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AN ESTIMATE OF THE RISK IN RADIATION THERAPY DUE TO UNWANTED NEUTRONS*

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Zeitz correctly points out an error in my paper.[1] At the same time he takes care to emphasize that the needed correction has no effect on my main conclusion regarding accelerator-produced neutrons.

The realization that, for 25-MV X-ray treatment, a majority of the integral dose deposited by photonuclear reactions in tissue is deposited by charged hadrons rather than neutrons[2] is a welcome one. The heavy charged particles have a very limited range compared to neutrons and the related high-LET dose closely follows the dose distribution of the high energy photons of the treatment beam. If the prescribed X-ray treatment is of net benefit to the patient, then this additional photonuclear dose, although small, must also be of net benefit, unless something more subtle than geometry is involved. Although the tumor volume is much smaller than the irradiated volume, the charged particle photonuclear secondaries augment the dose by a constant fraction throughout so that they do not significantly affect the therapeutic ratio. The subtleties ignored here of course involve differing RBEs of high-LET particles as they affect the balance of injury to healthy tissue and tumor reduction.

Although it has a much larger penumbra, the dose from photoneutrons produced within the patient also approximately follows the X-ray dose distribution. Thus its harmful effects are also partly cancelled by its contribution to the treatment, especially for large fields. For

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small fields, for which most of the neutrons escape the irradiated volume, the related integral dose becomes insignificant.

New calculations by Ing et al. confirm this picture for 25-MV treatment and show that the tissue-produced neutron integral dose is even less than previously believed.[3] *Using more recent photonuclear data, together with computer programs to study the transport of both photons and neutrons, they find that neutrons produced within the patient lead to integral absorbed doses of about 0.012% of the treatment photon integral absorbed dose. This fraction is independent of field size and is less than the 0.03% inferred by Zeitz from the older work of Horsley et al. Furthermore, from the results of Ing et al. one can infer the fraction of the tissue-produced neutron integral dose which is imparted outside of the irradiated volume. This unwanted fraction is about 0.53 and 0.20 for fields of 100 and 600 cm^2, respectively. If we now multiply by the treatment photon integral dose imparted per treatment rad for these field sizes (nominally 1800 and 10800 g rad for 100 and 600 cm^2 fields, respectively), we find unwanted tissue-produced neutron integral doses outside of the irradiated volume in the range 0.1 - 0.3 g rad per treatment rad. This is insignificant compared to that of the accelerator-produced neutrons (about 4 - 6 g rad neutron integral dose per treatment rad for the average accelerator at 25 MV*[1]*) and even more insignificant when compared to the integral dose of scattered photons outside the irradiated volume. This is higher again by about two orders of magnitude.*

This corrected picture of the dose deposited by photonuclear reactions in the patient militates against the argument that higher energy photon treatment is to be shunned because of the increased risk imposed by neutrons. The effect of the accelerator-produced neutrons has been shown to be negligible for all treatment energies[1] and the unwanted integral dose of those produced in tissue is now seen to be far smaller.

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1. W. P. Swanson, Medical Phys. 7, 141 (1980). I take this opportunity to correct a copying error in the abstract. The second sentence should read "The leakage neutron component contributes about 5 g rad (1 rad = 10^{-2} Gy) per treatment rad, or 25000 g rad for a typical treatment course of 5000 rad.".

2. This is based on results of R. J. Horsley, H. E. Johns and R. N. H. Haslam, Nucleonics 11, 28 (1953).

3. H. Ing, W. R. Nelson and R. A. Shore, Stanford Linear Accelerator Center, Preprint, to be submitted for publication (1980). I thank these authors for permission to cite their work prior to its regular publication.

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ABSTRACT

The integral dose of accelerator-produced leakage neutrons to patients undergoing high-energy photon therapy is estimated and compared to other sources of integral dose. The leakage neutron component contributes about 5 g rad for a typical treatment course of 5000 rad. When averaged over a 70-kg tissue volume, the corresponding dose amounts to only 0.36 rad. From this, the risk of inducing fatal malignancies by leakage neutrons is estimated to be about 50×10^{-6} per year following treatment. This is compared to other risks to which the patient is unavoidably exposed, and it is argued that the unwanted neutrons pose such small additional risk that regulatory intervention is not warranted. This assessment is performed without reference to neutron RBE or quality factor.

