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Progress Report on Hot Particle Studies

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Prepared for
U.S. Nuclear Regulatory Commission

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ABSTRACT

NCRP Report 106 on the effects of hot particles on the skin of pigs, monkeys, and humans was critically reviewed and reassessed. The analysis of the data of Forbes and Mikhail on the effects from activated UC_2 particles, ranging in diameter from 144 μm to 328 μm, led to the formulation of a new model to predict both the threshold for acute ulceration and for ulcer diameter. In this model, a point dose of 27 Gy at a depth of 1.33 mm in tissue will cause an ulcer with a diameter determined by the radius to which this dose extends. Application of the model to the Forbes and Mikhail data obtained with mixed fission product beta particles yielded a "threshold" (5% probability) of 6×10^9 beta particles from a point source of high energy (2.25 MeV maximum) beta particles on skin. The above model was used to predict that approximately 1.2×10^{10} beta particles from Sr-Y-90 would produce similar effects, since few Sr-90 beta particles reach 1.33 mm depth. These emissions correspond to doses at 70-μm depth in tissue of approximately 5.5 to 5.5 Gy averaged over 1 cm^2, respectively.

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EXECUTIVE SUMMARY

A critical review of NCRP Report 106 and related work on the effects of hot particles on skin revealed several weaknesses in the data base. The NCRP recommendation of a limit of 10^{10} beta particles emitted from a point source on the skin was based on results from fission particle sources placed on the skin of pigs and a monkey. In the pig studies, the data were combined from studies of Forbes and Mikhail, who used particles of two sizes (150- and 300-μm diameter). The dose at 100-μm depth in tissue was taken as a reference parameter. Data plotted on log coordinates yielded a straight line when ulcer diameter was plotted vs. number of beta particles emitted from the sources. However, as we show, when the same data are plotted on linear coordinates, the data from the two sizes of particles do not fit a common line when a dose at 100-μm depth in tissue is considered. Numerous correlation analyses were made to search for an optimum relation so that the data from the two particle sizes would yield a common threshold; this was achieved when the dose at 1.33-mm depth in tissue was considered the critical depth (rather than 100 μm). The center-line or "point" dose that corresponds to a 5% probability of zero diameter ulcer (i.e., no ulcer) was 27 Gy at 1.33-mm depth in tissue. This dose is predicted to result from 6×10^9 beta particles from a point source of high-energy (2.25 MeV maximum) beta particles on the skin, or approximately 1.2×10^{10} beta particles from a Sr-Y-90 source. These emissions would deposit approximately 5.3 Gy average dose over 1 cm^2 at 70-μm depth in tissue for the former and approximately 5.5 Gy for the latter.

Hopewell et al. generated related data but scored % incidence of detectable acute tissue breakdown rather then ulcer diameter. They obtained dose-response data which were extrapolated to a "threshold" defined by two-thirds of the 10% incidence level. Since the end point scored was not ulcer diameter as for the above, the data from the two sources must be analyzed separately. The two were related by calculating the number of beta particles from a point source on skin needed to produce the dose at 1.33 mm depth in tissue that corresponds to the threshold defined for each study.

The BNL review of the studies by Hopewell et al. revealed problems in dosimetry which resulted from the difficulty of using extrapolation chamber techniques to determine dose from very small sources (e.g., <1-mm diameter). In Hopewell's studies, both Tm-170 and Sr-Y-90 sources were employed. BNL's reassessment of the dosimetry for the 1-mm diameter Sr-Y-90 source, using radiochromic dye film, yielded a correction factor of 3.3 for dose averaged over 1.1 mm^2 at 16-μm depth (the window thickness and collection area of the extrapolation chamber used in their studies). The reassessment also yielded 2.3 times larger ratios of dose averaged over 1.1 mm^2 compared to 1 cm^2 than had been measured with the extrapolation chamber. These differences are thought to reflect the source collimation and distance of the effective source center from the chamber window. These factors and the uncertainty about dosimetry for the Tm-170 sources make interpretation of the Hopewell data difficult. However, using the dose determined with radiochromic dye film at a depth of 1.33 mm in tissue, a point Sr-Y-90 source on skin emitting 3.1×10^{10} beta particles, giving 14 Gy average over 1 cm^2 at 70-μm depth in tissue, would yield a 5% probability of detectable ulcers (a practical threshold). The higher threshold value (3.1×10^{10} beta particles) deduced from the Hopewell et al. data may be due to the collimation and greater effective distance from skin of the 1-mm diameter Sr-Y-90 source used in their work compared to the UC_2 particles used by Forbes and Mikhail.

Questions remain about the predicted threshold, the energy dependence of the predicted threshold, the effect of distance from the skin, the persistence of the ulcers produced,

possible dose-rate dependence, and the importance of spatial distribution of the dose. These subjects are being studied at Brookhaven National Laboratory (BNL).

ACKNOWLEDGEMENTS

The authors wish to acknowledge that this report reflects important technical work of several other scientists. Drs. M.W. Charles and P. Darley of Berkeley Nuclear Laboratories in Berkeley, England, provided data obtained using their extrapolation chamber and small Tm-170 sources. They also exposed radiochromic dye film with their Sr-Y-90 source which was then analyzed at the National Institutes of Standards and Technology, Gaithersburg, Maryland, by Dr. C. Soares.

Numerous discussions with the above and Dr. John Hopewell of Churchill Hospital, Oxford, England; Messrs. Jack Bell (Project Manager), John D. Buchanan and Alan K. Roecklein (Project Manager), of the U.S. Nuclear Regulatory Commission; and Mr. Charles B. Meinhold and other members of the Committee that wrote NCRP Report 106, contributed greatly to this work.

Mr. Darryl Kaurin's [illegible] performed, in part, under appointment to the Operational Health Physics Fellowship [illegible] administered by Oak Ridge Associated Universities for the U.S. Department [illegible] Boyd Bird worked on the project as a consultant to Brookhaven National [illegible] report was typed by Ms. Grace Nubla with assistance from Ms. Maria Beckman. Ms. Sandra Lane assisted in literature retrieval and editorial review.

1. INTRODUCTION

Criteria for the radiation protection of the skin have been derived primarily from radiation therapy experience on exposure areas that are relatively large. The National Council on Radiation Protection and Measurements (NCRP) reviewed data on the effects of radiation on the skin, including the effects of very small radioactive particles. Their conclusions were published as NCRP Report 106, Recommendations on Limits of Exposure to "Hot Particles" on the Skin, (NCRP, 1989). "Hot particles" of concern to the nuclear power industry are activated corrosion, wear and fuel particles. The primary concern for skin exposure is from non-stochastic effects from the particle's beta-ray emissions. The NCRP recommendation is limited to particles less than 1 mm in any dimension in direct contact with skin. There are few experimental data on nonstochastic effects that are directly relevant to this particle size.

In its Report 106, the NCRP consider both stochastic and nonstochastic effects. Consideration of the biological effects that can be produced by small "hot particles" led the NCRP to choose skin ulceration as the non-stochastic effect to be prevented; the stochastic risk associated with the recommended limit based on ulcer production was considered acceptably small. To assess stochastic effects, the NCRP used a data base from humans exposed to low-energy x-rays (Shore et al., 1984) over areas of the skin that are large compared to areas exposed by hot particles. The rationale behind the assessment is that stochastic effects are directly related to the dose and to the number of cells exposed, which is a concept widely used in risk assessment. For non-stochastic effects, most of the limited experimental data were obtained over the last decade by a consortium of British researchers. They exposed the shaved skin of the live, young pigs to three different beta sources, with different maximum energies, ranging in size from 0.1-mm diameter to 40-mm diameter. This research yielded information on the mechanisms of damage to skin (Hopewell, 1986) as well as giving specific data relevant to small "hot particles." (Hopewell et al., 1986; Peel et al, 1984). Before these studies, experiments were done in the United States using small, fissioned-fuel particles for skin exposures. Miniature swine, mice (Forbes and Mikhail, 1969)[1], monkeys (Dean et al., 1986; Dean and Langham, 1969), and a human subject (Dean et al., 1970) were exposed.

The NCRP relied upon the results of the experiments with fissioned-fuel particles in the formulation of the recommendation in the their Report. The difference between the results of the Forbes and Mikhail experiments and the results of other studies were not fully resolved. Improvement of the "hot particle" data base is needed to clarify differences between the results of the various experiments and to verify the information upon which the NCRP recommendation is based.

1.1 Experimental Results on Nonstochastic Effects

Studies with the use of different beta sources has shown that skin lesions have both a depth-dose and an area-dose dependence. Moist desquamation in pig skin occurs from doses of approximately 20-30 Gy at the basal cell layer of the epidermis (depth approximately 100 μm) from a 20-mm diameter or larger source. As the source size is reduced, larger peak doses are required (directly below the particle) in order to have sufficient dose at the perimeter of a critical area of basal cells to produce a visible effect. However, at a

[1]Acute Lesions in Skin Produced by ^{235}Uranium-Carbide Microspheres, Forbes, P.D. and Mikhail, S.Z., 1989, unpublished due to lack of funding to continue the project.

sufficiently large peak dose, cell death was more rapid than for lower doses (Hopewell, 1986; Hopewell et al., 1986); ulceration occurred as a result of the loss of cells and damage to capillaries in the papillary dermis, below the basal cell layer. Such acute ulceration occurred with peak doses of approximately 80 Gy or larger in the basal cell layer and papillary dermis (Hopewell, 1986; Hopewell et al., 1986). A second radiation-sensitive region of pig skin is the vasculature at the base of the dermis (depth approximately 1.4 mm). Doses (averaged over 1.1 mm^2) greater than approximately 20 Gy at this depth can cause necrosis and late ulceration when given by sources having diameters ≥ 5 mm. However, for very small sources, late ulceration was not observed. For example, a 1-mm diameter Sr-Y-90 source with a reported[2] "surface" dose of 570 Gy, approximately 40 to 50 Gy at 1.4 and 1.33 mm depth, respectively, (based on data in Section 6 below), did not produce late ulceration (Hopewell et al., 1986), nor did any of the 150-μm and 300-μm diameter fissioned-fuel particles[3] with approximate (calculated) "surface" doses of 500 Gy and larger (NCRP, 1989). Possibly, early ulceration and healing, that included the formation of scar tissue, precluded late ulceration; alternatively, the dose to the volume of tissue at a depth corresponding to the base of the dermis, which may be necessary for such a response, may not have been exceeded.

Studies with other laboratory animals, mainly rodents, have shown similar radiation responses due to the sensitivity of the basal cell layer of the epidermis, which is the important tissue for production of desquamation. However, with small sources such as hot particles, the doses at which acute and late ulceration effects may be expected have not been adequately quantified.

As mentioned above, the NCRP's recommended limit for hot particles was based on experiments with fissioned-fuel particles. However, Forbes and Mikhail[4] exposed miniature swine, and mice to microspheres with dimensions grouped closely around 150-μm and 300-μm diameters, including a 25-μm carbon coating. Dean, Langham, and Holland (1970) similarly exposed the forearm of a human and the skin on the back of a monkey to microspheres with diameters approximately 200 μm. The uranium fuel particles were irradiated in a nuclear reactor for several minutes, then applied to the experimental skin for timed exposures within several hours of the particle activation. The beta-ray spectra of the fission products were of relatively high energy, and differed from the spectra from fuel-fragment particles found recently at a few power reactors; nevertheless, they were a reasonable model for fission product "hot particles."

Forbes and Mikhail's data from the swine experiments were uniquely evaluated with respect to ulcer diameter versus exposure magnitude. In their report (1986), exposures were given as "point" doses at 100-μm depth either at a point directly below the particle or at a radial distance of 4 mm [the so-called Krebs' dose (Krebs, 1967)]. In NCRP report 106 (NCRP, 1989), all exposures were converted to number of beta-rays emitted from the source. Unfortunately, the experimental data did not include exposures that did not cause ulceration nor an overlap of exposures for the two particle sizes. These shortcomings cause the extrapolation to an exposure producing no ulcers to have a greater uncertainty than

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[2]As measured with 1.1-mm^2 chamber through a 16-μm thick window of plastic material (Hopewell et al., 1986).

[3]Forbes and Mikhail, 1989, loc. cit.

[4]Ibid.

otherwise. A linear best-fit (on a logarithmic scale) to particles was used for the extrapolation. The result is 3 x 10^{10} beta particles emitted from the source, thus supporting the recommended limit on exposures from hot particles. Considering self-absorption and size of the particles, the beta emissions from a point source on the skin needed to produce the same dose at 100-μm depth would be 10^{10}. The NCRP report notes that a lower value would be obtained from an extrapolation using only the smaller emission values. The committee rejected this lower value based on results of Dean, Langham, and Holland (1970). Alternatively, different linear slopes for the two particle sizes could have been assumed, or a nonlinear fit to all the data could have been used.

The data of Dean et al. (1970) on the monkey, to which the report refers in support of their extrapolation, include exposures that did not produce ulcers. An approximate interpolation value between exposures that produced ulcers (3.4 x 10^{10} beta particles emitted from the source) or do not produce ulcers (3.2 x 10^{10} beta particles), therefore, is available (ulcer sizes were not scored). The interpolation value is in good agreement with the extrapolation value. Thus, the experiments of Dean et al. and of Forbes and Mikhail are complementary; however, different experimental animals were used. The NCRP document does not argue for biological similarity but does point out similarities in terms of the dimensions of damage relative to epidermal thickness in the species. We noted also that Forbes and Mikhail reported that a small ulcer (and tumor!) was observed in the skin of a mouse after exposure to approximately 1.6 x 10^{10} beta particle emissions. This occurred at one of 44 spots exposed, a much higher tumor frequency than predicted for humans (NCRP, 1989).

