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PREFACE

At its meeting in Como, Italy, in September of 1987 the Commission approved a proposal by its Committee 1 on Radiation Effects to set up a Task Group on Risk to evaluate the new estimates of cancer risk, genetic risk and the risk to the fetus that were being developed by committees such as United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and U.S. National Academy of Sciences Committee on the Biological Effects of Ionizing Radiations (BEIR). Eventually as the programme of the Commission evolved in the preparation of new radiation protection recommendations (*ICRP Publication 60*, 1991), the work of this Task Group became part of the background on which Annex B, "Biological Effects of Ionising Radiation" in the new recommendations, was based. In order to provide a complete record of the biological basis of the recommendations, the preparation of five papers by individual members of the Task Group was agreed upon. These papers were subsequently reviewed, first by the other members of the Task Group, and then by all the members of Committee 1 of ICRP. Thus these papers are approved for publication by Committee 1 of ICRP, and are published in the *Annals of the ICRP* as refereed papers not specifically adopted by the Commission.

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RISK ESTIMATES FOR CARCINOGENIC EFFECTS OF RADIATION

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This paper was prepared as part of the work of the Risk Task Group of Committee 1 of ICRP and approved by the Task Group and the Committee

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1. INTRODUCTION

During the past decade, new information about the carcinogenic effects of radiation has come from epidemiological studies of Japanese atomic bomb survivors; patients irradiated therapeutically for ankylosing spondylitis, cancer of the uterine cervix, tinea capitis, and other conditions; workers exposed to radiation in various occupations; and populations residing in areas of high natural background radiation. New data have also come from long-term studies of the carcinogenic effects of irradiation in laboratory animals and from experiments on neoplastic transformation in cultured cells. The new data, summarised recently in the UNSCEAR (1986, 1988) and NAS/BEIR (1988, 1990) reports, call for reassessment of ICRP's previous risk estimates for carcinogenic effects of radiation.

2. MAJOR NEW FINDINGS SINCE *ICRP 26*

2.1. Atomic Bomb Survivors

Per unit dose, the carcinogenic effects of A-bomb radiation on the survivors of Hiroshima and Nagasaki are now estimated to be somewhat larger than previously, owing to revisions in the dosimetry of the A-bomb radiations and increase in the numbers of excess cancer deaths on continued follow-up of the population, particularly in cohorts of survivors irradiated early in life (Preston and Pierce, 1988).

As analysed with the new dosimetry, the contribution of neutrons to the total dose received by survivors is no longer judged to be highly significant in either city, with the result that there no longer remains any significant basis for estimating the RBE of neutrons for carcinogenic effects. Also, the tissue dose of gamma radiation is now estimated to be higher at Hiroshima and slightly lower at Nagasaki than heretofore, so that if an RBE of 10 or more is assumed for neutrons, the estimated risk per unit dose equivalent is increased, depending on the depth of the tissue in question, and the difference between Hiroshima and Nagasaki in overall risk per unit dose is no longer statistically significant.

During the most recent decade of follow-up, the radiation-induced excess in the cumulative number of deaths from cancer has increased by more than 50 per cent, from an estimated 205 deaths by 1975 to 340 deaths by 1985 (Shimizu *et al.*, 1988, 1990). The increase in radiation-related deaths is roughly proportional to the increase in baseline rates associated with the aging of the cohort, while the excess relative risk of fatal cancer has remained comparatively constant over time (Table 1). Thus, the overall cancer mortality data are now more compatible with the "relative" (or "multiplicative")

Table 1. Relative risk, as compared with absolute risk, of cancer death in A-bomb survivors at 1 Gy (shielded kerma), 1950–1985, in relation to age at the time of bombings (ATB) and age at death (from Shimizu *et al.*, 1988, 1990)

Age ATB	Age at time of death						
	0–19	20–29	30–39	40–49	50–59	60–69	70+
				(Relative Risk at 1 Gy)			
Leukaemia							
0–9	44.16	3.41	8.64	0.95			
10–19	54.74	—	2.45	1.02	0.82		
20–29		5.33	3.54	43.09	1.02	0.82	
30–39			0	24.05	10.58	1.47	3.89
40–49				0.83	3.82	0.82	3.10
50+					15.63	5.18	6.90
All ages	46.47	9.81	4.75	5.68	3.98	1.70	4.40
All cancers except leukaemia							
0–9	(70.07)	5.89	1.96	1.86			
10–19	(40.90)	(0.82)	1.66	1.59	1.68		
20–29			(1.38)	2.09	1.74	1.37	
30–39			(0.84)	(1.12)	1.11	1.23	1.48
40–49				(1.25)	(1.12)	1.13	1.33
50+					(2.58)	(0.95)	1.15
All ages	75.32	2.22	1.60	1.58	1.39	1.13	1.29
				(Excess Deaths Per 10^4 PYGy)			
Leukaemia							
0–9	6.71	0.93	1.27	−0.01			
10–19	3.95	—	0.56	0.02	−0.06		
20–29		3.93	1.52	4.84	0.01	−0.28	
30–39			0	3.18	2.26	1.09	3.89
40–49				−0.35	3.07	−0.24	3.50
50+					4.31	3.84	5.12
All ages	6.48	2.17	1.16	1.88	1.54	1.09	4.24
All cancers except leukaemia							
0–9	(0.43)	1.32	2.85	5.16			
10–19	(3.96)	(−0.12)	2.00	5.84	13.91		
20–29			(1.39)	9.40	15.71	14.33	
30–39			(−1.32)	(1.33)	3.16	11.00	41.01
40–49				(2.48)	(3.37)	7.31	37.30
50+					(35.29)	(−2.88)	17.21
All ages	0.79	0.54	1.98	5.35	9.62	6.85	30.53

risk projection model than with the "absolute" (or "additive") risk projection model, although the validity of either model for cancer of a given type or site, or for those survivors who were irradiated at younger ages, remains uncertain.

Although the data for leukaemia conform to a linear-quadratic function (Table 2, Fig. 1; also see NAS/BEIR, 1990), the dose–mortality relationship for cancers other than leukaemia reveals no significant departure from linearity in the range below 3 Gy (Table 2). The estimated absolute and relative risks at 1 Gy for mortality from cancers of those relatively few types for which sufficient data are available to enable numerical risk estimates are summarised in Table 3.

2.2. Patients Treated with x rays for Ankylosing Spondylitis

New information has been derived also from further study of 14,106 patients followed

Table 2. Excess relative risk of death from cancer in A-bomb survivors per Gy of organ absorbed dose, 1950–1985 (from Shimizu *et al.*, 1988, 1990)

Site of cancer	Dose range (Gy) 0–6	<0.20	<0.50	<1.00	Equality of excess RR <0.50	0.50+	Test
Leukaemia	5.21[d]	−0.12	2.40[b]	3.96[d]	2.44	5.53	[b]
All cancers except leukaemia	0.41[d]	0.54	0.38[b]	0.46[d]	0.37	0.42	
Stomach	0.27[d]	0.17	0.45[a]	0.41[c]	0.45	0.26	
Lung	0.63[d]	0.17	1.09[b]	0.83[c]	1.06	0.60	
Female breast	1.19[d]	0.21	0.88	1.78[c]	0.82	1.21	
Colon	0.85[d]	−2.95[a]	−0.53	−0.10	−0.52	0.98	[a]

[a] $p<0.10$.
[b] $p<0.05$.
[c] $p<0.01$.
[d] $p<0.001$.

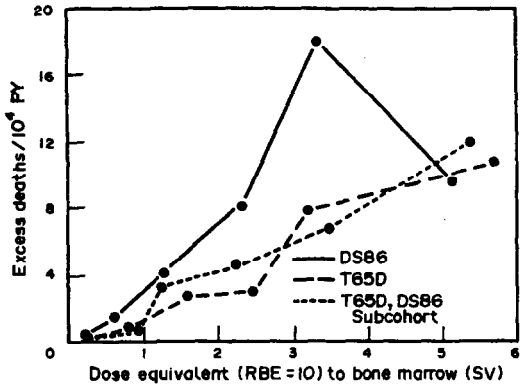

Fig. 1. Dose-mortality relationship for leukaemia (excluding CLL) in A-bomb survivors, 1950–1985 (from Preston and Pierce, 1988).

for up to 48 years (average of 23.0 years) after a single course of x-ray therapy to the spinal column for ankylosing spondylitis (Darby *et al.*, 1987).

