CANCER RISK ESTIMATES AND NEUTRON RBE BASED ON HUMAN EXPOSURES†

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1. INTRODUCTION

It was recognized in both the UNSCEAR (1) and BEIR (2) Committee reports that risk estimates deduced from the Japanese data should eventually be made using absorbed dose in organs of interest rather than tissue kerma in free air (kerma for short in the following); however, the detailed calculations of appropriate doses had not been completed at the time of issue of those reports. Recent reports (3-5) of the Oak Ridge National Laboratory group provide data on absorbed doses for various phantoms and organs of interest. Auxier, et al. (4) pointed out the implications of these data for risk estimates. More recently, Rossi (7), Kerr and Jones (8) and Beebe, et al.(9) have employed the newer dose data to deduce risk estimates and RBE values. The purpose of the present work is to provide a further analysis which stresses (a) the importance of careful selection of an appropriate control group, (b) the importance of making lifetime risk estimates for total malignancies, and (c) the uncertainties involved in these estimates.

2. DOSE ESTIMATES AND UNCERTAINTIES

Based on the data of Jones (5) and Jones, et al. (3) it is estimated that the dose to bone marrow is approximately 55% of the kerma value for gamma and about 25% of the kerma value for the fission neutron exposures. It is further assumed that bone marrow doses are an adequate measure of mean dose to organs of importance in the analysis of total malignancies.

These estimates apply for neutrons with 2.5 MeV effective energy, incident semi-isotropically on the ICRP adult reference man. Estimated mean bone marrow doses due to neutrons may be 20% lower if effective neutron energy is 1 MeV rather than 2.5 MeV. However, neutron doses may be 75% higher if irradiation is more nearly 1/2 semi-isotropic and 1/2 bilateral. Also, dose to kerma ratios are probably somewhat higher for typical Japanese persons than for ICRP standard man due to their somewhat smaller size.

For gamma rays, the uncertainty in gamma energy is less important, however, bilateral vs. isotropic exposure has an effect very similar to that for neutrons. Thus, the risk factors deduced below are uncertain by at least 40% due to uncertainties in exposure conditions and dosimetry. The dose to organs of interest may also differ from mean bone marrow dose by a comparable factor.

3. EPIDEMIOLGIC DATA AND UNCERTAINTIES

Listed on Table 1 are [1] exposure groups with exposure ranges expressed in kerma, based on 1965 estimates of kerma for a small mass of tissue in air; [2] and [3] the related mean kerma and mean bone marrow doses due to gamma and neutrons (based on above assumptions); [4] and [5] the observed and expected cases of leukemia and other malignancies; [6] a calculated value of total person-rem for each exposure group; and [7] and [8] estimated values of expected excess leukemia and malignancy deaths for the period 1950-72. Kerma values are taken from the report by Jablon and Kato (10). The products (persons x rem) were obtained using number of persons in each group (10) and applying a quality factor of 10 to the neutron component of dose. Observed and expected cases are based on 1967 Japanese mortality rates taken from the report of Moriyama and Kato (6).

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A comparison of the ratios of expected excess cases to uncertainty leads to the important conclusion that 1-9 kerma groups in both cities and the 10-49 kerma Nagasaki group have "signal to noise" ratios which are too small to be of value in deducing induction rate constants. The 50-99 rad (kerma) Nagasaki group is also weak, but not as seriously. From the relatively large (±19%) differences in the observed/expected ratios for the not in the city early entry (NIC-EE), not in the city late entry (NIC-LE), 0, and 0-9 kerma groups, it is clear that control group fluctuations can introduce large uncertainties into the final results. Unfortunately, similarly large uncertainties are introduced by the use of national rates as controls since total malignancy rates typically vary by ±20% from region to region within a given country. For these reasons I have estimated risk coefficients using a variety of control groups and various time periods in order to demonstrate the magnitudes of the differences which result.