Hopewell et al.'s (1986) experiments used a variety of isotope sources that differed from those employed in the fuel-particle experiments. The biological effect reported was moist desquamation or acute ulceration, rather than ulceration. The biological effects were reported as a function of measured doses obtained with quite small volume extrapolation chambers (1.1-mm^2 collecting electrode with 16-μm thick window). The incidence rate for the effect was determined rather than measuring the size of the lesion, and a statistical uncertainty was reported. A consequence of the emphasis on incidence is that in all cases, but especially for the smaller sources, a broad transition with increasing doses was obtained, from zero to one hundred percent. For example, the 2-mm diameter source of Tm-170 produced a broad transition extending from a threshold dose of approximately 100 Gy to a 100% incidence of approximately 400-500 Gy. Such a broad transition is not apparent from the linear extrapolation of the data for fissioned fuel particles.

To summarize, data from the NCRP report (their Figure 5.1) have been plotted on an expanded scale in Figure 1.1 to include additional comparisons: large- and small-fissioned fuel particles (approximately 150-μm and 300-μm diameters) that produced a range of ulcer sizes in swine are plotted; the data of Dean et al. on the monkey are plotted, along the axes representing 100% and 0% ulcer incidence; three human exposures are plotted including one at 6.5 x 10^9 beta particles that gave a small, dry desquamation (Wells, 1988); and the mouse exposure (mentioned above) that gave a small ulcer and tumor is shown as a point on the 100% incidence axis. For comparison, the incidence curves for a 1-mm diameter source of Sr-Y-90 and for 1 mm and smaller sources of Tm-170 are represented as a range of exposures from 1.5 x 10^{10} to 1.5 x 10^{11} beta particles that correspond to the change from zero to 100% incidence. These incidence values are deduced from studies described below. There are only a few data points less than the demarcation of 3 x 10^{10} beta emissions, even when the results on the monkey are included. Inclusion of the singular positive results for mouse ulcer and human desquamation are within the transition range defined by the Hopewell et al. data. This comparison suggests that the extrapolation used

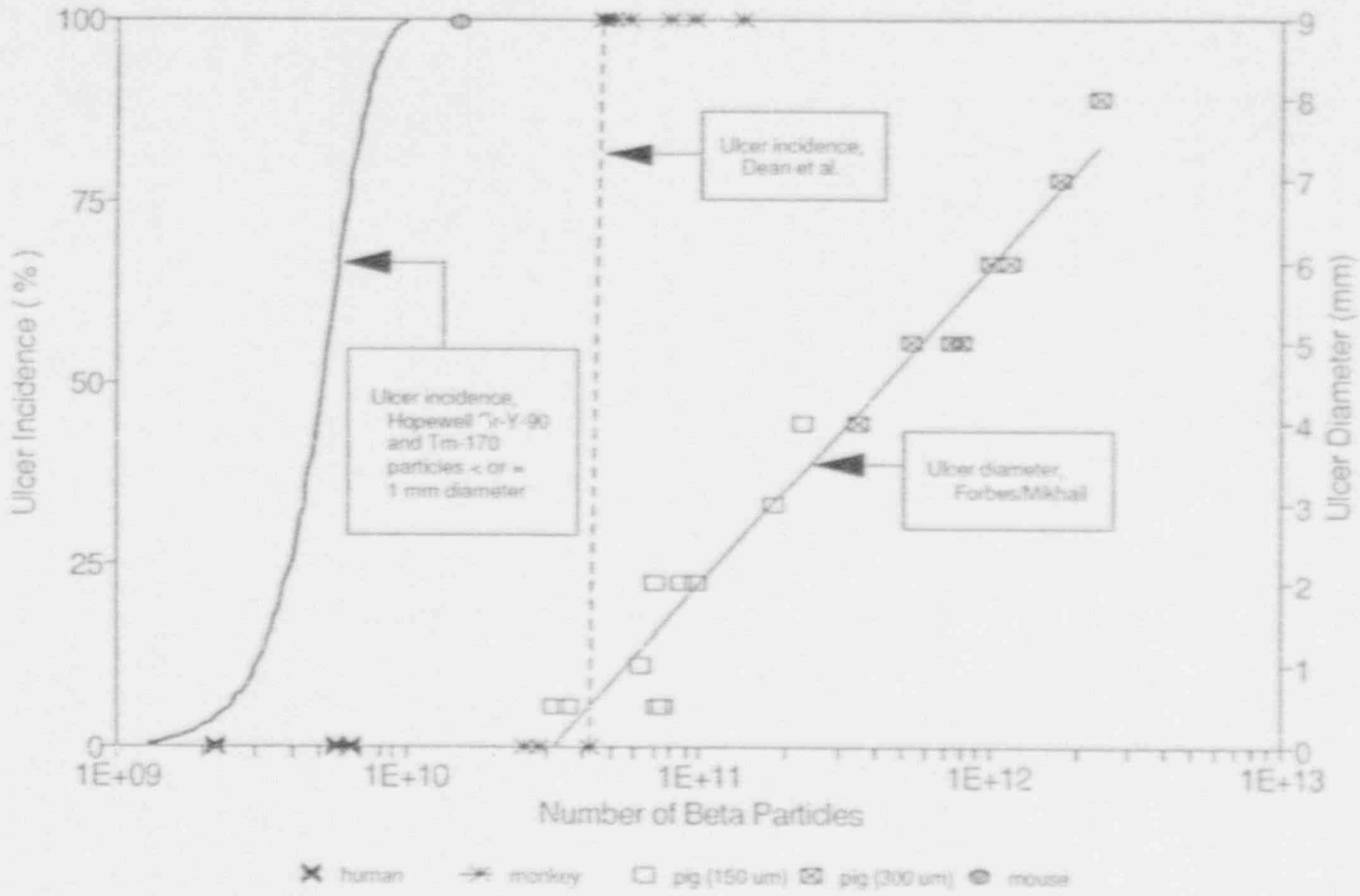

Figure 1.1. Ulcer incidence and ulcer diameter vs. number of beta particles emitted. Monkey data (*) of Dean et al. (1970) includes 7 points along the 100% incidence axis. None of the human skin exposures (x) resulted in an ulcer. The single mouse point (⊙) also caused a tumor at the exposure site.

for the NCRP document is not adequate to arrive at a preventive limit, rather it gives of occurrence. Statements in the NCRP report that prevention of ulceration is intended imply that limited probability of a small transient lesion is acceptable. Hopewell et al.'s (1986) studies constitute a much larger set of experiments and data than those used by the committee and were originally interpreted as suggesting a threshold for acute uceleration of approximately 1/5th the NCRP recommended value. The purpose of our work is to (a) critically review the above studies, (b) to understand the reasons for the differences between the Forbes and Mikhail studies and those of Hopewell et al., (c) to determine any weaknesses in the information, and (d) to suggest research that may be needed to strengthen the data base so that sound, scientifically-based regulatory decisions may be made.

2. FORBES AND MIKHAIL DOSIMETRY

Forbes and Mikhail (1969; 1989 draft[5]) used an extrapolation chamber as their basic dosimeter. They transformed the resulting measurements to obtain (a) centerline dose at 100-μm depth in tissue which they called "point" dose, and (b) a dose on the periphery of a circular field of 4-mm radius and 100-μm depth in tissue (the so-called "Krebs" dose). The measured doses were transformed using the transmission degradation dissipation (TDD) beta dose model developed at the Naval Radiological Defense Laboratory (NRDL) (Ulberg and Kochendorfer, 1966). Other measurements made with a 4-pi ionization chamber were used to determine the number of fissions per particle. Then, knowing the particle diameter, activation time, and residence time on the animal, they computed the dose to a disc area 1 inch in diameter at a depth of 100 μm in tissue for direct comparison to the extrapolation chamber measurements. Results were generally in agreement within a factor of two for the exposure times employed.

Forbes and Mikhail's report (Forbes and Mikhail, 1989 draft[6]) indicates that almost all of the extrapolation curves were straight lines, a fact which increased their confidence in the validity of the measurements. Their extrapolation chamber had an electrode area of 5.07 cm^2. They validated the measurements with this chamber by comparing the dose rates obtained at the NRDL with those obtained at the Oak Ridge National Laboratory using an independently constructed extrapolation chamber. Good agreement among the data was assumed by them to indicate that the apparatus was free of important systematic errors. This conclusion is supported by recent data obtained by Scannel[7] who used an extrapolation chamber with a 1-cm^2 area collecting electrode which gave good agreement with thin (5 mg/cm^2) LiF thermoluminescent dosimeter measurements of doses from small particles containing fission fragments or ^{60}Co. However, studies are needed to confirm Scannel's unpublished work to ensure that he did not have a measurement problem similar to that experienced by the British with their very small area (1.1 mm^2) electrode extrapolation chamber (see Section 5 below). Analytical studies at Brookhaven and experimental studies at Berkeley Nuclear Laboratory in England are examining this question.

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[5]Forbes and Mikhail, 1989, loc. cit.

[6]Ibid.

[7]"Solving Beta Dosimetry Problems at Nuclear Power Stations," Scannel, M.J., Presented at the Beta Dosimetry/Hot Particle Workshop of the New England Chapter of the Health Physics Society, Lowell, MA, March 27, 1990.

3. ANALYSES OF FORBES AND MIKHAIL DATA

3.1 Uncertainties in Earlier Statistical Approaches

In Report 106, the NCRP based its recommendation of a 75 microcurie-hour (10^{10} beta particles) limit partly on a least-squares analysis of 19 data points that were obtained by Forbes and Mikhail using particles grouped around 150- and 300-μm diameter and containing fission products. The data, plotted on a semi-log plot (Figure 5.1 in NCRP, 1989), showed nearly a straight-line relation between ulcer diameter and the log of the number of beta particles emitted[8]. Using all 19 points, the analysis yielded an intercept of 3×10^{10} beta particles emitted. For this number of beta particles emitted, the predicted diameter of the ulcer would be zero. However, the report states on page 19, "A straight line that was obtained by a least squares fit to the 8 points with smallest emission gave an intercept of 1.5×10^{10}. The value of 3×10^{10} beta particles was selected as the best estimate of threshold because it was believed to give the best fit to the Forbes and Mikhail data and it agreed with the data on monkeys (Dean and Langham, 1969; and Dean et al., 1970)." This factor of 2 difference (1.5 vs 3×10^{10}) was considered more carefully during the present studies.

Our early unpublished analyses of the Hopewell/Charles data yielded results that implied a threshold dose for ulceration approximately five times smaller than that obtained from analyses of the Forbes and Mikhail data. This difference is partly explained by a factor of approximately 2 to 3.3 discrepancy in the Hopewell/Charles dosimetry that was apparent from our analyses of their extrapolation chamber data and from recent unpublished radiochromic dye film dosimetry (see Sections 4 and 5 below for details). Correcting for this discrepancy would increase the Hopewell doses. Therefore, there remained a discrepancy of approximately 2. Because the NCRP report showed a factor of 2 difference between the threshold value obtained using all 19 data points from the Forbes and Mikhail study and the value (1.5×10^{10}) obtained from data for 8 points with smallest emission, we decided to do more statistical analyses of Forbes and Mikhail's data to better judge the appropriate intercept.

3.2 Linear Plots

The data were first plotted using linear coordinates to get a better understanding of the shape of the plots of dose vs. ulcer diameter plots. Figure 3.1 shows the results when number of beta particles, as deduced by NCRP (page 30, NCRP Report 106, 1989) is plotted against the diameters of the ulcers. The data are remarkable in that the points for 150-μm diameter particles fall on a distinctly different line than those for the 300-μm diameter particles. The number of beta particles at the interceptfor the extrapolation from the 150-μm particles was 1.9×10^{10}, whereas that for the 300-μm diameter particles was -2×10^{12}. Thus, looking only at the large particle data, one might conclude that ulcers of diameter less than approximately 3.5 mm probably could not be produced by these particles.

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[8]As discussed in Section 3.3 below, we conclude that the NCRP values for the number of beta particles emitted should have been stated as "from" the spheres rather than "in" the spheres for the data plotted in their Figure 5.1.

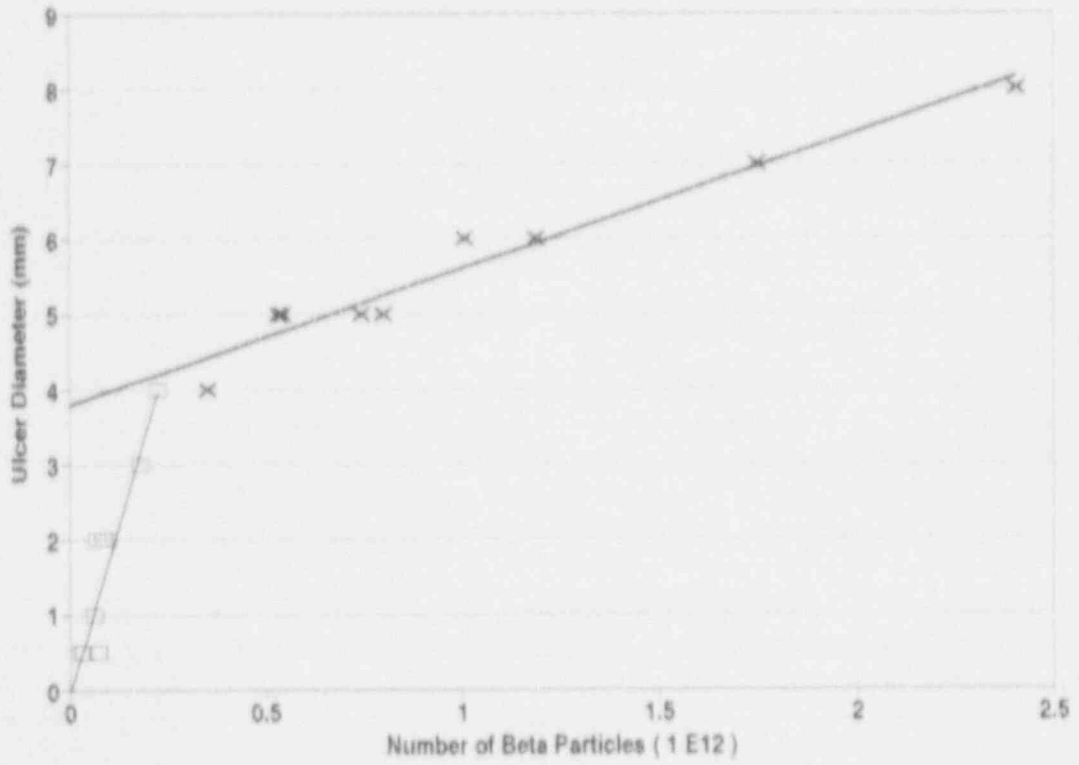

Figure 3.1 Number of beta particles vs. ulcer diameter from data of Forbes and Mikhail (1989). □=150 μm particles; X=300 μm particles. 150 μm particles, (threshold: (0.49±.7)E10; slope: (1.8±-0.28)E-11; R^2: 0.84. 300 μm particles, (threshold: (-2.1±-0.26)E12; slope: (-2.1±-0.15)E-12; R^2:0.95). See Appendix A for details on regression analyses.