In this population, mortality from cancers of several of the heavily irradiated sites has been observed to increase significantly between the 5th and 25th year following irradiation, after which the excess has appeared to diminish for certain sites; e.g., the lung (Table 4). Although the excess per unit dose has generally been smaller than that in the A-bomb survivors, analysis of the dose–incidence relationship is complicated by wide variations in dose among different organs of the body, wide variations in dose within a given organ such as the marrow, and the absence of dose data for many of the individual patients (Lewis *et al.*, 1988). Other limitations in comparing the data include the fact that the study sample was a selected subgroup, the average follow-up time was fairly short, and the irradiation was limited largely to the spine and pelvis.

2.3. Other Therapeutically Irradiated Populations

Other populations that have provided important new information include: (1) women

Table 3. Mortality from cancer of various sites in A-bomb survivors, 1950–1985 (from Shimizu *et al.*, 1988, 1990)

Site of cancer	Relative risk per Gy[a]	Excess deaths per 10,000 PYGy[a]
Leukaemia	6.21 (4.83–8.12)	2.94 (2.43–3.49)
All except leukaemia	1.41 (1.32–1.51)	10.13 (7.96–12.44)
Oesophagus	1.58 (1.13–2.24)	0.45 (0.10–0.88)
Stomach	1.27 (1.14–1.43)	2.42 (1.26–3.72)
Large intestine except rectum	1.85 (1.39–2.45)	0.81 (0.40–1.30)
Lung	1.63 (1.35–1.97)	1.68 (0.97–2.49)
Female breast	2.19 (1.56–3.09)	1.20 (0.61–1.91)
Ovary	2.33 (1.37–3.86)	0.71 (0.22–1.32)
Urinary tract	2.27 (1.53–3.37)	0.68 (0.31–1.12)
Multiple myeloma	3.29 (1.67–6.31)	0.26 (0.09–0.47)

[a] Organ-absorbed dose. 90% confidence interval in parentheses.

treated for carcinoma of the uterine cervix, in whom leukaemia and cancers of the urinary bladder, breast, kidney, stomach, and rectum have been observed in excess (Boice *et al.*, 1985, 1987); (2) children treated for leukaemia, in whom an excess of intracranial and other tumours has been observed (Tucker *et al.*, 1984; Meadows *et al.*, 1985); (3) patients treated for Hodgkin's disease, in whom cancers of the skeleton, soft tissues, skin, oropharynx, nervous system, respiratory system, and digestive tract have been observed in excess (Tucker *et al.*, 1984); (4) patients treated with intravenously injected radium-224 for tuberculosis and ankylosing spondylitis, in whom an excess of skeletal tumours has been observed (Mays and Spiess, 1984); (5) patients treated for tinea capitis with x-irradiation of the scalp, in whom thyroid and intracranial cancers (Ron and Modan, 1984) and, possibly, breast cancers (Modan *et al.*, 1989), have been observed in excess; and (6) patients treated for ovarian cancer, in whom uterine, colon, bladder, and haematologic cancers have been observed in excess (Reimer *et al.*, 1978). Salient features of some of the larger such study populations are summarised in Table 5. Although the numbers of cancers in these populations have generally been too small, and the relevant doses of radiation too uncertain, to provide highly quantitative dose–incidence information, the excess of thyroid cancer in the tinea capitis series is noteworthy in view of the small magnitude of the average estimated dose (< 100 mSv) to the thyroid gland in this series (NAS/BEIR, 1990).

2.4. Patients Exposed to Diagnostic Radiation

Further information pertaining to the carcinogenic risks associated with diagnostic irradiation has come from study of childhood cancer in twins born in Connecticut

Table 4. Relative risk (observed/expected) of mortality at ages less than 85 years from neoplasms other than leukaemia or cancer of the colon in ankylosing spondylitis patients in relation to time after first treatment (from Darby *et al.*, 1987).

Site	Time since first treatment (years) under 5	5.0–24.9	over 25	Total > 5[a]
Mouth	0.00	1.68	1.41	1.58
Pharynx	0.00	1.77	1.14	1.56
Oesophagus	0.84	2.05[b]	2.41[b]	2.20[b]
Stomach	1.01	1.20	0.62	1.01
Rectum	0.94	1.14	0.96	1.07
Liver	2.71	0.58	2.01	1.10
Pancreas	3.24[b]	1.13	0.86	1.02
Larynx	2.84	1.37	1.85	1.54
Lung	1.22	1.37[b]	0.97	1.21[b]
Breast	1.58	1.88[b]	1.02	1.62[b]
Uterus	0.00	1.15	0.65	1.02
Ovary	1.17	1.07	0.62	0.93
Prostate	3.04[b]	1.24	1.07	1.16
Kidney	1.11	1.61	1.36	1.52
Bladder	1.96	0.91	1.62	1.20
Skin	0.00	1.23	1.52	1.33
Spinal cord	90.61[b]	6.77	0.00	4.72
Other CNS	0.67	1.60[b]	1.49	1.57[b]
Bone	1.88	2.95	2.96	2.95[b]
Hodgkin's disease	2.42	1.66	0.00	1.32
Other lymphoma	2.03	2.89[b]	1.13	2.24[b]
Multiple myeloma	0.00	1.52	1.97	1.72
Other	1.90	1.35	1.10	1.25
Total				
O/E	76/52.80	385/279.39	178/166.56	563/445.95
Ratio	1.44[b]	1.38[b]	1.07	1.26[b]

[a] At least five years have elapsed since treatment.
[b] $p < 0.05$.

Table 5. Salient characteristics of some of the major study populations evaluated for derivation of numerical cancer risk estimates (from NAS/BEIR, 1990)

Incidence	Incidence or mortality	Cancer sites	Total cases	Total person years	Reference
Atomic bomb survivors	Mortality	All	5,936	2,183,335	Shimizu *et al.*, 1988
	Incidence	Breast	376	940,000	Tokunaga *et al.*, 1987
Ankylosing spondylitis	Mortality	Breast	36	30,770	Darby *et al.*, 1987
		All except leukaemia and colon	563	183,749	Darby *et al.*, 1987
Canadian fluoroscopy patients	Mortality	Breast	482	867,541	Miller *et al.*, 1989
Mass. fluoroscopy	Mortality	Breast	74	30,932	Hrubec *et al.*, 1989
NY postpartum mastitis	Incidence	Breast	115	45,000	Shore *et al.*, 1986
Israel tinea capitis	Incidence	Thyroid	55	712,000	Ron and Modan, 1984; Modan *et al.*, 1989
Rochester thymus	Incidence	Thyroid	28	138,000	Shore *et al.*, 1985

between 1930 and 1969, in whom the relative risks associated with radiography *in utero* (estimated median dose of 0.01 Gy) were calculated to be 1.6 (0.4–6.8) for leukaemia and 3.2 (0.9–10.7) for all other childhood cancers (Harvey *et al.*, 1985). Although the excesses are not statistically significant, they are consistent with those observed after prenatal diagnostic x-irradiation in British twins (Mole, 1974) and other population groups (e.g., Monson and MacMahon, 1984; Bithell and Stiller, 1988).

Additional follow-up of patients injected intravascularly with thorotrast for radiographic examination has provided further information about the carcinogenic effects of alpha-irradiation on the liver and other organs (NAS/BEIR, 1988).