4. RISK ESTIMATES FOR GAMMA EFFECTS

Gamma induction rates were deduced for the Nagasaki data shown on Table 1. The data must be examined carefully to appreciate the small size of the observed effects and the relatively great effect the lowest exposure group, 0-9 kerma, has on the data interpretation. If 1967 national rates are used as controls, the 0-9 kerma group shows a significant increase in leukemia over the expected number of cases (11 vs. 6.3). On the other hand, if one uses the 0-9 kerma group as controls, there is no apparent increase over expected until exposures of 100-199 kerma (doses of about 80 rad) were received. The function which best fits these data depends strongly on which control group is employed. If a power function is fitted to the data, it can have exponents less than or greater than one depending on the choice of control group. This illustrates the lack of confidence one must have in fitting equations to this data. Similar problems apply to total malignancy data for Nagasaki.

Since too few cases have been observed to make a very meaningful analysis of the shape of the dose effect curve, the data have been summed in terms of total person-rads and total excess cases of leukemia using various groups as controls. This procedure has some justifications for purposes of risk estimate in that exposed populations are also likely to receive a range of doses. Thus, the deduced risk estimates tend to reflect average effects on populations receiving acute doses from about 1 to 200 rad to bone marrow. The effects of low dose rates may be much less, however, apparent effects detected in the 1-9 kerma group do not support this expectation.

Results of these analyses are summarized in Table 2. Leukemia risks of .3 to .45 deaths per 10^4 person-rads are indicated for the periods 1950-72. Also listed in Table 2 are values which are predicted as lifetime risks. These values are 1.75 times the value observed between 1950-72 for leukemia since only 1/4 of the exposed population had died to date and the remaining population is still showing signs of elevated leukemia rates, however at about 1/4 the rate observed during the first ten years of observation (1950-60).

Results for total malignancies less leukemia yielded gamma risk estimates which varied from not significant (1 sigma level) to 1.8 deaths per 10^4 person-rad bone marrow dose based on observations from 1950-72. Since only 1/4 the exposed population has died, and since total cancer rates are not decreasing with time, it is estimated that total lifetime risks may be four times the above values. The most likely values for lifetime gamma risk coefficients are thought to be 0.67 leukemia deaths, 0.92 other malignancy deaths or a total of 1.6 malignancy deaths per 10^4 person-rad based on the 0-49 kerma Nagasaki groups as controls. The leukemia estimate is about 2.2 times the BEIR Committee estimate and the total malignancy estimate about 0.9 times (2). However, since estimated induction rates are about four times higher if national

rates were used as controls, a large uncertainty must be associated with these values.

5. RISK ESTIMATES FOR NEUTRON EFFECTS

Hiroshima data employed in this analysis (6) are shown in Table 1 and have considerably better statistical significance than the Nagasaki data. The neutron dose-effect relation for total malignancies less leukemia obtained from the Hiroshima data follows a $dose^{0.4}$ function if national rates are employed as controls or an approximately linear function if the zero rad group is employed as controls.

Deduced neutron risk coefficients listed in column 4 of Table 2 were derived after correcting the observed excess deaths by an amount determined from the total person-rad gamma dose and the corresponding gamma risk coefficient listed in column 3 of Table 2. RBE values listed in column 5 were obtained from the ratios of neutron to gamma risk coefficients. Values for lifetime risks were obtained as before by multiplying the observed excess to date by 1.75 for leukemia and by four for total malignancies. Total risk per rad for gamma and neutron doses were then obtained by summing the values for leukemia and total malignancies less leukemia. Final lifetime risk values thus obtained for neutron exposures are 7.9 leukemia and 96 other malignancy deaths per 10^4 person-rad based on national rates as controls, or 6.3 leukemia and 24 other malignancy deaths based on low dose control rates. These values yield an overall RBE of 9 to 10 for leukemias, 20 to 26 for other malignancies or 19 for all malignancies combined.

6. CONCLUSIONS

The principal uncertainties in the above analysis are a factor of about four attributable to effects which may yet occur in the surviving population and a factor of about four due to uncertainties associated with selection of a suitable control group. Uncertainties in relevant doses are probably less than a factor of two.

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Table 1. Exposures, Doses, and Observed and Expected Deaths Due to Leukemia or Total Malignancies.