3.3 Corrections for Self Absorption

The above results were obtained using the NCRP's determination of the number of beta particles emitted from the Forbes and Mikhail particles (NCRP, 1989). However, the NCRP Report 106 contains contradictory statements as to whether the emission values quoted were "in" (not corrected for self absorption) or "from" (corrected for self absorption) the particles. For example, the data plotted in Figure 5.1 of the NCRP Report 106 has a caption stating that the particles are those emitted "in" the source. The same data are tabulated in their Table B.1 with a title stating that the particles are emitted "from" the spheres. Therefore, doses reported at 100-μm depth in tissue by Forbes and Mikhail (1969 and 1989) were used to estimate the number of beta particles emitted from and in the spheres for comparison with the NCRP values given in Table B.1 of NCRP Report 106.

To evaluate self absorption in the particles emitted, we obtained two sets of values for the fraction of electrons emitted from UC_2 particles with 3.75- to 240-μm diameter from the report of Ulberg and Kochendorfer (1966). These results were obtained using (a) their transmission, degradation and dissipation (TDD) model, and (b) their empirical model. The former is a sophisticated Monte Carlo type code and the latter is based on an empirical

equation developed to fit the experimental dosimetry results obtained on similar particles analyzed at ORNL (Fish, 1966)[9]. These two sets of results were compared to a simple attenuation model, in which all beta particles are assumed to originate at the center of the particle which had an inner kernel of UC_2 and an outer coat of pyrolytic carbon. The fraction emerging, F, was assumed to be:

$$F = e^{-\mu (\rho_c \chi_c + \rho_{UC_2} \chi_{UC_2})}$$

where ρ_c and χ_c are the density (2.5 g/cm^3) and thickness (2.5 x 10^{-3} cm) of the carbon coating on the particles, and ρ_{UC2} and χ_{UC2} are the density (11.3 g/cm^3) and radius (cm) of the UC_2 kernels. The data of Ulberg and Kochendorfer (1966) show an average beta energy decreasing from 1.047 MeV at 10^3 seconds after shutdown to 0.873 MeV at 10^4 seconds after shutdown. These average beta energies correspond to maximum beta energies of approximately 2.6 and 2.1 MeV, respectively, based on data in Loevinger et al. (1956). To test the sensitivity of results to assumed beta particle energy, we employed mass attenuation coefficients (μ) of 4.6 cm^2/g, obtained from the empirical equation of Loevinger et al. (1956) for a 2.8 MeV maximum energy beta spectrum applicable at 10^3 seconds after irradiation, or a μ of 6.3 cm^2/g applicable to a 2.25 MeV maximum energy which is used as an approximate average value for the period of exposure to pig skin (approximately 10^3 seconds to 10^4 seconds) for the Forbes and Mikhail exposures.

The results for the four calculations are shown in Figure 3.2. The Monte Carlo code predicted the least attenuation, the empirical model of Ulberg and Kochendorfer predicted the greatest, and the simple attenuation model described last yielded intermediate results. For this reason, the latter model with absorption coefficient μ = 6.3 and 4.6 cm^2/g was selected and used to estimate the numbers of beta particles emitted from the various particles employed by Forbes and Mikhail. The data of Forbes and Mikhail are summarized in columns 1 through 6 of Table 3.1. Based on the point doses at 100-μm depth, we calculated the number of beta particles needed to produce this dose, for a spectrum of 2.25 MeV maximum energy, from a point source at the surface of the skin. The conversion factor employed was 4.5 x 10^6 beta particles per Gy (1 Gy = 100 rad). This conversion factor was obtained using the VARSKIN code (Traub et al., 1987), Sr-90 beta particles, and increasing the result obtained by a factor 1.3 (Cross, 1990) to compensate for lack of backscatter. The results are shown in column 7. For this same number of particles emitted, we calculated the number of beta particles emitted in the various particles, assuming that the beta particles came from a point at the center of the UC_2 particles and were attenuated by a distance^{-2} factor and absorption in the sources, in a 10-μm thick plastic tape that covered the sources, and in 100 μm of tissue. These results are shown in column 8; for comparison, column 9 shows the values employed by the NCRP. Note that the values in column 8 are consistently approximately a factor of two larger for the large particles and a factor 1.5 larger for the small particles than the corresponding NCRP values in column 9. We conclude from this that values employed by the NCRP (both its Figure 5.1 and Table B.1) represent values of beta particles emitted from the spheres.

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[9]Fish, B.R., Private communication to Ulberg and Kochendorfer, 1965 and 1966.

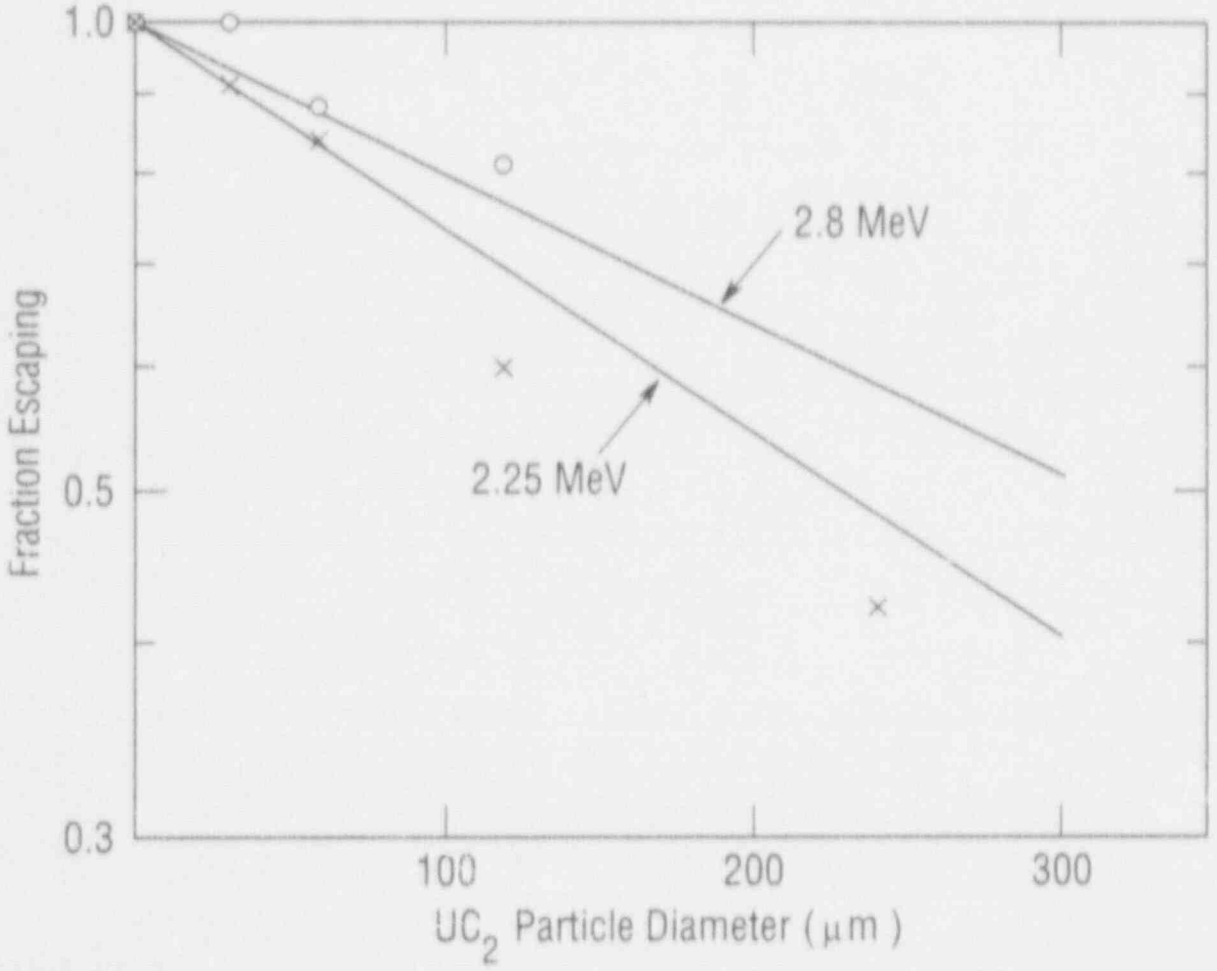

Figure 3.2 Fraction of beta particles escaping from UC_2 particles. Values predicted using Ulberg and Kochendorfer (1966) TDD model for emissions at 10^8 seconds after irradiation (x); values for their empirical model (o). Shown for comparison are solid lines for 2.8 MeV maximum energy beta particles (μ = 4.6 cm^2/g) and for 2.25 MeV maximum energy beta particles (μ = 6.26 cm^2/g).

Table 8.1. Dosimetry and Dose Effect Data (Pig Skin) Reported by Forbes and Mikhail (1989).

Particle Number (1)	Particle Diameter (μm)[a] (2)	Ulcer Diameter (mm) (3)	Point Dose at 100-μm depth in tissue (rad) (4)	Dose for Krebs' Level III Criterion[b] (rad) (5)	Dose for Krebs' Level IV Criterion[c] (rad) (6)	Beta Particles from point source on skin surface for column 6 dose (7)	Beta Particles Released in source[d] (8)	NCRP Number of beta particles emitted from source[e] (9)
Large Particles								
1	304	5	2.32×10^{6}	1.11×10^{4}	295	1.04×10^{11}	1.70×10^{12}	7.99×10^{11}
2	(fractured)	-	-	-	-	-	-	-
3	282	6	3.55×10^{6}	1.51×10^{4}	407	1.60×10^{11}	2.20×10^{12}	1.01×10^{12}
4	295	5	2.85×10^{6}	1.09×10^{4}	288	1.06×10^{11}	1.61×10^{12}	7.42×10^{11}
5	295	8	7.40×10^{6}	3.52×10^{4}	915	3.33×10^{11}	5.17×10^{12}	2.41×10^{12}
6	328	7	3.85×10^{6}	1.98×10^{4}	546	1.73×10^{11}	3.37×10^{12}	1.75×10^{12}
7	294	6	3.80×10^{6}	1.73×10^{4}	461	1.71×10^{11}	2.58×10^{12}	1.19×10^{12}
8	305	5	1.53×10^{6}	7.32×10^{3}	195	6.89×10^{10}	1.13×10^{12}	5.32×10^{11}
9	283	4	1.23×10^{6}	5.40×10^{3}	141	5.54×10^{10}	7.67×10^{11}	3.51×10^{11}
10	308	5	1.51×10^{6}	7.49×10^{3}	196	6.80×10^{10}	1.14×10^{12}	5.42×10^{11}
Small Particles								
11	149	4	1.70×10^{6}	2.88×10^{3}	93	7.65×10^{10}	3.43×10^{11}	2.24×10^{11}
12	150	3	1.37×10^{6}	2.31×10^{3}	75	6.17×10^{10}	2.79×10^{11}	1.82×10^{11}
13	148	0.5	2.40×10^{5}	4.05×10^{2}	13	1.08×10^{10}	4.80×10^{10}	3.14×10^{10}
14	140	0.5	2.66×10^{5}	4.44×10^{2}	15	1.29×10^{10}	5.31×10^{10}	3.54×10^{10}
15	152	2	6.42×10^{5}	1.06×10^{3}	36	2.89×10^{10}	1.33×10^{11}	8.65×10^{10}
16	148	0.5	5.69×10^{5}	9.44×10^{2}	31	2.56×10^{10}	1.14×10^{11}	7.44×10^{10}
17	153	2	5.14×10^{5}	7.71×10^{2}	29	2.31×10^{10}	1.08×10^{11}	6.97×10^{10}
18	145	1	4.68×10^{5}	7.70×10^{2}	26	2.20×10^{10}	9.49×10^{10}	6.25×10^{10}
19	154	2	7.17×10^{5}	1.21×10^{3}	40	3.23×10^{10}	1.52×10^{11}	9.80×10^{10}
20	144	0.5	5.63×10^{5}	9.21×10^{2}	30	2.53×10^{10}	1.09×10^{11}	7.16×10^{10}

a. Diameter includes 25-μm thick carbon coating.

b. Dose at 4-mm radius and 100 μm depth in tissue.

c. Dose at 6-mm radius and 1.5-mm depth in tissue.

d. Based on data in column (4) with adjustments for effective distance of source center from skin and absorption in the source and intervening material.

e. Values taken from NCRP Report 106, 1989.

3.4 Regression Analyses of Forbes and Mikhail Data

Regression analyses were made on the data of Forbes and Mikhail, summarized in NCRP Report 106 (1989). In these analyses various expressions for dose are used as the independent parameter. Equations, concepts, and terminology used in this type of analysis are discussed in Appendix A, along with a clarification of the statistical terms employed.