2.5. Occupationally Exposed Groups

During the past decade, a number of occupationally exposed groups have been investigated for carcinogenic effects (Modan, 1991). In general, the findings on such groups have either been negative or have suggested no more than such small excesses of cancer as would have been consistent with those predicted by extrapolation from observations on the rates of cancer induction observed in populations exposed at higher doses and dose rates (NAS/BEIR, 1990). In a few instances, however, excesses of certain cancers have been found which were larger than predicted, implying that: (1) the doses received by the workers in question were larger than estimated, (2) the risks per unit dose are larger than generally estimated, (3) the observed excesses may have been caused in part by agents other than radiation to which the populations were also exposed, (4) the excesses may have resulted from the action of other confounding or additive factors, and/or (5) the excesses may be attributable to methodological problems complicating interpretation of the data (Modan, 1991).

2.6. Experimental Data

New information from experiments with laboratory animals has extended our knowledge of the dose–effect relationships in radiation carcinogenesis, especially with respect to organ-, species-, and age-dependent differences in susceptibility; the influence of dose rate, LET, tumour-promoting agents, chemical carcinogens, and other extraneous modifying factors; the distribution of induced tumours in relation to time after irradiation and attained age; and the underlying biological mechanisms of carcinogenesis (UNSCEAR, 1986, 1988; NAS/BEIR, 1990). The new data and their implications for risk assessment are cited in the following paragraphs where pertinent.

3. DOSE–EFFECT RELATIONSHIPS

3.1. Dose

In A-bomb survivors, as noted above, the dose–effect relationship for overall mortality from cancers other than leukaemia shows no significant departure from linearity over the range from zero to 3 Gy (e.g. Table 2), while the dose–effect relationship for leukaemia (excluding chronic lymphocytic leukaemia) conforms best to a linear-quadratic function (Shimizu *et al.*, 1988, 1990). For solid cancers at certain specific sites (e.g. breast and thyroid) the data are also consistent with linearity, while for cancers at other sites (e.g. colon) the data appear to be more consistent with linear-quadratic or quadratic functions

(Shimizu *et al.*, 1988, 1990). Chronic lymphocytic leukaemia (CLL) and Hodgkin's disease have not been observed to be induced by irradiation in the A-bomb survivors or other human populations, in spite of their relatively high baseline prevalence among haematologic cancers as a group (UNSCEAR, 1988; NAS/BEIR, 1990). In view of the known diversity of dose–effect relationships for different types of neoplasms in laboratory animals (UNSCEAR, 1977, 1986), such differences are not surprising.

Other evidence suggestive of the carcinogenicity of low doses, although not sufficient in itself to characterise the dose–effect relationship, is the association between diagnostic x-irradiation *in utero* and the development of cancer in childhood. Interpretation of the association is complicated, however, by the absence of a similar excess of childhood cancer in prenatally irradiated A-bomb survivors (UNSCEAR, 1986).

The risk of carcinogenic effects at low doses is also implied by experiments on the effects of promoting agents in irradiated laboratory animals and cultured cells (UNSCEAR, 1986), in which the frequency of tumour-initiating effects has appeared to increase as a function of the radiation dose without threshold (Upton, 1987). The dose–incidence curve at low doses still remains highly uncertain, however, and the data do not suffice to rule out the possible existence of a threshold.

3.2. Dose Rate, Fractionation, Protraction

Experiments with laboratory animals have provided further evidence that the carcinogenic effectiveness of low-LET radiation in the low-to-intermediate dose range (i.e. the range below 1 Gy) generally decreases with fractionation or protraction of the dose over a period of days or weeks (NCRP, 1980), while that of high-LET radiation tends to remain unchanged or even to increase with similar fractionation or protraction of the dose (UNSCEAR, 1986; NAS/BEIR, 1990).

Comparable human data are fragmentary or lacking, except for carcinogenic effects on the female breast. Such effects appear for the most part to be similar in magnitude for a given dose, whether the dose is received acutely from A-bomb radiation or therapeutic x-radiation, or is received in multiple small fractions through repeated fluoroscopic examinations of the chest (Shore *et al.*, 1986; UNSCEAR, 1986; NAS/BEIR, 1990), although the data for certain cohorts are not entirely in accord with this interpretation (Miller *et al.*, 1989; NAS/BEIR, 1990).

Patients given diagnostic doses of iodine-131 have been observed to develop little, if any, excess in the incidence of thyroid cancer, in contrast to the appreciable excess that would be predicted on the basis of the effects of comparable doses of external x-radiation (Holm *et al.*, 1988). It is conceivable, however, that spatial as well as temporal differences in dose distribution may account for this discrepancy (NCRP, 1985), since the carcinogenic effects of therapeutic x-irradiation have not been observed to be diminished on fractionation of the dose (Shore *et al.*, 1985).

3.3. LET

In laboratory animals, the carcinogenic effects of radiation vary as a function of LET, depending on the neoplasm in question and the conditions of irradiation (UNSCEAR, 1986). In general, the RBE of high-LET radiation has been observed to increase with decreasing dose and dose rate, generally falling in the range of 2–30 for duration-of-life

exposure, although much higher values have been reported for the induction of certain types of tumours by fission neutrons (ICRU, 1986).

In humans, data for neutrons are lacking. The relative effectiveness of internally emitted alpha particles for carcinogenic effects on the skeleton and the lung is consistent with RBE values in the range of 20, as are the values for corresponding effects of alpha-emitters in laboratory animals (ICRU, 1986; NAS/BEIR, 1988, 1990; NCRP, 1990).

4. FACTORS AFFECTING SUSCEPTIBILITY

4.1. Age

For a number of different types of cancer, susceptibility to the carcinogenic effects of radiation appears to vary in relation to age at the time of irradiation. For the induction of leukaemia, susceptibility appears to be higher during prenatal development, infancy and childhood than in adolescence or early adult life (UNSCEAR, 1986, 1988; NAS/BEIR, 1990); it also appears to increase in advancing age (Fig. 2).

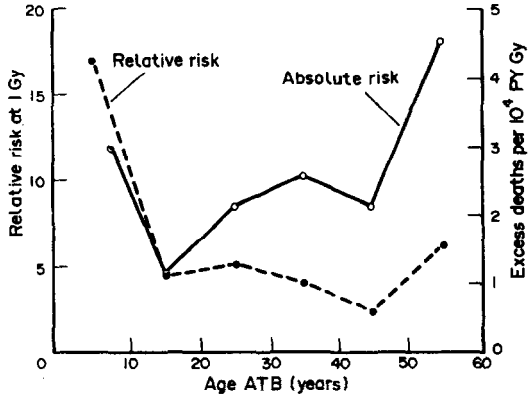

Fig. 2. Relative versus absolute risks of leukaemia in A-bomb survivors 1950–1985, in relation to age at the time of the bombings (ATB) (from Shimizu *et al.*, 1990).

For cancer of the thyroid gland, susceptibility appears to be 2–3 times higher in infants and children than in adults (Shore *et al.*, 1985). For cancer of the female breast, susceptibility also appears to be higher in childhood and adolescence than in adult life, decreasing in middle age to virtual disappearance after the menopause (Tokunaga *et al.*, 1984; Shimizu *et al.*, 1988, 1990). For the induction of skeletal cancer by injection of radium-224, susceptibility per unit dose appears no different in children than in adults (Mays and Spiess, 1984).

For cancers of other sites, the available data are not sufficient to define the relationship between susceptibility and age at the time of irradiation (UNSCEAR, 1988; NAS/BEIR, 1990).

In the atomic bomb survivors, the dose-dependent excess of cancers in adult life appears thus far to be approximately the same after prenatal irradiation as after irradiation during the first 10 years of life (Table 6).

Table 6. Comparison of cancer risks in A-bomb survivors exposed *in utero* with those exposed at 0–9 years of age (Yoshimoto *et al.*, 1988)

	In utero (1950–84) DS86 Uterus dose		0–9 Age ATB (1950–85) DS86 Tissue kerma	
No. of Cancers	18 (2)*		142 (31)*	
RR at 1 Gy	All cancer	3.77 (1.1, 13.5)	All cancer Leukaemia Other cancer	3.97 (2.9, 5.4) 17.25 (9.3, 38.9) 2.23 (1.6, 3.4)
Excess Risk/10^4 person-year-Gy	All cancer	6.57 (0.47, 14.5)	All cancer Leukaemia Other cancer	5.47 (3.54, 7.17) 2.93 (2.23, 3.60) 2.27 (1.11, 3.65)

( ): 90% confidence interval.
( )*: No. of cases of leukaemia.