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INTRODUCTION

One of the bothersome questions for radiotherapists in recent years concerns the seriousness of the risk to patients and the regulatory desiderata regarding stray neutrons from electron medical accelerators. Towards resolving these questions, a recent conference has reviewed current knowledge regarding the dose of accelerator-produced stray neutrons that accompany high-energy photon therapy.[1] Based in part on these data, this paper demonstrates that sufficient physical information is at hand to permit a reasonable estimate of the accompanying high-LET dose, averaged over body volume. Making use of a published risk coefficient for neutrons, an absolute risk assessment for an average treatment course is made directly, without invoking the concept of RBE or quality factor. It is then argued that the estimated additional risk is small compared to other risks to which the patient is unavoidably exposed. Finally, the desirability of various possible actions by regulatory agencies is discussed.

DOSE ESTIMATE

Figure 1 shows representative fluence measurements presented to the conference. The surprising variation in these data can be ascribed as much to difficulties in neutron measurement procedures as to differences in equipment design. Despite the absence of an easily recognizable trend, the consensus is that the average neutron entrance dose rises with treatment megavoltage to about 20 MeV and thereafter remains roughly constant at 0.03% (entrance neutron absorbed dose divided by treatment

dose) up to the highest therapeutic energies.[2] This refers to the neutrons outside of the treatment field. The entrance dose within the beam, also averaged over many measurements, rises to an average in the range 0.06-0.07% of treatment dose. These nominal averages, adopted for the following analysis, reflect an authoritative review of available data from real accelerator installations and include many more measurements than are shown here.[2] Because differences due to systematic error tend to cancel, the averages are better known than it would appear from the data shown and it is probably safe to say that the actual neutron entrance doses for most accelerator models operating above 20 MeV lie within a factor of two of the adopted averages.

The curves of Fig. 1 are calculated for an accelerator whose neutron-producing parts are entirely of W (or Pb, or a combination of W and Pb) and for one whose parts are all of Cu. The derivation of these curves is given by McCall and Swanson.[3] The W-curve represents the maximum possible fluence, i.e., for conditions in which the target, field flattener, shielding and movable jaws are of W (or Pb) and the jaws are (almost) closed. The nearly constant portion of the curve corresponds to 0.07% entrance neutron rad per treatment rad (for neutrons outside the useful beam)* and is therefore about a factor of two above the nominal average obtained from measurement. The calculated curves are considered to represent an "ideal" situation and do not take into account the effect of the variety of materials found in the treatment head that may alter the neutron fluence. Although the W-curve seems to overestimate

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* The fluence to entrance absorbed dose conversion factor is 3.3×10^{-9} rad neutron^{-1} cm^2, estimated from Fig. 11(b) of Ref. 3.

the actual neutron fluence it gives a better picture of the relative behavior of the fluence as a function of treatment energy than can be gained from the measurements alone. Points significantly above the W-curve of Fig. 1 are believed to be due to equipment in which the internal electron beam scrapes other components before the intended target, so there is effectively more than one neutron source for the same treatment dose.

Spectra of leakage neutrons from medical accelerators were also presented to the conference.[3,4] The median energy for photoneutrons from a bare W target was found to be about 1.5 MeV. After filtration by 10 cm of W shielding, the median energy is reduced to about 0.3-0.4 MeV, and becomes even lower ($\sim$ 0.2 MeV) if the additional effect of moderation by concrete shielding is taken into account.[3] Photoneutron spectra are not very sensitive to the energy of the primary electron beam and these median values can be regarded as representative of neutron spectra for the entire range of treatment energies for which neutron production is significant. This additional information on neutron spectra has made it possible to estimate the integral neutron dose and thereby assess the harm done by these neutrons. In what follows, calculations are given for 25 MeV, representative of the higher-energy therapy regime.

In Table I, the major sources of patient integral dose, both within and outside of the treatment field, can be compared. It is seen that the total unwanted photon integral dose is far greater than the total neutron integral dose for any field size. By far the biggest contribution is that of the useful beam traversing healthy tissue, but a substantial amount also comes from photons scattered within the patient.

The contribution of 0.1% photon leakage is quite negligible in comparison. However, these are low-LET doses and their effect on the patient is not discussed in this report; these data are shown only for perspective.