The results of linear regression analyses using the NCRP values for the number of beta particles released from the sources are shown as item 1A in Table 3.2. Those results obtained using the number of beta particles released from the source, based on the data in column 4 of Table 3.1 and our corrections for particle self-absorption, using an absorption coefficient of 6.3 cm^2/g applicable at 10^4 seconds after removal from the reactor, are shown as item 1B in Table 3.2. Similar results obtained using an absorption coefficient of 4.6 cm^2/g, applicable for beta particles released from the source at 1000 seconds after removal from the reactor, are shown as item 1C.

If the diameter of the ulcer is determined by a critical dose at its edge, it would be logical to assume that the number of beta particles that cause ulcers of various sizes should increase roughly in proportion to the ulcer diameter squared, or to the area of the ulcer. Thus, if the diameter increased from 1 to 2 mm, the number of associated beta particles should increase by a factor of 4, assuming only an inverse square attenuation of the beta particles (no absorption), or somewhat more if absorption is considered. The regressions for ulcer area vs. number of beta particles are shown as item number 2A in Table 3.2. Similar results based on data in column 4 of Table 3.1 and assuming the absorption characteristics of beta particles with 2.25 MeV maximum energy ($\mu = 4.6$ cm^2/g) are shown as item number 2B in Table 3.2. These regressions yielded slightly better coefficients (R^2)[10] than those for regressions of the number of beta particles with ulcer diameter (items 1A and 1B). However, once again the intercept for the larger particles was at a large negative value (-47 x 10^{10} beta particles based on NCRP values for number of beta particles emitted from the source and -97 x 10^{10} beta particles based on an attenuation coefficient of 6.3 cm^2/g), while the intercepts for the smaller particles were positive values (4.4 and 6.7) x 10^{10} beta particles, respectively. Thus, the results from the small particles and large particles again are inconsistent using ulcer area as the dependent variable.

Because Forbes and Mikhail's data on ulcer diameter were correlated with centerline dose (the so-called "point" dose) at 100-μm depth in NCRP Report 106, correlations were made using the diameter and the area of the ulcer as the dependent variable and point dose at 100-μm depth as the independent variable. Results for these correlations are shown as items 3 and 4 in Table 3.2. Here again, regression coefficients were reasonable; however, negative intercepts again were obtained for the 300-μm diameter particles. When regression was vs. ulcer diameter, the combined regression using all particles also yielded a negative intercept, whereas against ulcer area the combined values gave a positive, but not well defined, intercept (0.087 ± 1.9) x 10^5 rad.

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[10]Values of R^2 can range from zero to 1.0. As R^2 approaches 1.0, the points fall closer to the regression line.

Table 3.2. Dose-Response Regressions for Data of Forbes and Mikhail (1989) (continued)

Item #	Diam of Particles μm	Independent Parameters*	Dependent Variable	R^2	X Intercept**
1A	150 300 All	#βs from source NCRP Values	Ulcer Diameter	0.84 0.95 0.78	$(4.8\pm17) \times 10^9$ $(-2.1\pm0.26) \times 10^{12}$ $(-5.5\pm1.6) \times 10^{11}$
1B	150 300 All	#βs from source (4.5×10^6 β/Gy, $\mu = 6.3$ cm^2/g)	Ulcer Diameter	0.84 0.94 0.78	$(7.3\pm25) \times 10^9$ $(-4.4\pm0.61) \times 10^{12}$ $(-1.2\pm0.34) \times 10^{12}$
1C	150 300 All	#βs from source (4.5×10^6 β/Gy, $\mu = 4.6$ cm^2/g)	Ulcer Diameter	0.84 0.94 0.78	$(6.6\pm23) \times 10^9$ $(-3.4\pm0.50) \times 10^{12}$ $(-9.1\pm2.6) \times 10^{11}$
2A	150 300 All	#βs from source NCRP Values	Ulcer Area	0.91 0.98 0.95	$(4.4\pm0.88) \times 10^{10}$ $(-4.7\pm0.98) \times 10^{11}$ $(-1.1\pm0.52) \times 10^{11}$
2B	150 300 All	#βs from source (4.5×10^6 β/Gy $\mu = 6.3$ cm^2/g)	Ulcer Area	0.91 0.97 0.95	$(6.7\pm1.3) \times 10^{10}$ $(-9.7\pm2.3) \times 10^{11}$ $(-2.8\pm1.1) \times 10^{11}$
3	150 300 All	Point Dose at 100-μm Depth	Ulcer Diameter	0.82 0.88 0.77	$(3.5\pm13) \times 10^4$ $(-6.4\pm1.3) \times 10^6$ $(-1.2\pm0.47) \times 10^6$
4	150 300 All	Point Dose at 100-μm Depth	Ulcer Area	0.90 0.91 0.91	$(3.3\pm0.68) \times 10^5$ $(-1.4\pm0.57) \times 10^6$ $(0.087\pm1.9) \times 10^5$
5	150 300 All	1.1-mm^2 Area Dose at 100-μm Depth	Ulcer Diameter	0.82 0.88 0.75	$(1.1\pm4.3) \times 10^4$ $(-1.6\pm0.33) \times 10^6$ $(-2.6\pm1.2) \times 10^5$
6	150 300 All	1.1-mm^2 Area Dose at 100-μm Depth	Ulcer Area	0.90 0.91 0.89	$(1.1\pm0.22) \times 10^5$ $(-3.6\pm1.4) \times 10^5$ $(3.4\pm5.3) \times 10^4$
7A	150 300 All	Ln(#βs) from source NCRP Values	Ulcer Area	0.75 0.91 0.89	$(4.6\pm1.0) \times 10^{10}$ $(2.1\pm0.28) \times 10^{11}$ $(6.0\pm0.89) \times 10^{10}$
7B	150 300 All	Ln(#βs) (4.5×10^6 β/Gy, $\mu = 6.3$ cm^2/g)	Ulcer Area	0.75 0.90 0.88	$(6.9\pm1.6) \times 10^{10}$ $(4.6\pm0.61) \times 10^{10}$ $(9.1\pm1.6) \times 10^{10}$
8	150 300 All	Log (Point Dose at 100-μm Depth)	Ulcer Diameter	0.76 0.88 0.93	$(2.4\pm0.51) \times 10^5$ $(1.5\pm0.61) \times 10^5$ $(2.8\pm0.33) \times 10^5$

Table 3.2. Dose-Response Regressions for Data of Forbes and Mikhail (1989) (continued)

Item #	Diam of Particles μm	Independent Parameters*	Dependent Variable	R^2	X Intercept**
9	150 300 All	Log (Point Dose at 100-μm Depth)	Ulcer Area	0.75 0.86 0.87	$(3.5 \pm 0.56) \times 10^5$ $(6.6 \pm 1.5) \times 10^5$ $(4.5 \pm 0.58) \times 10^5$
10	150 300 All	Log (1.1-mm^2 Area Dose)	Ulcer Diameter	0.76 0.88 0.89	$(7.7 \pm 1.6) \times 10^4$ $(3.9 \pm 1.5) \times 10^4$ $(9.1 \pm 1.2) \times 10^4$
11	150 300 All	Log (1.1-mm^2 Area Dose)	Ulcer Area	0.75 0.86 0.84	$(1.1 \pm 0.18) \times 10^5$ $(1.6 \pm 0.37) \times 10^5$ $(1.4 \pm 0.18) \times 10^5$
12	150 300 All	Ln (Dose at Radius of Ulcer and at 1.33-mm Depth)	Ulcer Diameter	0.0052 0.18 0.011	$(5.1 \pm 26.4) \times 10^5$ $(2.0 \pm 1.6) \times 10^4$ 85 ± 210
13A	150 300 All	Log (#βs) from source NCRP Values	Ulcer Diameter	0.77 0.94 0.96	$(3.1 \pm 0.65) \times 10^{10}$ $(4.8 \pm 1.4) \times 10^{10}$ $(3.2 \pm 0.37) \times 10^{10}$
13B	150 300 All	Log (#βs) (4.5×10^6 β/Gy, 6.3 cm^2/g)	Ulcer Diameter	0.78 0.93 0.96	$(4.8 \pm 1.0) \times 10^{10}$ $(11 \pm 1.2) \times 10^{10}$ $(4.4 \pm 0.44) \times 10^{10}$
14	150 300 All	Dose at Radius of Ulcer and 100-μm Depth	Ulcer Area	0.38 0.010 0.26	$(1.4 \pm 0.45) \times 10^5$ $(4.6 \pm 13.1) \times 10^4$ $(1.3 \pm 0.45) \times 10^5$
15	150 300 All	Point Dose at Radius of Ulcer and 1.33-mm Depth	Ulcer Diameter	0.024 0.17 0.0015	$(8.9 \pm 14.3) \times 10^3$ $(8.5 \pm 4.7) \times 10^3$ $(-2.2 \pm 15.3) \times 10^4$
16	150 300 All	Point Dose at Radius of Ulcer and 1.33-mm Depth	Ulcer Area	0.027 0.19 0.00	$(6.1 \pm 7.6) \times 10^3$ $(5.5 \pm 2.1) \times 10^3$ $(-0.11 \pm 44.3) \times 10^7$
17A	150 (First 8 Points)	Log (#βs) NCRP Values	Ulcer Diameter	0.41	$(2.4 \pm 1.2) \times 10^{10}$
17B	150 (First 8 Points)	Ln(#βs) (4.5×10^6 β/Gy, μ = 6.3 cm^2/g)	Ulcer Diameter	0.43	$(3.6 \pm 2.1) \times 10^{10}$

*Ln = logarithm to base e; Log = logarithm to base 10.

**Intercepts are expressed in rad (1 rad = 0.01 Gy) or number of beta particles emitted from the sources.

Another set of regressions was run using ulcer diameter and ulcer area as the dependent variables correlated with dose averaged over 1.1 mm^2 at a depth of 100 μm. The dose was estimated using the approximations in Appendix A of NCRP Report 106, which assume a point source with the source located at the center of the particle and attenuation based on inverse square attenuation only; no account is taken of absorption in the particles. This dose estimate should be correct to within approximately 20% for the distances involved. These results, shown as items 5 and 6 in Table 3.2, yield reasonable regression coefficients but negative intercepts for the larger particles, and intercepts based on combined particle data that are not significantly different from zero. Items 7-13B of Table 3.2 give the results of other regression analyses using logarithmic (ln_e or log_{10}) transformations for the number of beta particles, point dose at 100-μm depth, or dose averaged over 1.1 mm^2; in all cases, there are positive intercepts for both the small and large particles as in the case of the NCRP correlation of ulcer area with natural logarithm of number of beta particles (item #7A). The logarithmic transformations cause the data to fit a straight line; however, they tend to give greater weight to smaller particles.

3.5 Critical Depth for Best Regression with Ulceration

Regression analyses also were made using the dose at the ulcer radius at various depths as the independent parameter and ulcer area or diameter as the dependent parameter (Table 3.2, items 14-16 and Figure 3.3). The best-fit line for the 300-μm particles for Figure 3.3 is a vertical line. This data pattern leads us to suggest that the dose at the margin of the ulcer should be the same for all ulcers at some critical depth. Doses were calculated at varying depths on the margin of each ulcer using the method described in Section 3.3. The average dose at the ulcer margins for all ulcers should best approximate the threshold dose when the relative standard deviation of the average dose is minimized, which occurs at a depth of 1.33 mm (Figure 3.4). The average dose at this depth is 27 ± 0.4 Gy. The approximate number of Y-90 beta particles required from a point source on the skin to produce a point dose of 27 Gy at 1.33-mm depth in tissue is estimated at 2.4×10^{10} based on output from the VARSKIN Code (Traub et al., 1987), which we divided by a factor of 1.3 (Cross, 1990) to correct for backscatter effects which we think are not adequately taken into account in VARSKIN (this point is currently under further study). Approximately 1.9 times this number of beta particles would be needed from a Sr-Y-90 source to produce this point dose because few of the lower energy beta particles from Sr-90 would reach this depth in tissue.

Tests were also made of the intercept from a regression with ulcer diameter as the dependent variable and logarithm of the number of betas as the independent variable using only the first eight points, as suggested in NCRP Report 106. A value of 2.4×10^{10} beta particles was obtained (item 17A of Table 3.1) rather than the value 1.5×10^{10} stated on page 19 of the report.

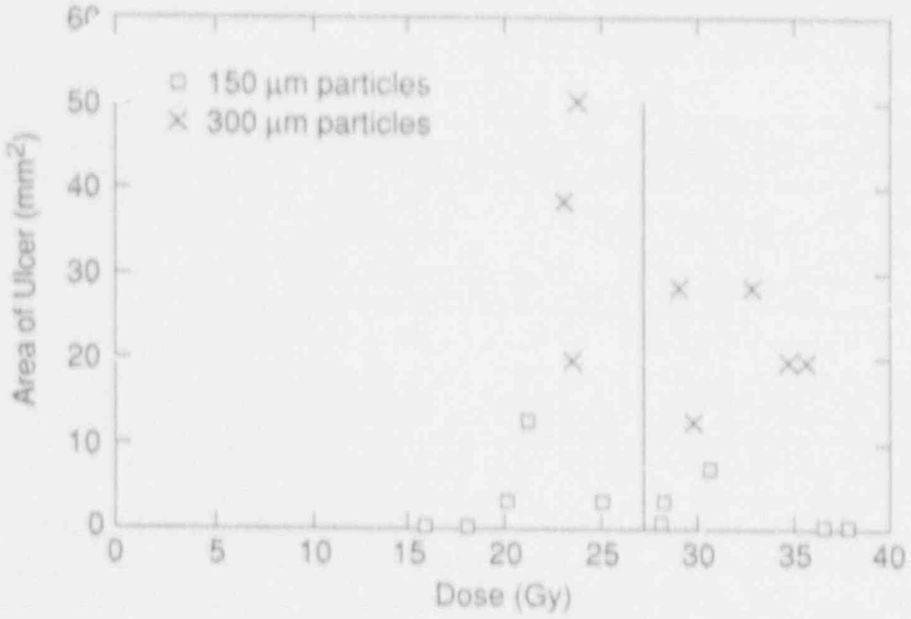

Figure 3.3 Dose at margin of skin ulcer at 1.33-mm depth.