4.2. Sex

The development of breast cancer is known to depend heavily on hormonal stimulation of the mammary gland. Hence it is not surprising that induction of the disease by irradiation has been documented conclusively thus far only in women (Shore *et al.*, 1986).

Although radiation-induced thyroid cancer occurs more commonly in females than in males, the ratio being about 3:1, the relative risk of the disease appears to be similar in the two sexes (NCRP, 1985).

For cancers of other sites, the sex differences are less pronounced (Table 7), but the relative risks appear generally higher in females than in males. Overall, the total absolute excess risk is only about 20 percent higher in females than in males (Table 7).

Table 7. Sex differences in relative and absolute risks of cancer mortality in A-bomb survivors (Shimizu *et al.*, 1988, 1990)

Site of cancer	Estimated RR at 1 Gy (shielded kerma)			Excess deaths per 10^4 PYGy		
	Male	Female	M/F ratio	Male	Female	M/F ratio
Leukaemia	4.96	4.92	1.00	3.14	1.80	1.74[a]
All cancers except leukaemia	1.17	1.44	0.81[b]	5.76	8.78	0.66
Oesophagus	1.19	2.99	0.40[a]	0.30	0.40	0.75
Stomach	1.15	1.36	0.85	2.01	2.18	0.92
Colon	1.45	1.67	0.87	0.60	0.51	1.18
Lung	1.26	1.86	0.68[a]	1.07	1.47	0.73
Urinary tract	2.00	2.15	0.93	0.81	0.42	1.93
Multiple myeloma	5.29	2.32	2.28	0.23	0.21	1.10

[a] $p < 0.05$.
[b] $p < 0.01$.

4.3. Constitutional and Physiological Factors

It has been suggested that susceptibility to the induction of some types of cancer is increased in association with certain inherited genetic disorders; e.g. susceptibility to osteosarcoma in association with familial retinoblastoma (Knudson, 1985), susceptibility

to breast cancer in association with heterozygosity for the ataxia telangiectasia gene (Swift *et al.*, 1987), and susceptibility to skin cancer in association with the nevoid basal cell carcinoma syndrome (Strong *et al.*, 1977). In general, however, apart from limited comparative data for experimental animals (Storer *et al.*, 1988), the influence of constitutional and physiological factors on susceptibility to radiation carcinogenesis is not well known.

4.4. Effects of Other Carcinogens and Co-Factors

A wide variety of interactions between radiation and other agents has been observed in laboratory animals and cultured cells, including synergistic, additive and antagonistic interactions, depending on the agents in question and the conditions of exposure (UNSCEAR, 1982; Fry and Ullrich, 1986). In humans, however, the data are limited as yet. In patients treated for cancer by combined therapy with drugs and radiation, the risk of a second, treatment-induced cancer is higher than in those treated for similar malignancies with radiation alone (Coleman, 1982; Fry and Ullrich, 1986). Similarly, the carcinogenic action of radiation on the skin appears to be enhanced by ultraviolet radiation, judging from the effects of sunlight in patients treated with x-irradiation of the scalp for tinea capitis in childhood (Albert and Shore, 1986). The combined effects of cigarette smoking and radiation in pulmonary carcinogenesis differ, depending on the conditions of irradiation (Cross *et al.*, 1982), appearing to be more than additive in uranium miners (Whittemore and MacMillan, 1983) but not more than additive in A-bomb survivors (Shimizu *et al.*, 1988, 1990; NAS/BEIR, 1988).

5. TEMPORAL DISTRIBUTION OF RISK

5.1. Latency

The average period intervening between exposure to radiation and the appearance of a resulting cancer is longer with some forms of cancer than with others. With leukaemia and osteosarcoma, the radiation-induced cases first become evident within 2–5 years after irradiation, reach their peak within the first decade, and gradually decrease in number thereafter (Fig. 3). With solid tumours other than those of bone, however, the excess cases do not become evident until about 10 or more years after irradiation, following which they tend to increase in numbers with advancing age. In A-bomb survivors, the overall excess of mortality from cancer has increased with attained age during adult life, roughly in parallel with the baseline rate, so that the relative risk during adult life has tended to remain more or less constant with age and time after irradiation (Table 1).

In patients with ankylosing spondylitis treated by x-irradiation of the spine, the overall excess of mortality from cancer reached its peak during the second decade after irradiation, after which it appeared to decline for cancers of certain sites (Darby *et al.*, 1987). The basis for the temporal difference in relative cancer excess between the spondylitics and the A-bomb survivors is not clear. Whether it may reflect differences between the two populations in the relative proportions of cancers of the lung and other organs, and/or the influence of extraneous factors remains to be determined.

5.2. Age at Expression

In general, the age-distribution of cancers induced by irradiation appears to parallel

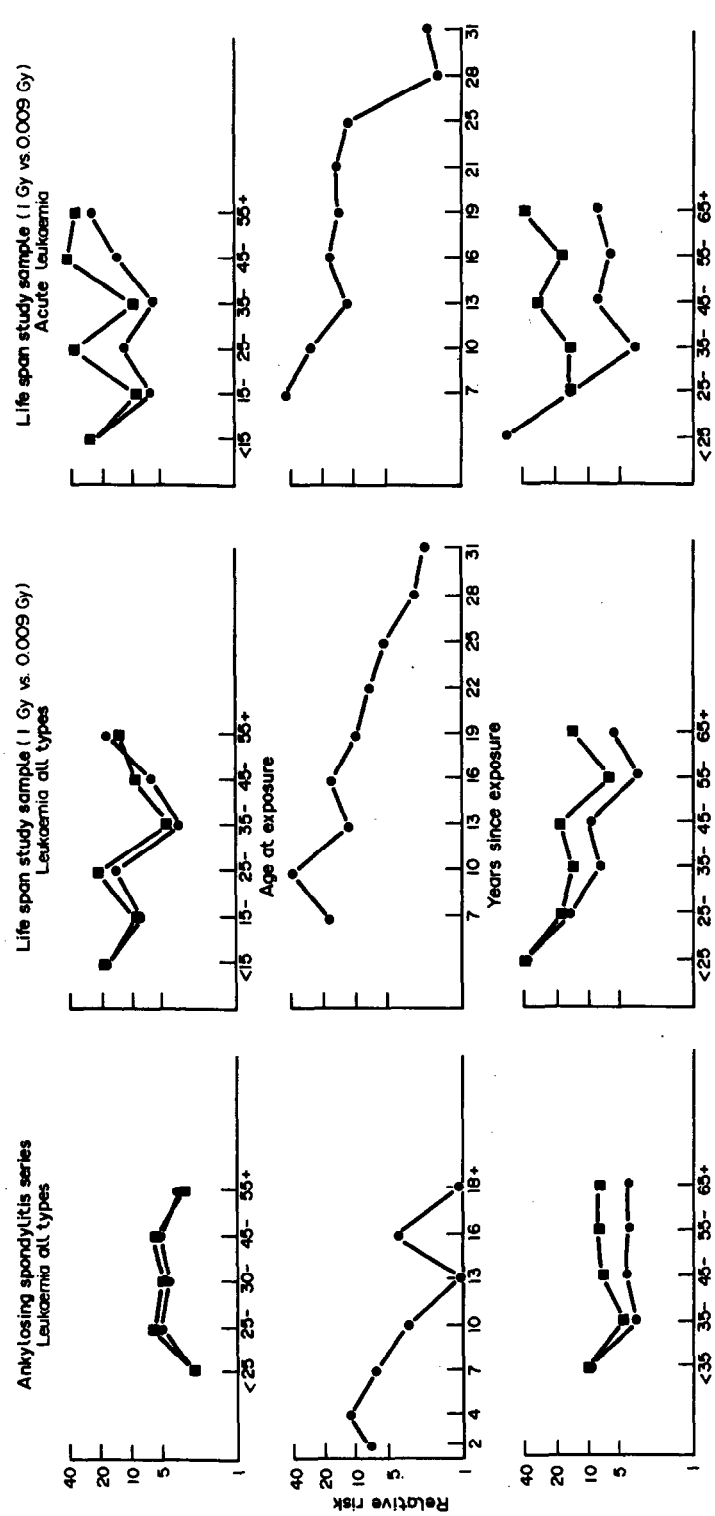

Fig. 3. Variability of relative risk of leukaemia with age at exposure, time since exposure, and age at observation in the Japanese Life Span Study series and in spondylitis patients, based on relative risk models fitted by the authors. Lines marked with circles are for unadjusted data. Lines marked with squares are adjusted by including a linear trend in log RR with time since exposure in the model. For the plotted points, time since exposure has been chosen so that the initial point coincides with the unadjusted value (from Darby *et al.*, 1985).