Of the three sources of neutron dose, that from neutrons produced within the patient must be regarded as an unavoidable concomitant of 25-MeV therapy.[5,6,7] The resulting high-LET dose is distributed approximately the same way as the treatment dose, but with a much larger penumbra (about 10 cm, as measured between 20 and 80% of the maximum). For large fields at 25 MeV, this dose component is much larger than the dose of neutrons from the accelerator but most of it remains within the treatment field (about 60% at 900 cm^2) and contributes to the treatment. For small fields the high-LET dose component is mainly deposited outside the treatment field but at the same time the integral dose becomes less in proportion to the smaller area. Whether this unavoidable component is "unwanted" or not at any field size depends on how it affects the therapeutic ratio. This, in turn, depends on the RBE for tumor cell killing vs. the RBE for permanent injury to healthy tissue. This neutron dose-component is very dependent on treatment energy[6] and a complete risk assessment would take all these factors into account as a function of both energy and field size. However, for the present assessment, which focuses on accelerator-produced neutrons, this is not considered further because it cannot be altered by regulating accelerator design, except by imposing a limit on the treatment energy.

The leakage neutron integral doses (inside and outside of the treatment field) are computed assuming the entrance doses quoted above and the attenuation of Fig. 11(b) of Ref. 3. The integration is performed numerically in a 30 cm diameter phantom, 100 cm long, centered perpendi-

cularly on the beam axis at 100 cm SSD and inverse-square reduction with distance is taken into account. Both categories of accelerator-produced neutron dose are regarded as "unwanted"; those outside of the treatment field provide no benefit whatever and the depth-dose distribution of those within the treatment field is not favorable for therapy. It declines much more rapidly than that of the 25 MeV photon beam and therefore is different from that prescribed by the treatment plan, giving a relatively higher dose to tissue near the surface.

The right-hand column shows that the total integral dose due to accelerator-produced neutrons amounts to about 4-6 g rad per treatment rad over a wide range of field sizes (we exclude the unavoidable component produced within the patient) and 5 g rad is taken as a nominal value. When averaged over the entire 70 kg phantom (Table II), this dose is only 0.36 rad for a 5000 rad treatment course. This surprisingly small result is of course related to the rapid falloff of the neutron dose distribution within tissue.

It is the average dose to the bone marrow that is pertinent to the risk assessment that follows, whereas the 0.36 rad of Table II is an average over the entire phantom without regard to the location of organs or their radiosensitivity. Jones[9] has derived a method of assessing the mean insult to the active bone marrow from incident neutron fluences and given his results in such a form that the dose can be obtained easily from a graph if the incident neutron energy and fluence are known. By using values of median neutron energy indicated above, together with the choices of radiation environment considered by Jones, we obtain bone-marrow doses consistent with our own estimate of 0.36 rad.* A more thorough analysis would involve folding the spectra of Refs. 3 or 4 together with Jones'

data, and would be for a specific treatment plan. In view of other uncertainties in the overall risk analysis, this is not warranted for the present assessment and the average phantom dose used here (0.36 rad from Table II) has the advantage that it can be more easily verified by the reader.

RISK ESTIMATE

In a 1978 paper, Rossi and Mays re-analyze the leukemia incidence in atomic bomb survivors at Hiroshima and Nagasaki and give quantitative estimates of the magnitude of this risk for occupational exposure to neutrons.[10] Following their argument we use the risk coefficient 28×10^{-6} leukemias yr^{-1} rad^{-1} (neutron dose to active bone marrow) to estimate 10×10^{-6} induced leukemias per year following a 5000 rad treatment course. Again following Rossi and Mays, we multiply by 5 to estimate the rate of 50×10^{-6} for all fatal malignancies induced per year following treatment.** These steps are summarized in Table II.

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* To illustrate, assume an average fluence per treatment rad of 10^5 neutrons cm^{-2} rad^{-1} (see Fig. 1 and discussion of p. 3). When multiplied by 5000 rad for the treatment course this gives a fluence of 5×10^8 neutrons cm^{-2}. Assuming 1 MeV nominal neutron energy, Fig. 8 of Ref. 9 would give 0.35 rad for an A-P, bilateral or rotational exposure. This is fortuitously close to our own estimate of 0.36 rad. Isotropic or P-A exposures of the same energy would give bone-marrow doses a factor of two above and below this, respectively. As the spectra under discussion have median energies near 1 MeV (1.5 MeV direct from a W target or 0.3-0.4 MeV filtered by W shielding) we consider the agreement good enough to confirm our own estimate, which is a simple average over phantom volume.