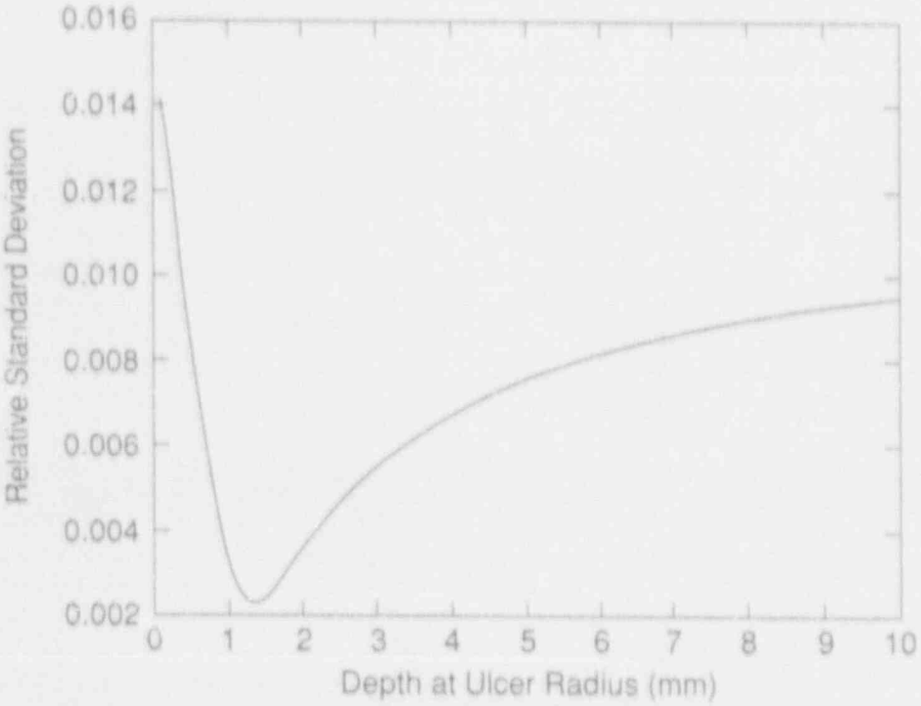

Figure 3.4 Relative standard deviation of average dose at ulcer margin at varying depths.

3.6 Tests of Krebs' Criteria

Krebs (Krobs, 1967) concluded that "If the radiation dose at the margin of a circular field of 4-mm radius at a depth of 100 μm below the surface of the skin does not exceed 1,500 rads, development of Level III injury within the field is improbable...," and "If the radiation dose at the margin of a circular field of 6-mm radius at a depth of 1.5 mm below the surface of the skin does not exceed 1,500 rads, development of Level IV injury within the field is improbable." He defined a Level III injury as moist desquamation and a Level IV injury as ulceration. Based on his work, Forbes and Mikhail related their exposures to Krebs' Level III dose criterion (point dose at 4-mm radius and 100-μm depth) as well as the centerline point dose at 100-μm depth. Table 3.1 column 5 shows doses calculated using Krebs' Level III criterion and reported by Forbes and Mikhail (1989 draft)[11] and doses we calculated using Krebs' Level IV criterion and the attenuation coefficient (μ = 4.6 cm^2/g) derived as described above. Column 3 of Table 3.1 shows that particles 13 through 20 produced ulcers even, though the doses shown in column 5 were below the Krebs' Level III criterion for moist desquamation (1,500 rad). As shown in column 6, the doses were below the Krebs' Level IV criterion for ulcer induction for all particles, but all produced ulcers. Our results show clearly that the Krebs' criteria are not applicable for predicting thresholds for either moist desquamation or ulcers after exposures to hot particles.

Using his criteria, Krebs predicted a Level II injury (dry desquamation) for point source exposures of 1,280 μCi-hr to Y-90 beta particles, a Level III injury for 19,800 μCi-hr exposures, and a Level IV for 155,000 μCi-hr. These values are approximately two to three orders of magnitude above the values at which effects were observed by Forbes and Mikhail (1989 draft)[12] and by Hopewell et al. (1986) if their doses are converted to estimated number of beta particles emitted.

Krebs also predicted that Level III and Level IV damage would be produced by much smaller exposures if the activity were distributed over a circular area with a radius 20% larger than the radius specified for the expected biological effect. For example, Level III injury was expected by Krebs from only 514 μCi-hr exposures to Y-90 beta particles if the activity was spread over an area with a radius of approximately 9 mm. These predictions were inconsistent with the findings of both Hopewell et al. (1986) and Forbes and Mikhail (1989 draft).

3.7 Conclusions

From our analyses of Forbes and Mikhail's data, we conclude that the best estimate for ulcer threshold is approximately (2.4 ± 1.1) x 10^{10} beta particles emitted from point sources on the skin, having effective maximum beta particle energies of 2.25 MeV (e.g., mixed fission products or Y-90). The uncertainty of ± 1.1 x 10^{10} beta particles is 1 standard deviation, based on the variability of dose required to induce the four smallest ulcers (0.5-mm diameter). Because of the large variations in dose required to produce an ulcer of a given size, it is impossible to specify a true threshold. Therefore, a practical threshold is arbitrarily defined as 5% probability of a detectable ulcer (a range of 1 to 5% was used in ICRP 41, 1984). For a normal distribution, a 5% chance is expected that an ulcer may be detected at (2.4 ± 1.1 x 1.65) x 10^{10} beta particles of maximum energy 2.25 MeV, or 6 x

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[11] Forbes and Mikhail, 1989, loc. cit.

[12] Ibid.

10^9 Y-90 beta particles, or 1.2×10^{10} Sr-Y-90 beta particles. This latter number of beta particles from a point source on skin would produce a dose at 70-μm depth in tissue of approximately 550 rad averaged over 1 cm^2 (based on the VARSKIN code corrected for backscatter). This value can be compared with a dose of approximately 830 rad averaged over 1 cm^2 at 70-μm depth as the threshold appropriate to an ED_5 of 1.8×10^{10} beta particles for the corrected Hopewell/Charles data for the Sr-Y-90 source of 1-mm diameter (see Section 6 below) and for the Tm-170 sources of 0.1, 0.5, and 1 mm, assuming the dosimetry corrections for these sources are approximately the same magnitude as for the 1-mm Sr-Y-90 point source.

4. REASSESSMENT OF THE BRITISH EXTRAPOLATION CHAMBER MEASUREMENTS

British scientists made extensive studies of the effects of discrete radioactive particles on pig skin using an extrapolation-type ionization chamber for dosimetry. Most of the measurements were made with a 1.2-mm diameter collecting electrode and a 16-μm thick plastic chamber window. Several preliminary measurements made with this instrument using a variety of source sizes and collecting electrode diameters were reported by Wells (Wells, 1988). This type of instrument measures the current in the ionization chamber at various spacings of the collecting electrodes. Plots of the values of the current collected as the ordinate versus electrode spacing as the abscissa are then made. If the chamber is uniformly irradiated, these results will fall on a straight line, the slope of which provides a measure of dose rate averaged over the collecting volume. However, to obtain this straight line, the collecting volume must be uniformly irradiated. When a small radioactive particle is placed near the center of the ionization chamber window, ionization produced throughout the chamber is extremely non-uniform. Correspondingly, the plot of current versus electrode spacing would not be a linear function, but rather, have a curvature with quadratic or cubic components. At the intercept with the abscissa, where current measured is zero, the slope of this non-linear function reflects dose rate at the inside surface of the ionization chamber window.

The only example of extrapolation chamber data included in the related dosimetry report (Wells, 1988) was for a plaque source which was large in comparison to the diameter of the ionization chamber window. Wells fitted these data with a simple linear function. Similarly, we fitted the extrapolation chamber data obtained using the 0.1-mm diameter and 0.5-mm diameter Tm-170 sources employed in Hopewell's studies of pigs to a linear function (Figure 4.1). However, reexamination of the Tm-170 data at Brookhaven National Laboratory revealed small but important non-linearities. The data in Table 4.1 were obtained by reading the ordinate and abscissa for each plotted point from Figure 4.1 since the tabulated raw data were not available. Since the earlier British analyses (Wells, 1988) had employed only linear fits to the data to estimate dose, we performed additional analyses.

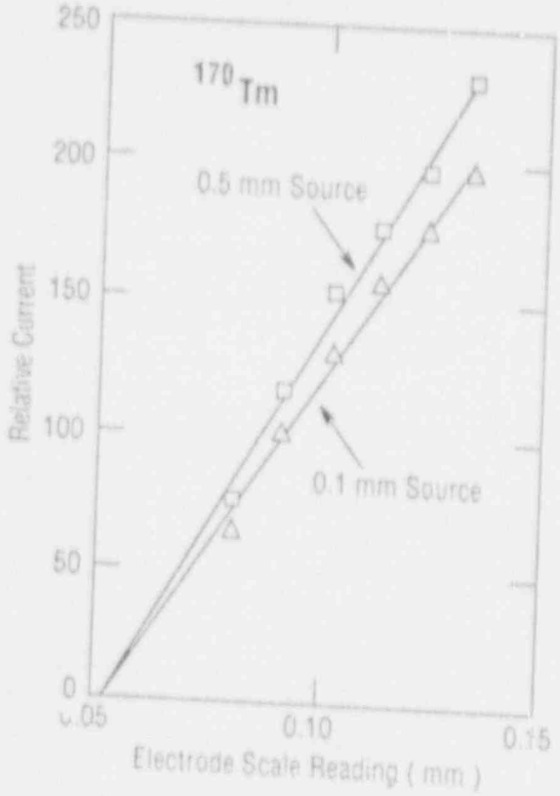

Figure 4.1. Linear fits to extrapolation chamber data for "0.1 mm" (0.0051-mm^2 triangle) and "0.5 mm" (0.132-mm^2 hexagon) Tm-170 sources used by Hopewell et al. (1986). Scale reading reflects changes in electrode separation, the intercept on the abscissa represents zero separation of electrodes.

Table 4.1 Extrapolation Chamber Data Deduced from Plot Supplied by M. Charles

Electrode Position (mm)	Current	
	0.005 mm^2 triangle	0.132 mm^2 hexagon
0.08	65	75
0.09	101	115
0.10	129	151.5
0.11	155	175
0.12	176	198
0.13	198	230

First, second, and third degree polynomials were fitted to these data using the Grapher software routines (Golden Software V 1.75, 1987); the results are displayed in Figures 4.1, 4.2 and 4.3, respectively. The "0.1-mm" source was actually triangular (tri.) in shape and had an area of 0.0051 mm^2, whereas the "0.5-mm" source approximated a hexagon (hex.) with a 0.132-mm^2 area. Slopes of these fitted curves at the intercept on the x-axis were obtained by solving each equation to determine the intercept, and then taking the differential of each equation to determine the slope at that value of the intercept. The slope ratios for the quadratic to linear, and cubic to linear fits are shown in Table 4.2. These ratios are, in effect, corrections that may be needed to correct for the non-linear nature of the extrapolation curves for the published data of Hopewell et al. (1986). An even larger correction may result when the Tm-170 doses are re-evaluated, as suggested by the following discussion of the 1-mm Sr-Y-90 source and related dosimetry.

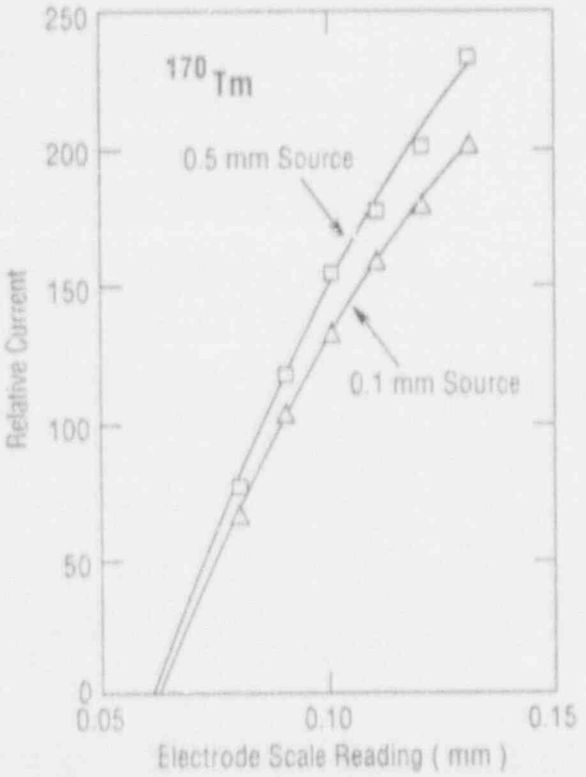

Figure 4.2. Quadratic fits to Tm-170 extrapolation chamber data.