that of cancers of the same histologic types in the general population. It is noteworthy, therefore, that cancers of the female breast that have been induced by irradiation in childhood have not become evident until 30–40 years later, when the affected women have reached the age at which breast cancer typically starts to appear in the general population. This pattern of age distribution implies that irradiation merely initiates carcinogenesis in the breast, and that completion of the process requires further changes in the breast that are dependent on age-related hormonal stimulation or other factors.

6. MOST RECENT UNSCEAR AND BEIR RISK ESTIMATES

6.1. Risk Coefficients and Lifetime Projections

6.1.1. *Mortality*

6.1.1.1. *All cancers combined*

(i) *Whole population (all ages, both sexes).* In the Japanese A-bomb survivors, the relative risk of mortality from all malignant neoplasms combined, over the follow-up period 1950–1985 (2.2 million person-years), has been estimated to approximate 1.39 (1.32–1.46) per Gy (shielded kerma), which corresponds to an absolute risk of 13.1 (10.4–15.9) excess deaths per 10^4 PYGy organ absorbed dose (Shimizu *et al.*, 1988, 1990). In the x-irradiated spondylitics, by comparison, the relative risk of mortality from all cancers except carcinoma of the colon, averaged over a mean follow-up of 23.0 years (184 thousand person-years), has been estimated to approximate 1.33, corresponding to 6.7 excess deaths per 10^4 PYGy (Smith and Doll, 1981; Darby *et al.*, 1987; UNSCEAR, 1988). The difference in the magnitude of the estimated excess mortality per unit dose may conceivably be attributable to differences between the A-bomb survivors and the spondylitics in: (1) temporal and spatial distribution of the radiation dose, (2) age and sex structure of the population at risk, (3) duration of follow-up, (4) methods of cancer ascertainment, (5) nature of the reference population used for comparison, (6) constitutional differences in susceptibility, (7) subgroup selection, and (8) competing causes of death (e.g. Table 8). Because the influence of any one of these factors on the risk estimates is not precisely known, it is not clear how to combine the two risk estimates. Hence the mortality experience of the A-bomb survivors was selected in both the UNSCEAR (1988) report and the NAS/BEIR V (1990) report as the more appropriate basis for projecting risk estimates for the general population.

Present data from the follow-up of the A-bomb survivors cover only the first 40 years after irradiation, with the result that those survivors who were irradiated in childhood are just now attaining the age at which cancer becomes prevalent in the general population. It is not clear, therefore, how the cancer mortality that they will experience at later ages will compare to the dose-dependent excess of cancer mortality that has already been observed in cohorts which were irradiated at later ages. The most recent data suggest that the overall excess relative risk of mortality from all cancers except leukaemia has varied less with age for a given age at exposure than has the absolute risk, at least during adult life (Table 1). To this extent, therefore, the data are more consistent with a multiplicative risk projection model than with an additive risk projection model.

In both types of models, which incorporate the use of standard, double-decrement lifetable techniques, the computation of lifetime risk following exposure to dose D at age a_0 depends on $q(a)$, the usual rate of death at age a for someone who has reached that

Table 8. Main characteristics of the A-bomb survivor, ankylosing spondylitis, and cervical cancer series (from UNSCEAR, 1988)

Characteristic	Atomic bomb survivor series	Spondylitis series	Cervical cancer series
Nature of study	Prospective	Retrospective–prospective	Retrospective–prospective
Sample size	76,000	14,000	83,000
Sex composition	F = 59%	F = 17%	F = 100%
Age at irradiation (years)	0–>90	>15	<30–>70
Average follow-up (years)	28.8	23.0	7.6
Type of control	Internal	National rates	National rates and internal
Dosimetry	Individual (DS86)	Individual for leukaemia, 1/15 random sample elsewhere	Mean dose of a sample
Irradiation	Instantaneous, whole-body	Fractionated, non-uniform, partial-body	Chronic, fractionated, partial-body
Dose distribution			
Mean dose (Gy)	0.24	1.9	Inhomogeneous
Range of doses (Gy)	(0.01–6.0)	(0–8.06)	
Person-years at risk	2,183,335	184,000	623,800

age (for $a > a_0$), and $\delta(a;a_0,D)$, the excess rate of death at that age resulting from exposure to dose D. Both q and δ can be expressed as cause-specific sums:

$$q(a) = q_1(a) + \ldots + q_k(a)$$
$$\delta(a;a_0, D) = \delta_1(a;a_0,D) + \ldots + \delta_k(a;a_0,D). \quad (1)$$

The probability of survival to age a, given exposure to dose D at age a_0, is $L(a;a_0,D)$. That quantity is calculated from the many values of $q'(a';a_0,D)$ for $a' \leq a$, where

$$q'(a;a_0,D) = q(a) + \delta(a;a_0,D), \quad (2)$$

where $L(a+1;a_0,D) = L(a;a_0,D) \times (1 - q'(a;a_0,D))$ for $a = 0, 1, 2 \ldots$, and where $L(0;a_0,D) = 1$. Death from cause i at age a resulting from the exposure is proportional to $\delta_i(a;a_0,D) \times L(a;a_0,D)$.

In the additive risk projection model, the cause-specific excess risk coefficients δ_i depend on a only in terms of whether or not a exceeds a_0 by at least a minimal latent period P_i:

$$\delta_i(a;a_0,D) = \begin{cases} A_i(a_0,D) & \text{if } a > a_0 + P_i \\ 0 & \text{if } a \leq a_0 + P_i \end{cases}$$

In the multiplicative risk projection model, δ_i is a multiple of q:

$$\delta_i(a;a_0,D) = \begin{cases} M_i(a_0,D) \times q_i(a) & \text{if } a > a_0 + P_i \\ 0 & \text{if } a \leq a_0 + P_i \end{cases}$$

The coefficients $A_i(a_0,D)$ and $M_i(a_0,D)$, which depend only on dose D and age at exposure a_0, for a given sex, are the so-called absolute and relative risk coefficients for the cause denoted by the index i.

For most cancer sites, population risks increase with age, with the result that risks projected from the results of an incomplete follow-up tend to be substantially larger using the multiplicative model than using the additive model. This difference must gradually disappear with continued observation, as a follow-up nears completion. Projected lifetime risks according to both models are now somewhat larger than heretofore, partly because of the dosimetric changes discussed elsewhere in this report. But it is noteworthy that the estimates projected by the additive model have increased appreciably more than those projected by the multiplicative model, with the result that the difference between the two types of estimates has diminished substantially (Table 9).

Table 9. Projected excess cumulative lifetime mortality from cancer, all types combined, attributable to 1 Gy acute whole-body low-LET irradiation of the general population

Source of estimate	Additive risk projection model	Multiplicative risk projection model
	(deaths per 10,000 persons)[a]	
BEIR I, 1972	120[b]	620[b]
UNSCEAR, 1977	250[b]	—
BEIR III, 1980	80[c]–250[b]	230[c]–500[b]
NUREG, 1985	290[c]	520[c]
UNSCEAR, 1988	400[b,d]–500[b,e]	700[b,e]–1100[b,d]
BEIR V, 1989	—	885[b,f]

[a] Values rounded; estimates based largely on follow-up of Japanese A-bomb survivors, analysed with T65D dosimetry prior to 1988 and with DS-86 dosimetry thereafter.