** Although there is considerable controversy surrounding the paper of Rossi and Mays there appears to be a consensus regarding the risk coefficient for neutrons. (See Refs. 11, 12 and 13.) The controversy is basically centered on the RBE or quality factor of neutrons and this uncertainty mainly reflects lack of knowledge of the photon risk coefficient. Neither the photon risk coefficient, nor the RBE or quality factor of neutrons is needed in the analysis presented here.

This additional risk seems small in view of the accepted detrimental effects of radiation therapy. These may be on the order of 10% if aggressive treatment is pursued.[14] Perhaps a natural comparison would be to the average incidence of leukemia, and of all malignancy for the general population. These rates are 57×10^{-6} and 2900×10^{-6} yr^{-1}, respectively, averaged over both sexes and all ages.[15] The average mortality rate due to all causes is 9500×10^{-6} yr^{-1}. But note that the average age for cancer incidence is close to 60 years. The rates for "natural" incidence of leukemia, all malignancy and mortality for the decade following treatment at age 60 are closer to 140×10^{-6}, 10000×10^{-6} and 25000×10^{-6} yr^{-1}, respectively (averaged over the general population of age 60-70). Of course these comparisons are only meant to provide a rough perspective; a complete analysis would take into account the patient's age and condition, the actual treatment plan and different assumptions regarding latencies. But for the "average" patient it is clear that the effect of accelerator-produced neutrons on the number of symptom-free years following treatment is negligible.

Making a different but related comparison, Rossi has suggested that the risk be expressed as the total cancer mortality to be expected over a "long lifetime" following exposure.[16] This corresponds to integrating the risk per year over the latency periods for all types of malignancies. Based on data published by Rossi and Mays[10] he has given an estimate of 800×10^{-6} total fatal leukemias per rad developing at any time following a neutron exposure. The mortality from solid tumors is estimated as five times this amount. When combined, the total mortality expected following neutron exposure is estimated as 4.8×10^{-3} per rad. When multiplied by

0.36 rad (from Table II) we obtain 1.7×10^{-3} per lifetime. This probability, which greatly exaggerates the risk to the average patient, is appropriate for one young enough that he or she is expected to survive a time corresponding to the latency period of all neutron-induced malignancies. It is 100 times smaller than the probability of death due to all cancers for the general population, which is 170×10^{-3} per lifetime. (The corresponding probability for the limited cohort in question, all members of which already suffer from a malignant condition, is certainly higher than this; the probability of death due to all causes is exactly 1000×10^{-3} per lifetime for all members of the general population.)

REGULATORY ACTIONS

A main purpose of the conference was to gather information to enable agencies to formulate regulations regarding this unwanted dose of accelerator-produced neutrons. However, an important point is that this dose is already "regulated" by natural effects; the W-curve of Fig. 1 represents a limit to the fluence that cannot be exceeded except by loss of electron beam before the intended target, or by the use of materials heavier than Pb. This natural limit is about a factor of two above the fluence outside the beam assumed for Table I. The substitution of a lighter material such as Cu for all of the neutron-producing components would result in about a factor of 3 reduction in neutron fluence at 25 MeV (Fig. 1). However, the effective use of accelerators for therapy requires the use of high-Z materials to produce intense, wide fields with sharp edges; the treatment beam may not have as desirable characteristics, particularly at the edge of a wide field, and there may be space

limitations if lighter materials are used. Using combinations of materials, for example Cu to shield high-Z components, may be practical, but it may be a wiser course to permit machine designers maximum flexibility in optimizing these devices towards most effective therapy rather than to limit the choice of materials. Based on the above observations, at least these suggestions come to mind in regard to possible regulatory steps:

(a) Take no action whatsoever regarding accelerator-produced neutrons.

(b) Issue a statement to the effect that, owing to the manifest smallness of the risk, no regulation regarding these neutrons is needed for photon (or electron) therapy.

(c) If a limit is desired, set it high enough so that a therapy unit containing neutron-producing components of all W or Pb would be acceptable, by some margin, under the standard. This limit should be distinct from the 0.1% limit for leakage photons.

