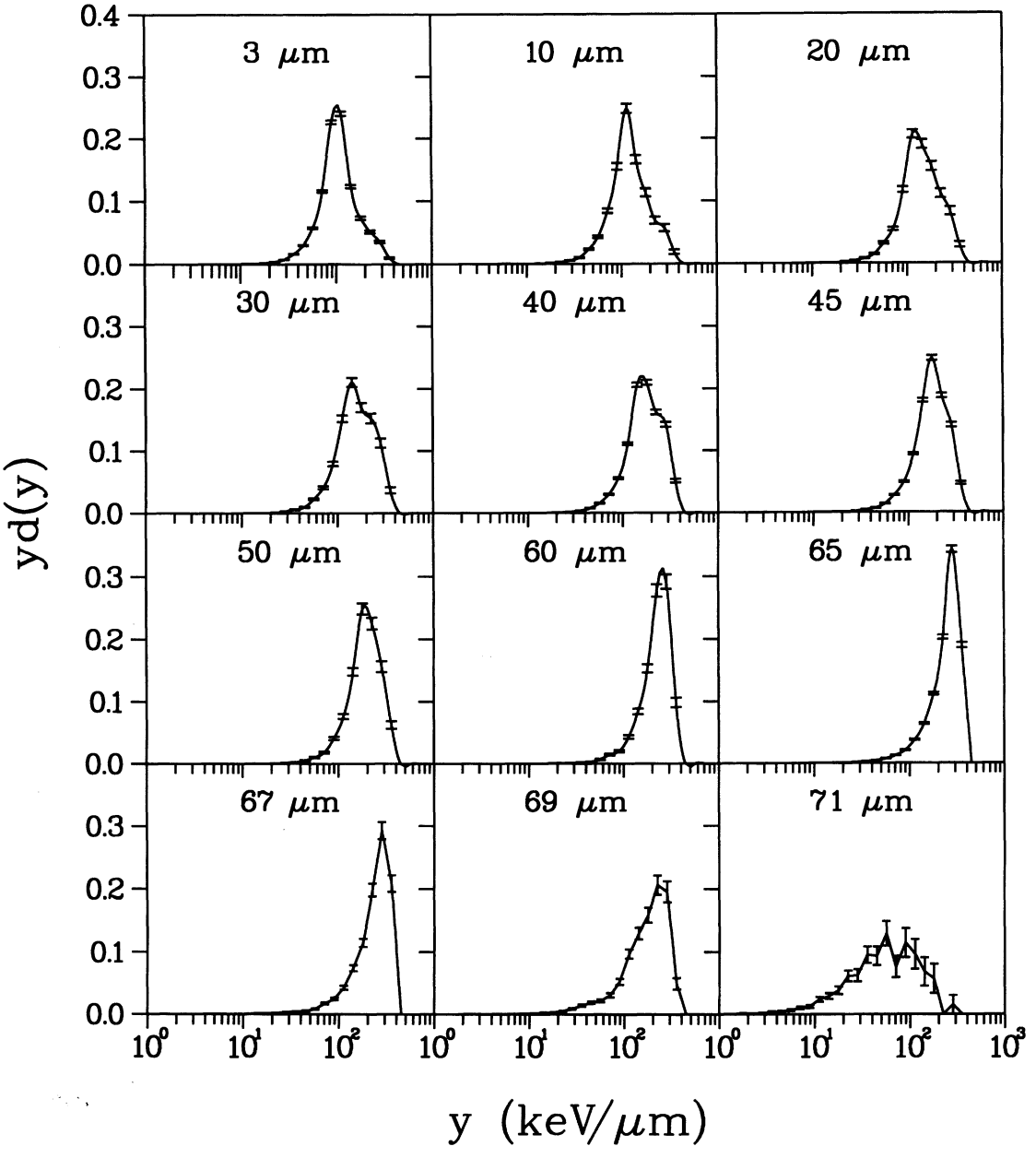


**FIG. 6.** Calculated lineal energy distributions as a function of depth, for a nonsmoker source geometry. The curves are plotted such that the area between any two values of lineal energy ($y$) is proportional to the relative dose deposited in that lineal energy region. Bars refer to statistical uncertainties due to the use of Monte Carlo techniques.