[b] Linear dose–incidence model.

[c] Estimate based on linear-quadratic dose–incidence model.

[d] Estimate for Japanese population, based on age-specific risk coefficients.

[e] Estimate for Japanese population, based on age-averaged risk coefficient.

[f] Estimate for U.S. population, based on modified multiplicative model (see footnotes to Table 11).

(ii) *Mortality, all cancers combined, as influenced by age at exposure.* In an effort to evaluate the influence of age at the time of exposure on the subsequent risk of cancer, the above risk projection models have been applied to the cancer mortality data for A-bomb survivor cohorts of different ages. If limited to an age range as narrow as 10 years, however, the resulting estimates are highly uncertain, owing to the small numbers of cases in any such narrowly restricted cohort. In the 1988 UNSCEAR report, therefore, estimates were presented only for cohorts of broader age ranges; namely: (1) the entire population, including persons of every age, (2) all adults over the age of 25, and (3) adults predominantly of working age (25–64 years). For these three broad age groups, the estimates (Table 10) indicate the lifetime risk of radiation-induced cancer in those exposed during adult life to be substantially lower than in those exposed during childhood and adolescence. This conclusion is supported and amplified by BEIR V (NAS/BEIR, 1990) estimates for narrower, 10-year age cohorts (Table 11).

(iii) *Mortality, all cancers combined, as influenced by sex.* In general, the sex ratios of radiation-induced cancers at specific sites appear to resemble those of the corresponding

Table 10. Projections of lifetime risk of fatal cancer for 10,000 persons (5,000 males and 5,000 females) exposed rapidly to 1 Gy whole-body low-LET radiation (from UNSCEAR, 1988)

	Risk projection model	Excess fatal cancers[a]	Years of life lost[a]
Total population	Additive	400[b]–500[c]	9500[b]–12000[c]
	Multiplicative	700[c]–1100[b]	9500[c]–14000[b]
Working population (aged 25–64 years)	Additive	400[c]–600[b]	8800[c]–13300[b]
	Multiplicative	700[b]–800[c]	8200[b]–9700[c]
Adult population (over 25 years)	Additive	500[c]	8400[c]
	Multiplicative	600[c]	6200[c]

[a] Based on cancer mortality rates for the population of Japan.
[b] Derived with age-specific risk coefficients.
[c] Derived with constant (age-averaged) risk coefficient.

Table 11. Estimated excess lifetime mortality from cancers of various organ systems after acute exposure to 0.1 Sv in relation to age at exposure and sex (from NAS/BEIR, 1990)[a]

Males (deaths per 10^5)

Age at exposure	Total	Leukaemia	Nonleukaemia	Respiratory	Digestive	Other
5	1276	111	1165	17	361	787
15	1144	109	1035	54	369	612
25	921	36	885	124	389	372
35	566	62	504	243	28	233
45	600	108	492	353	22	117
55	616	166	450	393	15	42
65	481	191	290	272	11	7
75	258	165	93	90	5	—
85	110	96	14	17	—	—
Average[c]	770	110	660	190	170	300

Females (deaths per 10^5)

Age at exposure	Total	Leukaemia	Nonleukaemia[b]	Breast	Respiratory	Digestive	Other
5	1532	75	1457	129	48	655	625
15	1566	72	1494	295	70	653	476
25	1178	29	1149	52	125	679	293
35	557	46	511	43	208	73	187
45	541	73	468	20	277	71	100
55	505	117	388	6	273	64	45
65	386	146	240	—	172	52	16
75	227	127	100	—	72	26	3
85	90	73	17	—	15	4	—
Average[c]	810	80	730	70	150	290	220

[a] Based on a single exposure to radiation, and on a lifetable weighted average over each of the age groups listed, in a stationary population having U.S. mortality rates.
[b] Based on the sum of cancers of respiratory tract, digestive tract, breast, and other organs.
[c] Values rounded to nearest 10.

The age-specific cancer risk $y(d)$ was expressed as:

$$y(d) = y_0[1 + f(d)g(\beta)].$$

where y denotes the age-specific background risk of death due to a specific cancer for an individual at a given age, which also depends upon the individual's sex and year of birth, $f(d)$ represents a function of the dose, d

(in sievert), which is a linear or linear-quadratic function—i.e. $f(d) = \alpha_1 d$ or $f(d) = \alpha_2 d + \alpha_3 d_2$—and $g(\beta)$ is the excess risk function, which may depend on sex, attained age, age at exposure (E), and time after exposure (T).

For the leukaemia model, the parameters were:

$$f(d) = \alpha_2 d + \alpha_3 d_2$$

$$g(\beta) = \begin{cases} \exp[\beta_1 I(T \leq 15) + \beta_2 I(15 < T < 25)] \text{ if } E \leq 20 \\ \exp[\beta_3 I(T \leq 25) + \beta_4 I(25 < T \leq 30)] \text{ if } E > 20, \end{cases}$$

where the indicator function $I(T \leq 15)$ is defined as 1 if $T \leq 15$ and 0 if $T > 15$. The estimated parameter values and their standard errors, in parentheses, are:

$\alpha_2 = 0.243(0.291)$, $\alpha_3 = 0.271(0.314)$,

$\beta_1 = 4.885(1.349)$, $\beta_2 = 2.380(1.311)$, $\beta_3 = 2.367(1.121)$,

$\beta_4 = 1.638(1.321)$.

For cancer of the respiratory tract (ICD 160–163), the model parameters were as follows:

$$f(d) = \alpha_1 d$$

$$g(\beta) = \exp[\beta_1 ln(T/20) + \beta_2 I(S)],$$

where $I(S) = 1$ if female, 0 if male, with $\alpha_1 = 0.636(0.291)$, $\beta_1 = 1.437(0.910)$, $\beta_2 = 0.711(0.610)$.

For breast cancer (female only), the model parameters were:

$$f(d) = \alpha_1 d$$

$$g(\beta) = \begin{cases} \exp[\beta_1 + \beta_2 \ln(T/20 + \beta_3 \ln^2(T/20)] \text{ if } E < 15 \\ \exp[\beta_2 \ln(T/20) + \beta_3 \ln^2(T/20) + \beta_4 (E - 15)] \text{ if } E \geq 15, \end{cases}$$

where $\alpha_1 = 1.220(0.610)$, $\beta_1 = 1.385(0.554)$, $\beta_2 = -0.104(0.804)$, $\beta_3 = -2.212(1.376)$, $\beta_4 = -0.0628(0.0321)$.

For cancer of the digestive system (ICD 150–159), the model parameters were:

$$f(d) = \alpha_1 d$$

$$g(\beta) = \exp[\beta_1 I(S) + \sigma E]$$

where $I(S)$ equals 1 for females and 0 for males and

$$\sigma E = \begin{cases} 0 \text{ if } E \leq 25 \\ \beta_2 (E - 25) \text{ if } 25 < E \leq 35 \\ 10\beta_2 \text{ if } E > 35 \end{cases}$$

with $\alpha_1 = 0.809(9.327)$, $\beta_1 = 0.553(0.462)$, $\beta_2 = -0.198(0.0628)$.

For cancers other than those listed above (ICD 140–209 less those listed above), the model parameters were:

$$f(d) = \alpha_1 d$$

$$g(\beta) = 1 \text{ if } E \leq 10 \text{ and } \exp[\beta_1 (E - 10)] \text{ if } E > 10,$$

with $\alpha_1 = 1.220(0.519)$, $\beta_1 = -0.0464(0.0234)$.

cancers in the general population. The relative risks for many epithelial cancers, however, tend to be slightly higher in females than in males (e.g. Tables 7 and 11), as discussed below. This fact, plus the substantial contribution of breast cancer to the total mortality from all cancers combined, accounts for a significantly higher projected cumulative lifetime excess in females (Table 12).