Of these proposals, (a) and (b) have the advantage that they allow maximum flexibility for innovation and design. Proposal (b) is superior to (a) in that it would remove the present ambiguity as to whether the neutron leakage is to be included with the photon leakage, and if so, which quality factor is to be used. Proposal (c) would permit most currently available machines to be used, but would induce manufacturers to reduce stray neutrons coming from points on the electron beam path ahead of the intended target.

In case regulations are introduced which would require significant treatment-head redesign, authorities should be prepared to assure radiologists and their patients that the mandated changes are really in

their best interests and do not merely eliminate an insignificant risk at the cost of less efficacious treatment. Whatever steps are taken, authorities should advance clear arguments that the overall therapeutic ratio is improved by the changes.

CONCLUSIONS

In conclusion, the author believes that the additional risk due to leakage neutrons from medical accelerators is so small that no regulatory intervention is needed. However, a statement to the effect that neutrons need not be considered as a component of the leakage to which the 0.1% limit applies would be extremely helpful. On the other hand, if a more detailed study of neutron doses is to be undertaken, it should disregard the accelerator-produced neutrons and focus on the component produced within the patient. This source is very energy-dependent, is poorly "collimated", and exceeds the high-LET integral dose from accelerator-produced neutrons by about an order of magnitude at the largest field sizes. Indeed, a more detailed study of adverse effects of all the categories of Table I would probably be worthwhile at this time. Such a study would involve risk estimates for a variety of specific treatment modes and be reported in such a manner that the results can be easily scaled by simple factors as risk-parameter estimates become better known.

Finally, it is also worth re-emphasizing that the much-discussed neutron quality factor is shown to be irrelevant to the type of direct risk assessment given here.

ACKNOWLEDGEMENTS

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Table I. Integral Dose (g rad) to Patient for Therapy at 25 MeV (per treatment rad at 100 cm SSD).

Field Size (cm^2)	Within Treatment Volume			Outside Treatment Volume			Total for Accelerator-Produced Neutrons
	Photons of Useful Beam	Neutrons from Treatment Unit	Neutrons Produced within Patient	Photons Scattered within Patient	Photon Leakage (0.1 %)	Neutron Leakage	
100	1800[a]	0.6[b]	5[c]	500[d]	38[e]	3.4[f]	4.0
900	16200[g]	4.3[b]	50[c]	1390[g]	52[g]	2.3[f]	6.6

(a) Based on published attenuation with depth, ignoring buildup, assuming 30-cm-thick patient.

(b) Calculated for 30-cm diam x 100 cm phantom assuming 0.0007 rad entrance dose at 100 cm SSD and an attenuation coefficient of 0.12 cm^{-1} and including inverse-square reduction with distance. Phantom is centered perpendicularly on beam axis.

(c) Taken as 0.3% of treatment dose (Horsley et al. give 0.27% of treatment dose at 24 MeV).[5] This is roughly consistent with Laughlin[6] and Frost and Michel[7].

(d) Rough estimate.

(e) Calculated as for (b) but assuming 0.001 rad photon entrance dose (disregarding buildup) and attenuation coefficient of 0.037 cm^{-1}.

(f) Calculated as for (b) but using an 0.0003 rad neutron entrance dose and attenuation coefficient of 0.20 cm^{-1}, after Ref. 3, Fig. 11(b).

(g) From Rawlinson and Johns, for 70-kg phantom of 20 x 30 cm^2 cross section[8]

Table II. Effect of Accelerator-Produced Neutron Dose.

Total integral dose (nominal)	5	neutron g rad per treatment rad
Dose averaged over 70-kg patient	$7.1\ 10^{-5}$	neutron rad per treatment rad
For 5000-rad treatment course	0.36	rad average dose per treatment course
Times 28 10^{-6} leukemias yr^{-1} rad^{-1}[a]	$10\ 10^{-6}$	leukemias/yr following treatment course
Times 5 for all fatal malignancies[a]	$50\ 10^{-6}$	malignancies/yr following treatment course

(a) After Rossi and Mays (Ref. 10). Differences in latency periods are disregarded here.

FIGURE CAPTION

Fig. 1. Neutron fluence per treatment dose as a function of treatment megavoltage (from Ref. 3). The upper curve corresponds to the case in which all neutron-producing components are of W (alone, or in combination with Pb), and represents the maximum possible fluence if the electron beam strikes only the intended target. The lower curve is for all neutron sources being of Cu. Points are representative determinations for several accelerator types. See Refs. 1 and 2 for complete data.