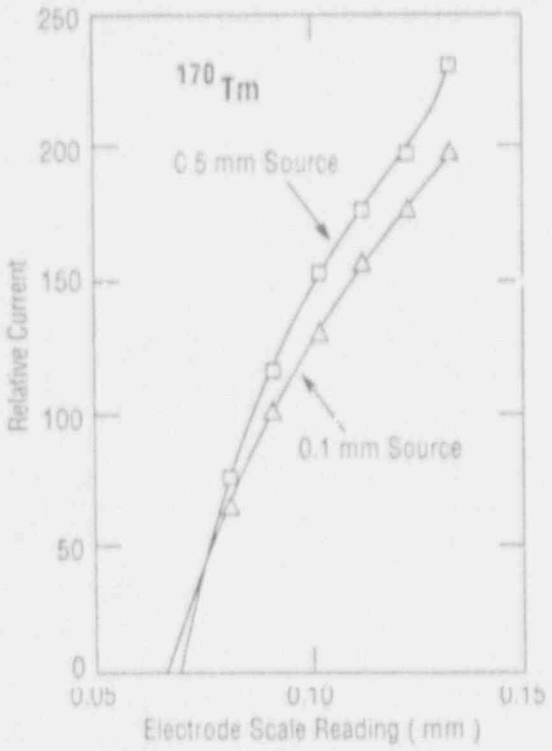

Figure 4.3 Cubic fits to Tm-170 extrapolation chamber data.

Table 4.2 Results of Polynomial Fits to British Extrapolation Chamber Data for Tm-170 Sources

Source	Quadratic/Linear	Cubic/Linear
0.1 mm (tri.)	4101/2617 = 1.6	5346/2617 = 2.0
0.5 mm (hex.)	4456/2993 = 1.5	7538/2993 = 2.5

Results of the quadratic fit to the data show approximately 1.5 and 1.6 times larger doses than those reported should be attributed to the 0.1- and 0.5-mm sources, respectively. The cubic fits yield even larger corrections by a factor of approximately 2.0 to 2.5. A theoretical analysis to determine the expected shape of the extrapolation chamber characteristic curve is in progress at Brookhaven National Laboratory. The findings will be used to judge the best function for fitting the above data and similar future data. The sensitivity of results to the size of the source and collecting electrode, and to the distance between the effective center of the source and the extrapolation chamber window will be studied also.

The Tm-170 sources used by Hopewell et al. have now decayed; however, additional dosimetric studies were made on the 1-mm diameter Sr-Y-90 source employed in Hopewell's

studies to further test the possibility that the data for this source was also in error. These studies are briefly summarized below and will be reported in detail in other publications[13,14].

5. DOSIMETRY OF BRITISH SOURCES USING RADIOCHROMIC DYE FILM

Radiochromic dye film (Gafchromic)® manufactured by GAF Chemicals Corporation (Wayne, NJ), consists of a colorless, transparent,100-μm thick polyester base, coated with a very thin layer (≈6 μm) of colorless, transparent dye. The film produces a very fine-grain, blue image when exposed to ionizing radiation such as electrons and photons. Results obtained using this technique are thought to be accurate because (a) the film has a highly uniform radiochromic dye coating, well established reproducibility of results from repeat readings on individual samples, and dose-rate independence (Saylor et al., 1988); (b) dye films exposed to known x-radiation at Berkeley Nuclear Laboratories in Berkeley, England, at approximately the same time as the Sr-Y-90 exposures, confirmed the accuracy and stability of the system; and (c) there was good agreement between the dye film and extrapolation chamber measurements made on 176- to 277-μm diameter Co-60 particles (McWilliams et al., 1990).[15]

In collaboration with C. Soares at the National Institute of Standards and Technology (NIST) in Gaithersburg, Maryland, and with M. Charles and P. Darley at Berkeley Nuclear Laboratories, 1-cm squares of this film were obtained from NIST, exposed, and subsequently evaluated at NIST using a scanning laser densitometer with an automated 633-nm beam set to read out at either 0.12-mm or 0.2-mm increments. Because the film tends to saturate at doses above approximately 1.5 kGy, both 2-minute and 4-minute exposures were made using the British Sr-Y-90 source employed in the Hopewell et al. studies (source number T13510). This is a 1-mm diameter "point" source manufactured by the Amersham Corporation in England. The radioactive material is incorporated in a 1-mm diameter glass bead and sealed in a 2.0-mm diameter welded stainless-steel capsule with a 50-μm (40 mg/cm^2) thick stainless-steel window. It is typical of small sources used in applicators in medical therapy. When the dye film was exposed, the source had decayed to a nominal dose rate of 0.79 Gy/s, averaged over 1.1 mm^2, at the 16-μm depth of the chamber window, as determined from the earlier British extrapolation chamber measurements, and the 29.1 year half-life of Sr-Y-90.

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[13]Darley, P.J., Coley, M., Wells, J., Charles, M.W., Hart, C.D., "Dosimetry of Planar and Punctiform Beta Sources Using an Automated Extrapolation Chamber and Radiochromic Dye Films," Presented at the Workshop on Skin Dosimetry, Radiological Protection Aspects of Skin Irradiation, Dublin, May 13-15, 1991.

[14]Soares, C.G., Darley, P., Charles, M.W., and Baum, J.W., "Hot Particle Dosimetry Using Extrapolation Chambers and Radiochromic Foils," Presented at the Workshop on Skin Dosimetry, Radiological Protection Aspects of Skin Irradiation, Dublin, May 13-15, 1991.

[15]"Hot Particle Dosimetry Using Micron Size Co-60 Spheres," McWilliams, F.F., Scannell, M.J., Chabot, G.E., Lorenzen, W.A., Coursey, B., Soares, C., McLaughlin, W., and Walker, M., Presented at the New England Chapter of the Health Physics Society Beta Dosimetry/Hot Particle Workshop, March 27, 1990.

Exposures were performed by P. Darley and M.W. Charles at Berkeley Nuclear Laboratories. Figure 5.1 illustrates the arrangement for irradiation. Five radiochromic dye films, numbered n through n+4, were positioned under the source, separated from it by a 16-μm thick aluminized Mylar® sheet which represented the Mylar® window employed in the extrapolation chamber measurements. The aluminum coating on the Mylar® was facing the dye film, simulating exposures in the extrapolation chamber measurements. Radiochromic dye films were positioned with the dye facing upward in each case. A 1-mm thick Perspex® plastic sheet was placed between dye films n+2 and n+3 in order to measure dose at deeper dermal depths, and for comparisons with extrapolation chamber and calculated depth-dose data. A 10-mm thick Perspex® sheet was placed under the last dye film to simulate the backscattering present in the extrapolation chamber measurements. The results from these measurements are summarized in Table 5.1. Depths of measurement were estimated, assuming that each film had a 100-μm thick base and a 6-μm thick dye coating. The film in position n yielded values 3.3 times higher than that reported for the extrapolation chamber. The ratio of dose measured with radiochromic dye film averaged over 1.1 mm^2, compared to that measured over 1 cm^2 at an average depth of 19 μm was a factor of 41. This value compared to a factor of 18 as determined from the measurements by the British at approximately the same depth using their extrapolation chamber (Wells, 1988; Charles, 1990).

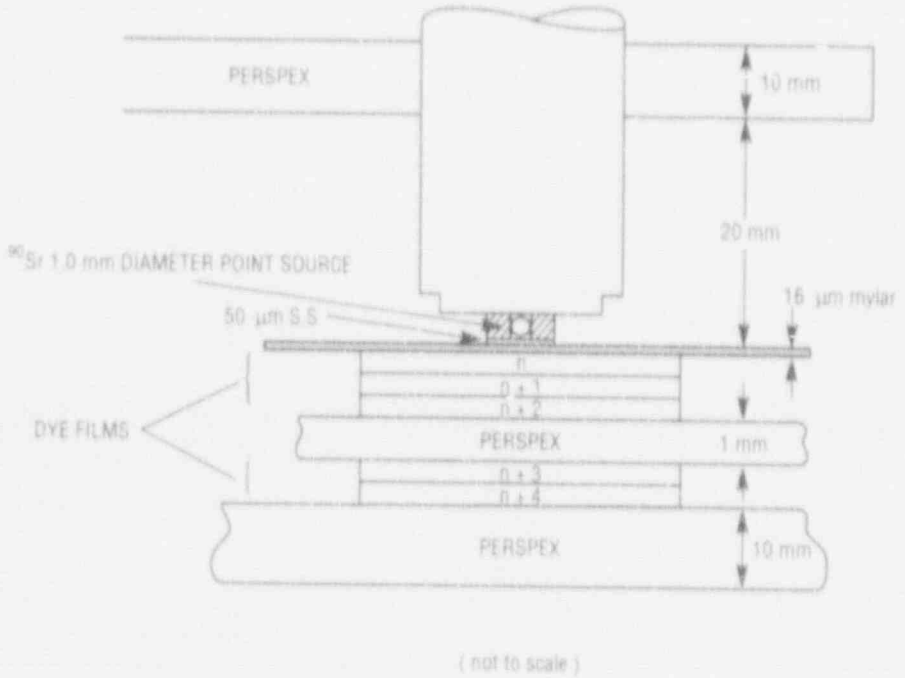

Figure 5.1. Experimental arrangement for exposures of Gafchromic® film to 1-mm diameter Sr-Y-90 point source.

Table 5.1. Results from Radiochromic Dye Film Dosimetry Study of British 1-mm Sr-Y-90 "Point" Source

Film Position	Depth (μm)	Dye Film 1.1-mm^2 Area Average Dose Rate (Gy/s)	(Relative to Extrapolation Chamber*)	Dye Film 1-cm^2 Area Average Dose Rate (Gy/s)	(Relative to Extrapolation Chamber*)	19-μm depth, (1.1-mm^2 dose rate) ÷ (1-cm^2 dose rate)**
N	19	2.58	(3.3)	0.0629	(0.079)	41
N + 1	125	1.78	(2.3)	0.0549	(0.069)	47
N + 2	231	1.35	(1.7)	0.0467	(0.059)	55
N + 3	1,337	0.190	(0.33)	0.0237	(0.030)	199
N + 4	1,443	0.173	(0.30)	0.0227	(0.029)	114

*Extrapolation chamber dose rate at 16-μm depth corrected for decay = 0.79 Gy/s (Personal communication, Charles, 1990).

**This ratio provides a factor that may be used to obtain dose averaged over 1 cm^2 at various depths from a measurement obtained with the extrapolation chamber, which measures dose rate averaged over 1.1 mm^2 at 16-μm depth.

6. REASSESSMENT OF HOPEWELL ET AL. DATA ON ACUTE ULCERATION

The results of the British studies were summarized recently (Hopewell, 1990; Charles, 1990). Charles analyzed the British biological data and tabulated the doses for 50% (ED_{50}) and 10% (ED_{10}) probability of acute ulceration. These doses are summarized in columns 2 and 3 of Table 6.1 for the Sr-Y-90 and Tm-170 sources ≤ 2 mm in diameter. Charles suggested establishing a 'practical' threshold of two-thirds of the ED_{10} doses. We calculated these doses as shown in column 4 of Table 6.1. To determine the approximate probability of ulceration associated with these doses, normal probability distributions were assumed and differences between the given ED_{50} and ED_{10} doses were used to deduce standard deviations, and, from these values, $ED_{2.5}$ and ED_5 doses were determined. The results for ED_5 are shown in column 5 of Table 6.1. The doses for two-thirds of ED_{10} agree well with the calculated ED_5 doses for 0.1, 0.5 and 1-mm diameter Tm-170 data but differ by approximately 30% for both the 2-mm diameter Sr-Y-90 and Tm-170 sources. Because the ED_5 derived dose has a known statistical basis, we employed it as a more appropriate practical threshold (than 2/3 of ED_{10}) for the 1-mm diameter Sr-Y-90 source. This value, corrected for radiochromic dye dosimetry (a factor of 3.3), is 210 Gy (63 from Table 6.1 x 3.3 from Table 5.1 then rounded to two significant figures) based on dose at 19-μm depth in tissue, averaged over 1.1 mm^2; or 1.9 Gy averaged over 1 cm^2 at 1.33-mm depth (210 ÷ 109 from Table 5.1).

The VARSKIN code (Traub et al., 1987) was used to estimate the number of beta particles required from a point source on skin to produce these doses in tissue. However, because the VARSKIN code is based on doses produced at various depths in an infinite medium, a correction was applied to provide a better estimate for the case of a point source with air, rather than tissue or water, as the backscattering medium. The data of Cross (1990)[16] indicate that the dose from a 0.5 to 3 MeV beta particle source at an air/tissue interface will be approximately 0.74 to 0.76 of that in an infinite condensed medium (e.g., solid). Also, the plastics employed as absorbers in the dye film studies have a density of approximately 1.2. Therefore, the dose measured at 1.33 mm-depth in plastic was approximately 5 to 10% lower than would be expected in tissue at the same depth due to the greater density thickness at this depth (approximately 150 mg/cm^2 vs. 133 mg/cm^2). This correction for density was applied to doses measured at 1.33-mm depth, but it was small (and therefore, neglected) for doses at the 19- and 125-μm depths as shown in Table 6.2. The resulting conversion factors and predicted threshold doses and beta particle emissions are a strong function of assumed critical depth, varying from 6.6×10^9 beta particles for dose measured at 19 μm depth to 3.1×10^{10} for dose measured at 1.33-mm depth (Table 6.2). The differences are due to the differences in depth dose patterns for point vs. actual sources located on or near the skin, respectively.

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[16] "Beta-Ray Depth Dose Distributions from Incident Beams and Skin Contamination," Cross, W.G., Wong, P.Y., and Freedman, N.O., paper presented at the 35th Health Physics Society Annual Meeting, Anaheim, CA, June 1990.

Table 6.1 Doses Associated with Selected Probabilities of Acute Ulceration Based on Data of Hopewell et al., 1986, and Charles, 1990.

Source	1.1-mm^2 Dose (Gy)* at 16-μm Depth			
(1)	(2) ED_{50}	(3) ED_{10}	(4) 2/3 ED_{10}	(5) ED_5 (Uncorrected)
Tm-170				
0.1 mm	197	85.7	57	56
0.5 mm	339	147	98	95
1 mm	202	87.7	58	57
2 mm	179	77.7	52	68
Sr-Y-90				
1 mm	253**	104	69	63
2 mm	119	82	55	72

*The 1-mm diameter Sr-Y-90 values need to be adjusted upward by a factor of 3.3 based on dye-film studies. Corrections for Tm-170 are likely to be of the same order.