$Q_T(y)$ function (Fig. 3) decreases more rapidly at high lineal energies than does $Q_{ICRU}(y)$.

## APPROPRIATE QUALITY FACTORS FOR RADON PROGENY

Based on the results in Fig. 7, appropriate quality factors for radon progeny may well be less than the commonly used value of 20 (*3*, *16–21*). This is because many of the energy depositions are taking place in the high α-particle energy deposition region, where the biological effect is saturating because of an "overkill" phenomenon. In that the biological effect is changing rapidly with depth (Fig. 7), to produce quantitative estimates, it is necessary to make some assumptions about the depth or range of depths of target cells in the segmental bronchial epithelium.

The "classic" view is that the undifferentiated basal cells, assumed to be the progenitors of the other epithelial cells

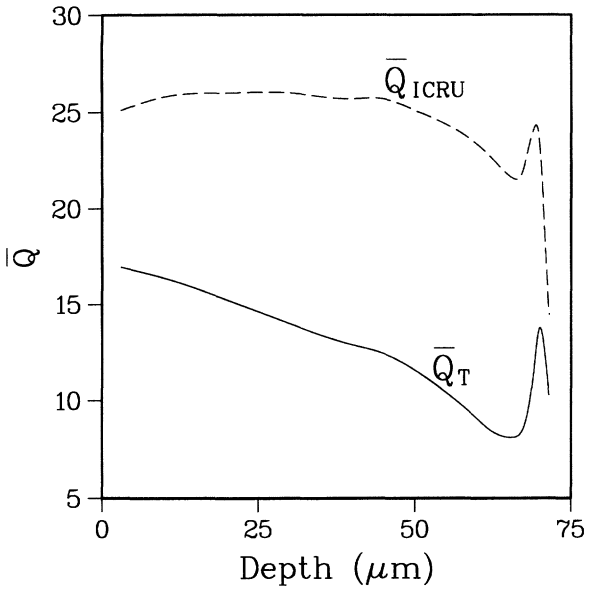


FIG 7. Variation in $Q_\varepsilon$ (see Eqs. 5 and 6) as a function of depth for radon-progeny α particles, for the nonsmoker geometry. The predictions based on recent data for oncogenic transformation ($Q_T$) are significantly smaller than the $Q_{ICRU}$ values.

(*37*), must be the target cells for carcinogenesis (*38*). In recent years, however, there has been a suggestion that the whole of the bronchial epithelium may contain dividing cells at risk (*39–41*). More recent work (*42–44*) appears to agree with the earlier view that the primary cells at risk are basal cells. In the calculations that follow, we shall assume mainly that basal cells are the relevant target cells, but results will also be given for the situation where the target cells are distributed uniformly throughout the bronchial epithelium.

There have been several studies of the location and depth of basal and serous cells in the human bronchial epithelium[3] (*36*, *46–48*). Evaluated models have also been described recently by a National Academy of Sciences panel on radon dosimetry (*2*) and the ICRP (*48*). Based on these models, and data from refs. (*32*, *33*, *36*, *46*, *47*) and from our own results,[3] we assume (see Fig. 4) that, in the segmental bronchial epithelium,

(a) basal cells lie, on average, 43 μm below the inner surface of the mucus/"sol" layer;

(b) if basal cells *and* secretory cells are both targets, the sensitive region is between 11 and 43 μm below the inner surface of the mucus/"sol" layer;

(c) for nonsmokers, the thickness of the mucus/"sol" layer is 10 μm;

(d) for smokers, the average thickness of the mucus/"sol" layer ranges from 20 to 40 μm, averaging ~30 μm.

(e) We also assume that ~90% of miners are smokers [based on six cohorts for which data are available (*49*)], and ~25% of domestic home dwellers are smokers (*50*).

Using these assumptions, and applying Eq. (5) to the data in Figs. 7 and 5 (nonsmoker geometry), and also to the corresponding data for the smoker geometry, we obtain the following estimates:

(*a*) *Assuming only basal cells are target cells:*

$Q_T$ [basal cells; smoker] ≈ 8.5

$Q_T$ [basal cells; nonsmoker] ≈ 11.1 (a 30% increase compared to smokers).

Weighting these values by the appropriate nonsmoker/smoker proportions, we obtain

$Q_T$ [basal cells; miner] ≈ 8.8

$Q_T$ [basal cells; home dweller] ≈ 10.4 (an 18% increase compared to miners).