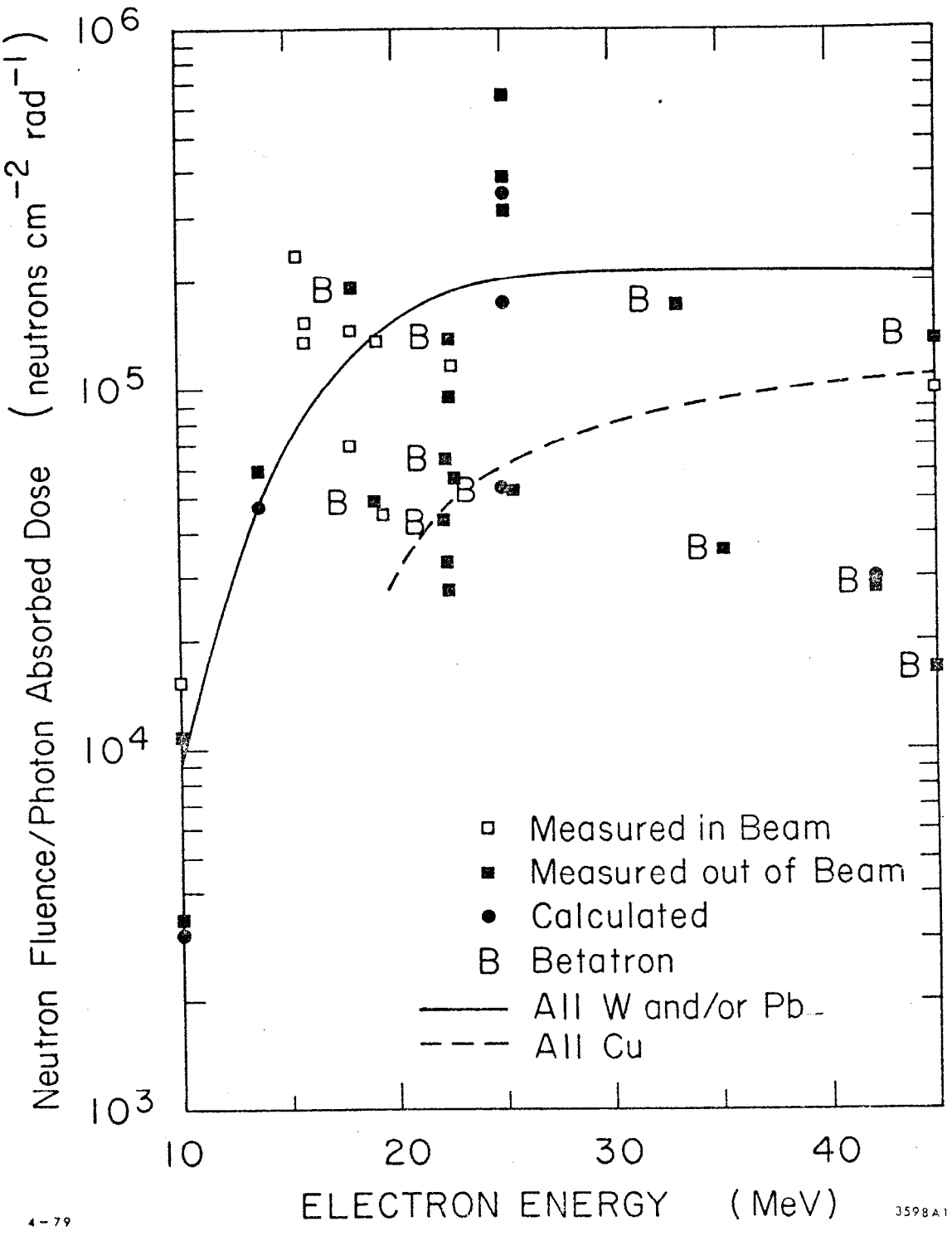
Neutron Fluence/Photon Absorbed Dose (neutrons cm^{-2} rad^{-1})
10^6
10^5
10^4
10^3
10
20
30
40
ELECTRON ENERGY (MeV)
Measured in Beam
Measured out of Beam
Calculated
B Betatron
All W and/or Pb
All Cu
4-79
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Fig. 1