Kerma[d] Range	Kerma[d] and (dose)[e] Gamma	Neutron	Leukemia Obs/Exp	Malig. less Leukemia Obs/Exp	[a]Persons x rem (10^4)	[b]Expected Excess Leukemias	Expected Excess Total Malignancies
				HIROSHIMA			
200+	269 (148)	94 (24.4)	28/0.9 = 33	91/54.9 = 1.66	57	17 ± 4.2	103 ± 13
100-199	109 (60)	30 (7.8)	12/1.0 = 12	89/70.3 = 1.26	23	6.9 ± 2.8	42 ± 11
50-99	57 (31)	13.3(3.5)	7/1.5 = 4.6	138/116 = 1.19	17.6	5.3 ± 2.6	32 ± 12
10-49	17.6 (10)	4.3(1.1)	17/6.2 = 2.8	501/448 = 1.12	22.5	6.7 ± 3.6	41 ± 22
1-9	2.9 (1.6)	0.8(.21)	37/25 = 1.5	1298/1193 = 1.09	5.1	1.5 ± 5.1[c]	9.2 ± 23[c]
0	~0	~0			~0		
NIC-EE	0	0	10/11.4 = 0.88	170/185 = 0.92	0	0	0
NIC-LE	0	0		585/560 = 1.04	0	0	0
				NAGASAKI			
200+	329 (181)	5.6 (1.5)	15/0.7 = 20	46/35.5 = 1.29	24	7.1 ± 2.8	43 ± 8.8
100-199	144 (79)	1.4 (.36)	3/0.7 = 4.30	36/35.6 = 1.01	9.8	2.9 ± 1.9	18 ± 7.3
50-99	70 (39)	0.2 (.05)	0/0.7 = 0	45/39.3 = 1.15	4.8	1.4 ± 1.4	8.3 ± 6.9
10-49	21.3(11.7)	~0	2/2 = 1.0	129/119 = 1.08	4.4	1.3 ± 1.8[c]	8.0 ± 11[c]
1-9	4.0 (2.0)	~0	11/6.3 = 1.74	233/202 = 1.15	1.47	0.4 ± 2.6[c]	2.6 ± 14[c]
0	~0	~0		136/143 = 0.95	~0		
NIC-EE	0	0	4/3.6 = 1.11	40/33.7 = 1.19	0	0	0
NIC-LE	0	0		172/158 = 1.09	0	0	0

a. Person-rem calculated assuming a quality factor of 10 for neutrons.
b. Expected values calculated assuming the BEIR Committee estimates of 0.3 leukemias or 1.8 total malignancies per 10^4 person-rem. ± values are 1 σ statistical fluctuations expected based on sum of excess plus national rates.
c. Uncertainties larger than expected excess.
d. Kerma for tissue in air, units of 100 erg/gm.
e. Mean bone marrow dose is given in parentheses, units of rads.

Table 2. Summary of Risk Estimates.

Years	Control[a]	Gamma Induced Deaths per 10^4 rad	Neutron Induced Deaths per 10^4 rad	RBE
LEUKEMIA				
50-64	National Rate	0.35	4.1	12
50-64	0-9	0.31	2.7	9
50-72	National Rate	0.45	4.5	10
50-72	0-9	0.30	4.5	15
50-72	0-49 (Nagasaki) 0-9 (Hiroshima)	0.38	3.6	9.5
Lifetime	National Rate	0.78	7.9	10
Lifetime	0-49 (Nagasaki) 0-9 (Hiroshima)	0.67	6.3	9.5
MALIGNANT NEOPLASMS LESS LEUKEMIA				
65-69	National Rates	0.8	5.0	6.0
65-69	0-9	0.13[b]	3.3	25[b]
65-72	National Rates	1.2	4.0	3.3
50-72	National Rates	1.2	24	20
50-72	0-9	0.24[b]	6.3	26[b]
50-65	0	1.4	<0[b]	0[b]
50-72	0	1.8	<0[b]	0[b]
50-72	0-49 (Nagasaki) 0-9 (Hiroshima)	0.23	5.9	26
Lifetime	National Rates	4.8	96	20
Lifetime	0-49 (Nagasaki) 0-9 (Hiroshima)	0.92	24	26
ALL MALIGNANT NEOPLASMS				
Lifetime	National Rates	5.6	104	19
Lifetime	0-49 (Nagasaki) 0-9 (Hiroshima)	1.6	30	19

a. Numbers refer to exposure group, Kermas in 100's of ergs/gm.
b. Lacks statistical significance.