6.1.1.2. *Leukaemia, excluding chronic lymphatic leukaemia (CLL)*

(i) *Whole population.* Estimates of the risk of radiation-induced leukaemia attributable to whole-body irradiation of the whole population are based primarily on the follow-up of the Japanese A-bomb survivors, the only population of all ages for which quantitative dose–effect data are available. These estimates, summarised in Tables 11 and 12, are based on a dose-dependent excess of deaths from leukaemia (all types excluding CLL) in the survivor population during the period 1950–1985 (Shimizu *et al.*, 1988, 1990).

Table 12. Comparison between men and women in projected excess cumulative lifetime mortality from cancer after rapid exposure to 1 Gy whole-body low-LET radiation as adults (from UNSCEAR, 1988)

Types of cancer	Duration of plateau period 40 years		Lifetime	
	Additive risk projection model	Multiplicative risk projection model	Additive risk projection model	Multiplicative risk projection model
	(Deaths per 10^4)[a]			
Leukaemia[b]				
males	130	90	—	—
females	70	81	—	—
average	100	86	—	—
Other cancers[c]				
males	290	370	300	410
females	390	460	420	520
average	340	420	360	470

[a] Based on A-bomb survivor data and cancer mortality data for Japan, 1982.
[b] Assumed latency: 2 years.
[c] Assumed latency: 10 years.

(ii) *Leukaemia by age at exposure.* In the A-bomb survivors and in the spondylitics, the relative excess mortality from leukaemia appears to vary less with age at the time of irradiation than the absolute excess, which is several times larger in those irradiated during childhood or late adult life than in those irradiated during early adulthood (Fig. 2). Lifetime risks are, likewise, projected to vary accordingly (Tables 11 and 13).

Also, as mentioned above, the association between prenatal diagnostic irradiation and childhood leukaemia suggests that the relative risk per unit dose is substantially higher in those irradiated late in intra-uterine life than in those irradiated at any age during postnatal life (Mole, 1990).

(iii) *Leukaemia by sex.* In the only population from which quantitative dose–response data are available for both sexes—namely, the A-bomb survivors—the relative excess mortality from leukaemia is slightly larger in males than in females (Table 7), but the absolute risks projected for males are much larger than those for females (Tables 7, 11 and 12).

6.1.1.3. *All cancers other than leukaemia*

(i) *Whole population.* In the only population from which data are available for both sexes and all ages—namely, the Japanese A-bomb survivors—the dose-dependent excess mortality from all cancers other than leukaemia during the period 1950–1985 corresponds to an excess relative risk of 0.41 (0.32–0.51) per Gy organ absorbed dose and an absolute risk of 10.13 excess cancer deaths per 10^4 PYGy (Shimizu *et al.*, 1988, 1990). On the basis of these data, the cumulative lifetime risk of mortality from such malignancies in a population of all ages following a single brief exposure to 1 Gy of whole-body low-LET radiation has been estimated to range from 420 to 1070 cancer deaths per 10^4 persons (Tables 11 and 13).

(ii) *Mortality from all cancers other than leukaemia, in relation to age at exposure.* For the reasons given above (Section 6.1.1.1.(ii)), risk estimates for each 10-year age cohort were not presented by the UNSCEAR (1988) Committee. The broader age-specific estimates that were reported indicate the excess to be substantially larger in those

Table 13. Projected excess cumulative lifetime mortality from leukaemia and other cancers after 1 Gy rapid whole-body low-LET irradiation, in relation to age at the time of exposure (from UNSCEAR, 1988)

Type of cancer	Additive risk projection model	Multiplicative risk projection model
	(Deaths per 10^4 at 1 Gy)[a]	
Leukaemia[b]		
adult population	100	86
population of all ages	100	100
Other cancers[c]		
adult population	360	470
population of all ages	420	1070

[a] Based on A-bomb survivor data and cancer mortality rates from Japan, 1982.
[b] Duration of plateau period: 40 years.
[c] Duration of plateau period: lifetime.

irradiated during childhood than in those irradiated during adult life (Table 13), in keeping with estimates by the NAS/BEIR V (1989) committee for each 10-year age cohort (Table 11).

(iii) *Mortality from all cancers other than leukaemia in relation to sex.* In A-bomb survivors during the period 1950–1985, the overall excess mortality from cancers of all types other than leukaemia was larger in females than in males; i.e., the excess relative risk at 1 Gy was 0.48 in females, as compared with 0.18 in males (Shimizu *et al.*, 1990). Thus the projected cumulative lifetime excess of mortality from such cancers in females is slightly higher than that in males (Tables 7, 11, and 12).

6.1.1.4. *Mortality from cancers of other specific sites*

(i) *Whole population.* The excess mortality from cancer in A-bomb survivors over the period 1950–1985 resulted largely from leukaemia and cancers of the stomach, lung, female breast, colon, and ovary, with cancers of other sites contributing fewer excess deaths (Table 3). Based on the findings in the A-bomb survivors, along with supporting data from epidemiological studies of other irradiated populations, estimates of the cumulative lifetime excess mortality from cancers of different types and sites range from $9–22 \times 10^{-4}$ Gy^{-1} for multiple myeloma to $59–151 \times 10^{-4}$ Gy^{-1} for cancer of the lung (Table 14).

Organs other than those listed in Table 14, for which the risks of fatal radiation-induced cancers are not derived from the A-bomb survivor data, include the thyroid gland, skin, liver, and bone. Since radiation-induced cancers of the thyroid gland and skin are preponderantly non-fatal, they are discussed below, in the section of the report dealing with incidence (Section 6.1.2).

As concerns radiation-induced cancers of bone, both UNSCEAR (1988) and BEIR V (NAS/BEIR, 1990) relied on previous estimates by BEIR III (NAS/BEIR, 1980) and BEIR IV (NAS/BEIR, 1988). From the latter, based on life table analysis and a lethality fraction of 0.70, the lifetime risk of bone cancer is estimated to approximate 93×10^{-4} Gy^{-1} of low-LET radiation, or 4.7×10^{-4} Sv^{-1} (RBE = 20).

Table 14. Projections of excess cumulative lifetime mortality from specific cancers after acute exposure to 1 Gy of organ absorbed dose of low-LET radiation (from UNSCEAR, 1988). (Based on age-averaged coefficients applied to rates for the population of Japan 90% confidence intervals in parentheses.)

Malignancy	Multiplicative risk projection model	Additive risk projection model
	(Deaths per 10^4 at 1 Gy)	
Red bone marrow	97 (71–132)	93 (77–110)
All cancers except leukaemia	610 (480–750)	360 (280–440)
Bladder	39 (16–73)[f]	23 (11–40)[f]
Breast[a]	60 (28–105)	43 (22–69)
Colon	79 (36–134)	29 (14–46)
Lung	151 (84–230)	59 (34–88)
Multiple myeloma	22 (6–51)	9 (3–17)
Ovary[a]	31 (9–68)	26 (8–48)
Oesophagus	34 (8–72)	16 (3–31)
Stomach	126 (66–199)	86 (45–131)
Remainder	114[b]	103[b]
	118[c]	66[c]
Total	707[d]	453[d]
	712[e]	416[e]

[a] These values have to be divided by 2 to calculate the total and other organ risks.

[b] This value is derived by subtracting the sum of the risks at the sites specified from the risks for all cancers except leukaemia.

[c] This value is derived by fitting a linear relative risk model to the basic cancer data after the exclusion of those cases of cancer at the specific sites listed. (Coefficient 0.19 excess relative risk per Gy and 1.87 per 10^4 PYGy.)

[d] Red bone marrow plus all other cancers.

[e] Red bone marrow plus other individual sites including remainder.

[f] Unadjusted for smoking habits.