**This value was incorrectly given as 353 in Charles, 1990 (Personal communication, Charles, 1991).

Table 6.2 Threshold Number of Beta Particles and Doses Deduced from Hopewell's 1-mm Diameter Sr-Y-90 Exposures and Corrected (Dye Film) Dosimetry Results.

	Depth in Tissue		
	19 μm	125 μm	1.33 mm
Threshold Dose Avg. over 1.1 mm^2 (Gy)	210	144	15 (17)**
Beta Particles* per Gy for 1.1 mm^2 Area Dose	1.8×10^7	5.1×10^7	2.0×10^9
Threshold No. of Beta Particles* Based on 1.1 mm^2 Area Dose	3.8×10^9	7.4×10^9	3.3×10^{10}
Threshold Dose Avg. over 1 cm^2 (Gy)	5.1	4.4	1.9 (2.1)**
Beta Particles* per Gy for 1 cm^2 Area Dose	1.3×10^9	2.8×10^9	1.5×10^{10}
Threshold No. of Beta Particles* Based on 1 cm^2 Area Dose	6.6×10^9	1.2×10^{10}	3.1×10^{10}

*Number of beta particles from a point source on the skin.
**Doses in parentheses are those estimated from measurements using dye film. Increased by 10% for the 1.1-mm^2 area dose and by 5% for the 1-cm^2 area dose to compensate for the lower density and attenuation of tissue of unit density relative to that of the plastic material used in the experimental setup. These tissue doses were then used to estimate threshold (ED_s) number of beta particles.

Using doses measured at 19-μm depth, the estimated number of beta particles at the ulceration threshold for a point source on skin is 3.8×10^9 for dose averaged over 1.1 mm^2 (210 Gy), and 6.6×10^9 for dose averaged over 1 cm^2 (5.1 Gy). However, when the dose measured at 1.33-mm depth in tissue is used to estimate the threshold, values of approximately 3.3 and 3.1×10^{10} beta particles are deduced for a point Sr-Y-90 source on the skin based on doses averaged over 1.1 mm^2 (17 Gy) or 1 cm^2 (2.1 Gy), respectively (Table 6.2). These numbers of beta particles are two to three times the value deduced from Forbes and Mikhail's data.

The 1.1-mm^2 area average threshold doses at 16 μm reported for Tm-170 sources (see Table 6.1) are approximately the same as those for the 1-mm Sr-Y-90 source. This finding implies that the Tm-170 data are in agreement with the Sr-Y-90 data, however, the Tm-170 sources were only 0.1-mm thick and may need significant corrections for dosimetry as discussed in Section 4. The ratio of dose at 16-μm depth to that at 1.33 mm, and the results from the extrapolation chamber measurements, would be very sensitive to the distance of the source from the skin or from the extrapolation chamber window, especially for the Tm-170 sources. For this reason, we can draw no firm conclusions about the threshold number of beta particles for induction of ulcers by the Tm-170 sources until new dosimetry studies that better define the dose and its spatial distribution have been completed. Also, the 1-mm diameter Sr-Y-90 source was not an ideal simulation of a hot particle on the skin because it was a 1-mm diameter glass bead located in a stainless steel rod having 0.5-mm thick side walls and a 50-μm thick steel window. The side walls tended to collimate the source, and the source's effective center was farther from the skin surface than for a smaller particle on the skin. These factors may contribute to the apparent differences between predicted thresholds from Forbes and Mikhail's data (threshold = 1.2×10^{10} Sr-Y-90 beta particles) vs. those from Hopewell's data (threshold 3.1 - 3.3 x 10^{10} Sr-Y-90 beta particles) based on the dose at 1.33 mm depth criterion.

7. "POINT" DOSE, "AREA" DOSE, AND BETA EMISSION FROM PARTICLES

Dose has been expressed in several different but related ways in various studies reviewed. This difference has often led to serious misunderstandings. For example, it was stated before a meeting of the Subcommittee on Occupational and Environmental Protection of the Advisory Committee on Reactor Safeguards (U.S. NRC, 1989) that because ulcers were not produced in the recent PNL studies funded by EPRI using 3-mm and 11-mm diameter sources with exposures of approximately 3,500 to 3,600 μCi-hr (50×10^{10} βs), or doses of 220 to 430 Gy averaged over 1 cm^2, no such effects could be expected from smaller sources. In fact, the opposite is true as was shown at the same meeting by Baum. That is, smaller doses averaged over 1 cm^2 and a smaller number of beta particles are required to produce ulcers (or acute tissue breakdown) if given by smaller sources (e.g., 0.1- to 1-mm diameter) than if given by larger (e.g., 3- to 19-mm diameter) sources. The absence of questions, comments, and discussion on this very important issue, indicated that there may have been a lack of appreciation or understanding of this apparent contradiction. Therefore, the following discussion has been included.

The point is clearly illustrated by Figure 7.1 using the Tm-170 data of Hopewell et al. (1986), as summarized by Charles (1990). The doses are shown that are required to produce acute tissue breakdown with 10% probability from Tm-170 (0.967 MeV maximum beta particle energy). As discussed earlier, Charles estimated threshold doses as 2/3 the dose for 10% probability of effect. Similar data for threshold and 50% probability could be used. This set of data is convenient because Charles (1990) tabulated the values.

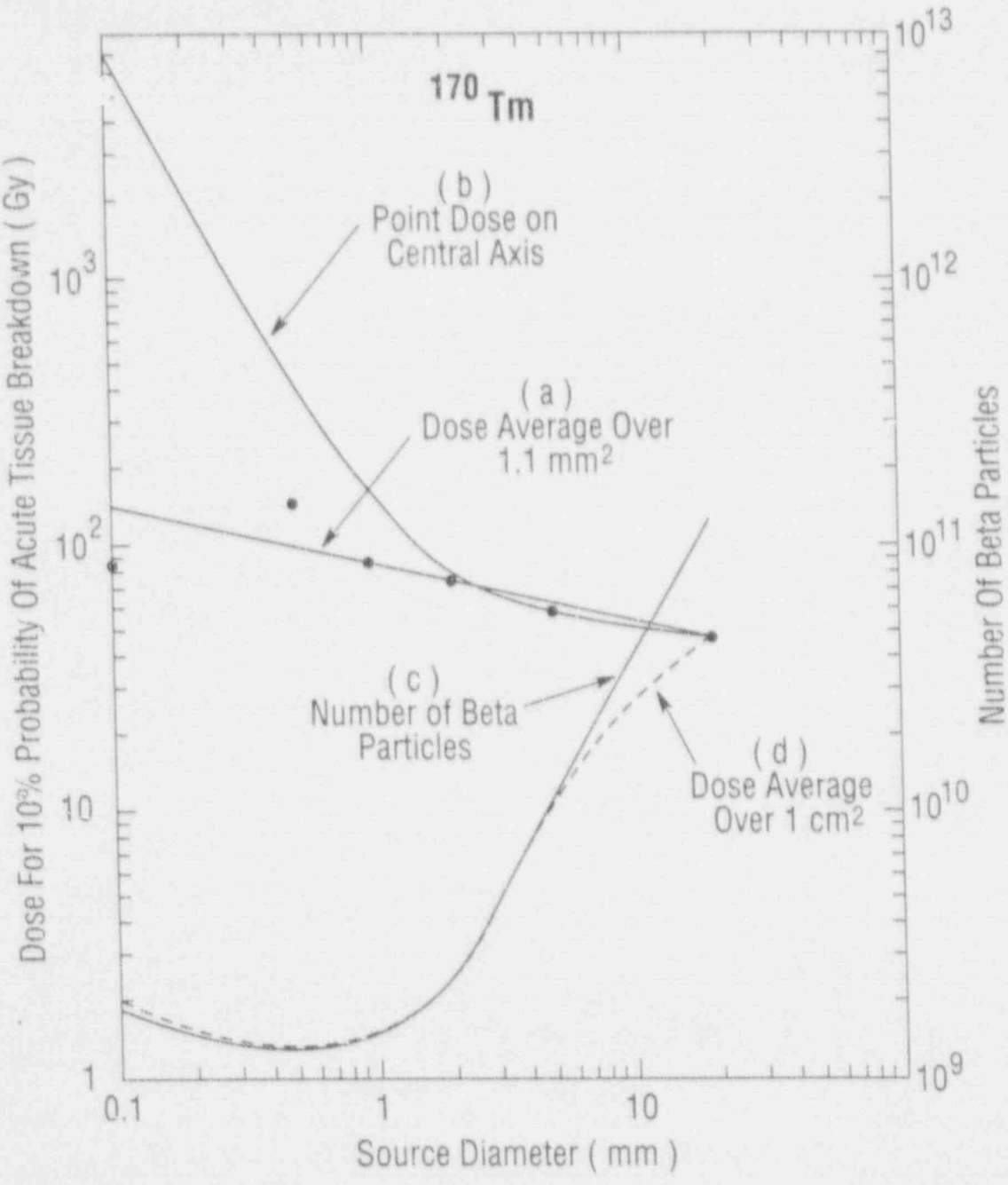

Figure 7.1. Comparison of point doses, area doses, and number of beta particles required for 10% probability of acute tissue breakdown (acute ulceration for particles ≤2-mm diameter and moist desquamation for larger particle sizes) due to exposure to Tm-170 beta particles. Curve (a) from data points (•) of Hopewell et al. (1986) summarized by Charles (1990). Curves (b), (c) and (d) calculated values corresponding to curve (a).

For the experiments of Hopewell et al., doses were measured using the extrapolation chamber discussed above, with a 16-μm thick window and a 1.2-mm diameter (1.1-mm^2 area) collecting electrode. For comparisons, central axis (point) doses, doses averaged over 1.1 mm^2, and doses averaged over 1 cm^2 were calculated for Tm-170 sources and various diameters using the VARSKIN Code (Traub et al., 1987). This code does not adequately reflect backscatter (or lack thereof) and applies to infinitely thin disk sources. Thus, the code does not provide accurate relations between doses at various depths from sources of finite volume such those used by Hopewell et al. Nevertheless, the results are adequate to show the differences in dose vs. source diameter of concern here.

Curve (a) in Figure 7.1 shows the data points for doses averaged over 1.1 mm^2 required for 10% probability of acute ulceration as reported by Hopewell et al., with a visual, straight-line fit to this data. Curve (b) shows the central axis (point) dose at 16-μm depth that corresponds to Curve (a). We note: that curve (b) it is sloping steeply downward from left to right. These data suggest much larger point doses are required for ulcer production if sources are small.

The PNL and EPRI representatives at the ACRS meeting (U.S. NRC, 1989) expressed their doses as μCi-hr (equivalent to number of beta particles) and dose averaged over 1 cm^2 at 70-μm depth as opposed to point doses. The corresponding plots for these are shown as (c) and (d), respectively, in Figure 7.1. Both of these plots have steep slopes upward suggesting that much larger doses or number of beta particles are required as particle diameters increase from 1-mm to 19-mm diameter. This finding demonstrates very clearly and decisively that the acute effects being measured may be produced more readily by smaller particles with much less dose (averaged over 1 cm^2) and with many fewer beta particles -- 1/10 to 1/100 as few.

Finally, it should be pointed out that Hopewell et al. (1986) indicated that moist desquamation is the early effect scored in their studies for Sr-Y-90 and Tm-170 sources with diameters 5 to 40 mm. When doses are approximately ED_{100} values ($\sim$ 100% probability of acute tissue breakdown), "...moist desquamation may progress to ulceration in a proportion of the irradiated fields..." (Hamlet et al., 1986). "For doses > 600 Gy all the areas irradiated develop acute ulceration, the diameter of the ulcers increasing with increasing dose..." (Hopewell, 1990). This 600 Gy dose refers to dose at 16-μm depth averaged over 1.1 mm^2. The corresponding doses averaged over 1 cm^2 would be approximately 40 Gy for a 3-mm diameter particle and approximately 300 Gy for an 11-mm diameter particle, or perhaps 1.5 to four times these values if extrapolation chamber dosimetry corrections are needed for these larger sources. Thus, the Sr-Y-90 doses (250 Gy for 3-mm diameter and 240 Gy for 11-mm diameter sources) given in the unpublished PNL study (U.S. NRC, 1989) are expected to produce moist desquamation for both source sizes. This event will likely be followed by the development of ulcers for the 3-mm diameter sources and, possibly, also the 11-mm diameter sources. However, the equivalent number of beta particles would be greatly in excess of the number required for ulceration (as opposed to moist desquamation followed by ulceration) if the beta particles had come from much smaller sources, as can be seen from Figure 7.1.

8. DISCUSSION

The regression analyses of Forbes and Mikhail's data described above are interpreted by us as indicating a "threshold" (<5% probability of any ulcer) of approximately 6 x 10^9 fission-product beta particles, based on regressions of ulcer area vs. dose at the ulcer radius and 1.33-mm depth in tissue. Because the regressions with dose at 1.33-mm depth yielded more

consistent predictions (item 16 in Table 3.2) for both 150-μm and 300-μm particle sizes than a similar regression at 100-μm depth (item 14 in Table 3.2), it seems likely that ulceration may involve damage to vascular dermal tissue lying deeper than 1 mm in tissue. This conclusion would be consistent with the findings of Moritz and Henriques (1952), in which ulcers were produced by medium- to high-energy beta rays but could not be produced by sulfur-35 beta particles, and those of Hopewell et al. (1986), in which ulcers were produced by Tm-170 and S-Y-90 beta particles, but not by Pm-147 beta particles. The maximum penetration of sulfur beta particles is approximately 300 μm in unit density tissue, and that for Pm-147 is approximately 560 μm. In electron beam studies, Albert et al. (1967) found that the surface dose necessary to produce ulceration in the skin of rats varied inversely with the electron beam energy. The average maximum depth of the hair follicles in the rat was 0.23 to 0.3 mm. Doses required at this depth below the skin to produce ulceration were 15 to 20 Gy. The somewhat larger dose (27 Gy) at greater depth (1.33 mm) in pig skin implied by the above analysis may reflect the greater depth of vascular tissue and of hair follicle canals in both human and pig skin. The large variability in dose associated with the induction of small (e.g., 0.5-mm diameter) ulcers, illustrated in Figure 3.3, may reflect the influence of (presence or lack of) hair follicles in the repair process in the local area irradiated by small particles, as well as variations in dosimetry, exposure, and observational factors.