(*b*) *Assuming target cells are distributed uniformly throughout the segmental bronchial epithelium* (and using Eq. 7):

$Q_T$ [all cells; smoker] ≈ 11.8

$Q_T$ [all cells; nonsmoker] ≈ 13.7 (a 16% increase compared to smokers).

Weighting these values by the appropriate nonsmoker/smoker proportions, we obtain

$Q_T$ [all cells; miner] ≈ 12.0

$Q_T$ [all cells; home dweller] ≈ 13.2 (a 10% increase compared to miners).

Again we stress, through the subscript on $Q$, that these results are based on a single end point, namely oncogenic transformation in a rodent cell line.

## CONCLUSIONS

In this work, we have used the most complete quantitative data set currently available for the *in vitro* end point of oncogenic transformation at high LET to contribute to estimating quality factors for radon progeny. Of course, a quality factor should ideally be derived from a consensus of many data sets for "relevant" end points. However, the C3H 10T1/2 *in vitro* system currently yields the most complete and quantitative data set for oncogenic transformation in the LET range important to the radon problem. Therefore, despite the potential drawbacks (*51*) of the system (specifically, the use of a partially transformed nonepithelial rodent cell line), it currently represents the best available source of data for estimating quality factors for radiation-induced cancer.

Our main conclusion is that quality factors of 20–25 for radon progeny used currently may well be too large. The reason is that radon-progeny α particles deposit most of their energy in the region where the biological effectiveness per unit dose is decreasing. Our estimates are in the range 10–13, depending on whether the target cells in the bronchial epithelium are restricted to basal cells (suggested value ~10) or also include secretory cells (suggested value ~13). Recent results tend to point to basal cells as being the primary target cells, which would result in an estimated quality factor, based on the end point analyzed here, of 10.

A second conclusion of this analysis is that our best estimate for the "effective $K$ factor" (effective dose/$WLM_{homes}$ / effective dose/$WLM_{miners}$) would be increased by about 18% compared with estimates of the $K$ factor (dose/$WLM_{homes}$ / dose/$WLM_{miners}$). This is because of the decreased mean distance traversed by $\alpha$ particles to reach target cells in nonsmokers compared to smokers, resulting in a lower average LET and a higher biological effectiveness at the target cells of nonsmokers. Such an increase in the "effective $K$ factor" would result in estimates of domestic radon risks based on epidemiological data for miners being increased by this same factor.

Assuming that a quality factor of 10 for radon progeny is realistic, radon risk estimates based on the dosimetric approach would be halved compared with those made using a quality factor of 20. Specifically, using a 70-year exposure estimate of 0.2 WLM/year (*3*), a dose conversion factor of 13 mGy/WLM in the segmental bronchial epithelium (*21*, *52*), the conventional quality factor of 20, a tissue weighting factor for bronchial lung tissue of 0.06 (*16*, *53*), and a lifetime fatality probability coefficient of 5%/Sv (*53*), we obtain a prediction of ~70,000 deaths per year in the U.S. caused by radon. Using a quality factor of 10, the prediction would be half as large (~35,000). For comparison, corresponding predictions based on data for miners are in the range from ~14,400 to ~21,600 (e.g. *1*, *49*, *54*), which would be adjusted up (see above) by 18% to a range from ~17,000 to ~25,000.

The three- to fivefold discrepancy between radon risk estimates based on data for miners, and those obtained by dosimetrically based methods with a quality factor of 20, has been discussed widely (e.g. *52*). A reduced quality factor would go some way toward reconciling miner-based and dosimetrically based radon risk estimates, which is of some importance if radon risk estimates are to be considered credible. Of course the quality factor is only one of several uncertainties inherent in extrapolating from data for the A-bomb survivors to the domestic radon situation. The other major uncertainty is the correction for dose rate, which probably has an uncertainty of 2–3 attached to it.

Finally, we emphasize again that quality factors should be based on as many relevant end points as possible. We suggest that the current best estimate for the quality factor for radon progeny is ~10, which would reduce the overall proportion of the collective effective dose taken to be caused by radon progeny from 55% (*18*) to ~38%. However, further work with other end points is strongly indicated.

## ACKNOWLEDGMENTS

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