The threshold deduced from Forbes and Mikhail's data by the NCRP was 3.3×10^{10} beta particles emitted in the source. This value was reduced to a recommended limit of 10^{10} beta particles for point sources on the skin, which would give approximately the same point dose at 100-μm depth as produced by a particle located at the center of a 150-μm diameter sphere emitting 3.3×10^{10} particles. The difference was due to the geometric ($1/r^2$) factor. Self-absorption (~ 20%) in the particle was neglected.

The very sharp drop from 100% probability to zero incidence for the data of Dean et al. (1970) on the monkey, as shown by the dotted line in Figure 1.1, is in contrast to the more normal sigmoid shape of the response as shown by the solid line in this Figure for the much larger sets of data of Hopewell et al. for particles ≤ 1-mm diameter. A broader range of exposures bracketing the ulcer threshold is needed in order to define an ED_5 probability from Forbes and Mikhail's studies.

The Hopewell experiments were much more extensive than either that of Forbes and Mikhail (which included no data points below threshold) or that of Dean et al. In the Hopewell studies, approximately 17 exposures were made at each dose level, and dose-response data were obtained over the entire range of doses from threshold (zero response) to 100% response. Thus, the sharp drop from 100% to zero incidence in the two smaller studies probably reflects the lack of statistical robustness of the data. A gradual increase in probability is also expected based on the variability of the Forbes and Mikhail data shown in Figure 3.3, which shows a factor of 2.4 spread in dose for the four data points with smallest ulcer area (0.5-mm diameter). The relative standard deviation of dose or number of beta particles required to produce 0.5-mm diameter ulcers is ± 45%. This deviation in dose does not indicate a sharp drop to a threshold.

The three data points of Dean et al. from monkeys and the three data points from humans that show no ulcers provide only very weak indications of the likely lower limit for a threshold; however, the four sets of data -- and, in particular, those of Hopewell et al. based on several hundred exposure points and three different energies -- provide reasonable assurance that a limit of 75 μCi-hr (10^{10} beta particles) is not likely to cause ulcers at either significant frequencies or of significant size. However, additional studies of

dosimetry and radiobiology are needed to better define the probability of ulcer formation by fission product beta particles in the range of 10^9 to 3×10^{10} beta particles from point sources on skin, and also to normalize both the Forbes and Mikhail and the Hopewell et al. studies to better defined dosimetry.

If the criterion of point dose (e.g., 27 Gy as deduced in section 3.5) at 1.33-mm depth at ulcer radius is generally applicable, then this criterion expressed in terms of number of beta particles should follow the trend vs. beta particle energy shown in Figure 4.1 of NCRP Report 106. The approximate number of Y-90 beta particles required from a point source on the skin to produce a point dose of 27 Gy at 1.33-mm depth in tissue is estimated at 2.4×10^{10}, based on output from the VARSKIN Code (Traub et al., 1987), adjusted by a factor of 1.3^{16} for backscatter effects not adequately taken into account in VARSKIN. Approximately 1.9 times this number of beta particles would be needed from a Sr-Y-90 source because few of the lower energy beta particles from Sr-90 would reach this depth in tissue. As can be judged from Figure 4.1 of NCRP Report 106, a much larger number of beta particles emitted would be acceptable at energies below approximately 0.8 MeV maximum beta particle energy; for photon emitters, there may be a transfer of risk from beta dose to that from photon dose for maximum β particle energies below approximately 0.4 MeV. Thus, a dose expressed as the number of beta particles from a hot particle, or as beta particle dose averaged over 1 cm^2 at 70-μm depth in tissue, is probably a conservative criterion regarding ulcer induction for beta particles with maximum energies below 0.8 MeV.

The model with 1.33-mm depth in tissue as the relevant point for threshold dose determination would predict that approximately equal numbers of beta particles would be needed at threshold from a Sr-Y-90 point source or a similar Tm-170 source on the skin. This similarity results from a predicted absorption at depths in tissue of 1.33 mm of nearly all the Sr-90, only approximately 30% of the Y-90, and approximately 50% of the Tm-170 beta particles. These attenuation factors are based on tables given by Berger (1971).

9. RESEARCH NEEDS

Our assessments reveal several weaknesses and sources of uncertainty in the data on thresholds for acute effects from hot particles on the skin. In the biological area, questions remain on the critical depth for ulcer induction. Is the 1.33-mm depth employed in the model used here applicable for all beta particle energies? If so, a hot particle emitting beta particles with maximum energy of $\leq$ approximately 0.4 MeV should not produce acute ulceration, and an emitter such as Rh-106 with a maximum energy of 3.45 MeV may have a threshold (expressed as number of beta particles) only a third of that for Sr-Y-90, because of the greater penetration of the higher energy beta particles. Therefore, tests of the effectiveness of ulcer production vs. maximum beta particle energy are needed to better define the threshold and the way in which biological effects vary with particle energy.

It is also important to determine if sources off of the skin, e.g., on clothing or hair, are less effective per beta particle emitted, as implied by the data plotted in Figure 7.1. Particles off the skin would tend to spread absorbed energy over larger areas. This should cause a response similar to that from a larger area source with the same emission. Acute tissue breakdown should then require a greater number of beta emissions from the source than would be needed from a particle on the skin. Experimental verification of this prediction is needed.

The depth and persistence of ulcers as a function of dose are of interest because they relate to probability of infection and scarring which may be measures of detriment and may

influence possible weighting factors for acute ulceration if deterministic and stochastic risks are to be compared or summed. Other similar regulatory issues are the risk-related relations between the dose limits for hot particles and the limits for larger area skin exposures. What is the depth, area, or volume over which dose should be averaged? What are the relationships between dose averaged over 1 cm^2 and number of beta particles emitted from various source geometries and locations (on or off the skin) for the same effect (e.g. acute ulceration)? Additional attention should also be given to the effects of particles in the eye, ear, nose, throat, gastrointestinal tract, or lung tissues. How do detriments expected in these cases compare to those for particles on skin?

The data of Ulberg and Kochendorfer (1966) for UC_2 particles of 90- to 260-μm diameter, on measured doses at 0.7-mm depth in tissue-equivalent material differ from calculated values by factors of 4 to 5 for decay times of 250 hours. Additional measurements are needed to resolve these differences and, if necessary, modify the computer codes used for calculations in hot particle studies and risk assessments. Additional experimental work is also needed to resolve the large differences in dose between results from extrapolation chamber and dye-film measurements.

We are continuing to study several of these problems. Specifically, we plan to expose pig skin on live animals to sources of activated UC_2 spheres having a 250-μm diameter to validate and extend to lower doses the work of Forbes and Mikhail. Exposures using particles of Tm-170 are planned for comparison with work of Hopewell et al. and to study the energy dependence of the threshold for ulceration. A set of exposures using lower energy (0.6 to 0.4 MeV) beta particles also is planned to better define the energy dependence of ulcer induction. In addition, experimental studies of the effectiveness of beta particles emitted by particles (a) separated from skin by 0.4-mm thick denim, and (b) approximately 1 mm off the skin are planned.

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APPENDIX A

Statistical Analysis of Forbes and Mikhail Data

The regression line which fits the data the best is given by

$$y = a + bx$$

where

a = y intercept
b = the slope

The y intercept and slope are calculated using

$$a = \frac{1}{\Delta}\left(\sum_{i=1}^{n} x_i^2 \sum_{i=1}^{n} y_i - \sum_{i=1}^{n} x_i \sum_{i=1}^{n} x_i y_i\right)$$

$$b = \frac{1}{\Delta}\left(n\sum_{i=1}^{n} x_i y_i - \sum_{i=1}^{n} x_i \sum_{i=1}^{n} y_i\right)$$

$$\Delta = n\sum_{i=1}^{n} x_i^2 - \left(\sum_{i=1}^{n} x_i\right)^2$$

where

$x_i y_i$	=	each data point
n	=	the number of data points

(Bevington, 1969, p. 104).

The standard deviation of the regression, s, is given by

$$s^2 = \frac{SSE}{n-2}$$

$$SSE = \sum_{i=1}^{n} (y_i-(a+bx_i))^2 = S_{yy}-bS_{xy}$$

$$S_{yy} = \sum_{i=1}^{n} (y_i-\bar{y})^2 = \sum_{i=1}^{n} y_i^2 - \frac{\left(\sum_{i=1}^{n} y_i\right)^2}{n}$$

$$S_{xx} = \sum_{i=1}^{n} (x_i-\bar{x})^2 = \sum_{i=1}^{n} x_i^2 - \frac{\left(\sum_{i=1}^{n} x_i\right)^2}{n}$$

$$S_{xy} = \sum_{i=1}^{n} (x_i-\bar{x})(y_i-\bar{y}) = \sum_{i=1}^{n} x_i y_i - \frac{\left(\sum_{i=1}^{n} x_i\right)\left(\sum_{i=1}^{n} y_i\right)}{n}$$

The standard deviation of the slope, s_b, and the y intercept, s_a, are calculated using

$$s_b^2 = \frac{s^2}{S_{xx}}$$

$$s_a^2 = \frac{\sum_{i=1}^{n} x_i^2}{nS_{xx}} s^2$$

(Walpole, 1978, pp. 286, 287).

The standard deviation of the regression, s, and the standard deviation of the regression slope, s_b, were calculated using predefined functions of the spreadsheet software package, Quattro Pro. The standard deviation of the regression intercept, s_a, was calculated from previously given equations using the same spreadsheet.

The independent axis intercept, z (threshold dose or number of betas), was calculated using

$$z = \frac{-a}{b} \quad \textit{for linear regressions}$$

$$= e^{\frac{-a}{b}} \quad \textit{for natural log transformed regressions}$$

$$= 10^{\frac{-a}{b}} \quad \textit{for common log transformed regressions}$$

The standard deviation of z, s_z, was determined using the standard error propagation formula (Bevington, p. 113).

$$s_z^2 = \sum_{i=1}^{n} \left[s_i^2 \left(\frac{\partial z}{\partial y_i} \right)^2 \right]$$

where

z	=	equation to determine the intercept, a
s_z	=	standard deviation of the parameter determined by z
i	=	data point index
s_i	=	standard deviation of the i^{th} data point
	=	s (assumed)
y_i	=	y value for the i^{th} data point

This formula yields

$$s_z^2 = \frac{s^2}{b^2\Delta}\left(\sum x_i^2 + 2\frac{a}{b}\sum x_i + \frac{a^2}{b^2}n\right)$$

for the linear data regression.

The standard deviation of the independent axis intercept for the natural log transformed data yielded

$$s_z^2 = \left[\frac{s^2}{b^2\Delta}\left(\sum x_i^2 + 2\frac{a}{b}\sum x_i + \frac{a^2}{b^2}n\right)\right] e^{-\frac{2a}{b}}$$

The standard deviation of the independent axis intercept for the common log transformed data is similar to that for the natural log transformed data, except that "e" is replaced with "10".

The "R^2" value in Table 3.2 is also called the "coefficient of determination" and is the square of the correlation coefficient, ρ, where

$$R^2 = \rho^2 = \frac{S_{xy}^2}{S_{xx}S_{yy}}$$

(14)

(Ott and Mendenhall, 85, pp. 316-319). This statistic was used to determine which regression model best fit the data. A zero R^2 value indicates no predictable linear relationship between the independent and dependent variables. This was desired in items 12, 15, and 16 of Table 3.2 because the dose at the radius of the ulcer should vary randomly about some mean value (Figure 3.4).

The R^2 value, as with the correlation coefficient, can not be used to prove or disprove the model presented, as the ulcer sizes and doses that produced them do not constitute a bivariate normal distribution, and a causal relationship between the two was known to exist (Arni, 1971). The R^2 value was used as a tool for determining which model approximated the data the best.

Repeated Measurements

It should be mentioned that if the errors for each data point are not independent, then repeated measurements may bias s (Walpole and Myers, 1978, pp. 298-299). If repeated measurements are made for all data points, then the distribution for each independent variable point can be estimated. Knowing all the distributions will provide an unbiased estimate of σ. This could not be performed with the Forbes and Mikhail data because some distributions had only 1 data point, so a standard deviation for those distributions could not be calculated without additional assumptions being made about the distribution. The linear regression performed treated each data point as an independent measurement.

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NCRP Report 106 on the effects of hot particles on the skin of pigs, monkeys, and humans was critically reviewed and reassessed. The analysis of the data of Forbes and Mikhail on the effects from activated UC_2 particles, ranging in diameter from 144 1m to 328 1m, led to the formulation of a new model to predict both the threshold for acute ulceration and for ulcer diameter. In this model, a point dose of 27 Gy at a depth of 1.33 mm in tissue will cause an ulcer with a diameter determined by the radius to which this dose extends. Application of the model to the Forbes and Mikhail data obtained with mixed fission product beta particles yielded a "threshold" (5% probability) of 6×10^9 beta particles from a point source of high energy (2.25 MeV maximum) beta particles on skin. The above model was used to predict that approximately 1.2×10^{10} beta particles from Sr-Y-90 would produce similar effects, since few Sr-90 beta particles reach 1.33 mm depth. These emissions correspond to doses at 70-1m depth in tissue of approximately 5.3 to 5.5 Gy averaged over 1 cm^2, respectively.

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