With respect to cancer of the liver, existing estimates are based primarily on the hepatocarcinogenic effects of locally deposited internal emitters, which have been well documented in both humans and laboratory animals (NAS/BEIR, 1988). The human data come largely from patients injected intravascularly with thorotrast, in Portugal, Denmark, West Germany, Japan, and the United States, in whom primary cancers of the liver (including haemangiosarcomas, bile duct carcinomas, and hepatocellular carcinomas) have been observed to be increased greatly in frequency decades later, after accumulation of alpha doses to the liver in the range of 2–15 Gy (NAS/BEIR, 1988). Comparable hepatocarcinogenic effects of external irradiation have not been evident in the spondylitics (Darby *et al.*, 1987). In the A-bomb survivors dying during the period 1950–1985, however, the relative risk of liver cancer was estimated to be 1.26 at 1 Gy (90% confidence interval, 1.05–1.53) (Shimizu *et al.*, 1988, 1990), but this estimate is complicated by the inclusion of unknown numbers of cases of metastases of other cancers to the liver. On the basis of the observed effects of thorotrast in humans, complemented by the comparative effects of various alpha- and beta-emitters in laboratory animals, the lifetime risk of radiation-induced human liver cancer has been estimated to approximate 300 cancers/10^4 person Gy for alpha radiation, and to be

lower by at least an order of magnitude for beta radiation (NAS/BEIR, 1990). If an RBE of 20 is assumed for alpha particles, the corresponding risk estimate for low-LET radiation is 15×10^{-4} Sv^{-1}.

(ii) *Mortality from cancers of other specific sites, in relation to age at exposure.* Owing to the long latency for radiation-induced cancers and the fact that no population group irradiated early in life has been followed for an entire lifespan, the susceptibility of young, as compared with old, individuals is yet to be fully determined. Nevertheless, the existing data suffice to indicate large age-dependent differences in susceptibility to certain types of cancer; e.g. susceptibility to the induction of cancer of the female breast appears to be highest in those irradiated in childhood or adolescence and to decrease markedly with age during adult life, virtually disappearing after the menopause (Fig. 4).

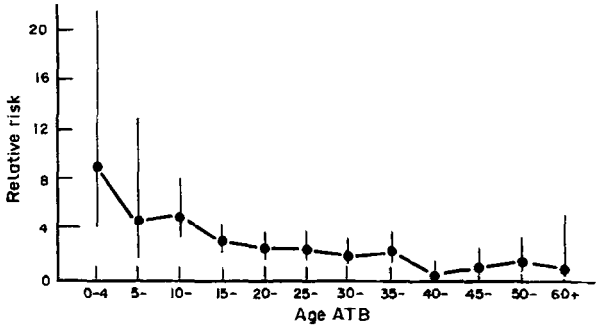

Fig. 4. Relative risk of breast cancer in A-bomb survivors exposed to 0.5+ Gy versus that in A-bomb survivors exposed to 0–0.09 Gy kerma (including those not-in-city), in relation to age at the time of the bombings. The vertical bars denote the 90% confidence intervals (from Tokunaga *et al.*, 1984).

(iii) *Mortality from cancers of other specific sites, in relation to sex.* Apart from cancer of the breast, the induction of which has yet to be documented conclusively in men, cancers of epithelial tissues in general appear to be induced at higher relative rates in women than in men, as noted above (Tables 7 and 11). Projections of the cumulative lifetime excess mortality from specific cancers were not presented separately for each sex, however, in the UNSCEAR (1988) and NAS/BEIR (1990) reports, owing to the small numbers of cases for such projections. Instead, data for certain specific sites were pooled to enable projections for the organ systems in question, as shown in Table 11.

6.1.2. *Incidence*

6.1.2.1. *Ratio of incidence to mortality for cancers of different sites.* The existing epidemiological data on radiation-induced cancer come largely from studies of the mortality of irradiated populations. Data on the incidence of radiation-induced cancer in such populations are, by comparison, relatively sparse. Insofar as they are available, however, the incidence data are generally consistent with the mortality data in respect to the magnitude and age-distribution of radiation-induced cancers. For most anatomical sites, to estimate the risks of radiation-induced cancers in terms of incidence it has generally been customary to increase the mortality estimates by factors that adjust for the survivability of the cancers in question (e.g. Table 15).

Table 15. Lethality data for cancers in adults by site (U.S. DHHS, 1989)[a]

	5 year 1980–85	20 year lethality 1950–70	Proposed lethality fraction[b]
Bladder	0.22	0.58	0.50
Bone	—	0.72	0.70
Brain	0.75	0.84	0.80
Breast	0.24	0.62	0.50
Cervix	0.33	0.50	0.45
Colon	0.45	0.62	0.55
Kidney	0.48	0.78	0.65
Leukaemia (acute)	0.98	0.99	0.99
Liver	0.95	0.98	0.95
Lung and Bronchus	0.87	0.96	0.95
Oesophagus	0.92	0.97	0.95
Ovary	0.62	0.74	0.70
Pancreas	0.97	0.99	0.99
Prostate	0.26	0.84	0.55
Skin	—	—	0.002
Stomach	0.85	0.90	0.90
Thyroid	0.06	0.15	0.10
Uterus	0.17	0.35	0.30

[a] Numbers were derived from tables and graphical data of U.S. DHHS, 1989 by F. A. Mettler and W. K. Sinclair.
[b] Recommended in Annex B, *ICRP Publication 60* (ICRP, 1991).

6.1.2.2. *Risk estimates for thyroid cancer.* Cancers of the thyroid gland represent an exception to the above generalisation, since those caused by radiation tend to be predominantly papillary growths which carry a relatively low (10–15%) rate of mortality (UNSCEAR, 1988; NAS/BEIR, 1990). Studies of the incidence of thyroid cancer in A-bomb survivors, persons treated with x rays to the scalp for tinea capitis in childhood, persons treated with x rays to the neck in infancy for enlargement of the thymus gland and other benign conditions, Marshall Islanders exposed to nuclear fallout, and other populations irradiated at relatively high dose rates have been interpreted to indicate that the risk of thyroid cancer increases as a linear, non-threshold function of the dose (e.g. Fig. 5), but at a rate for any given dose that varies with age, sex, and type of radiation according to the formula:

$$E = RFSAY \tag{3}$$

where E is the estimated absolute risk specific for the population in question, R is the risk coefficient (taken to be 2.5 thyroid cancers per 10^4 PYGy) for doses in the range of 0.06–15.0 Gy, F is the dose-effectiveness factor (taken to be 1.0 for external x-irradiation, ^{132}I, ^{133}I, and ^{135}I, and taken to be 1/3 for ^{125}I and ^{131}I), S is the sex factor (taken to be 4/3 for women and 2/3 for men), A is the age factor (taken to be 1.0 for persons < 18 years and 1/2 for those > 18), and Y is the anticipated mean number of years at risk (NCRP, 1985). The lower risk coefficient used with ^{125}I and ^{131}I is based on the substantially lower risks that have been observed in patients injected with diagnostic doses of these radionuclides (Section 3.2).

Estimates derived with the above formula lie in the range of $1\text{–}4 \times 10^{-4}$ PYGy for adults and $1.5\text{–}9.5 \times 10^{-4}$ PYGy for children, the average lifetime risk for the entire population approximating 75 cancers per 10^4 persons per Gy—corresponding to roughly 7.5 fatal cancers per 10^4 persons per Gy (NCRP, 1985; UNSCEAR, 1988; NAS/BEIR, 1990).

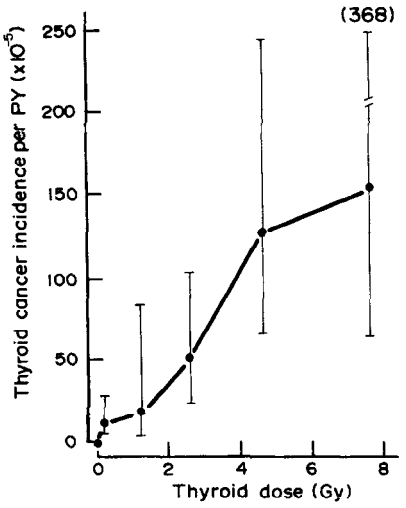

Fig. 5. Thyroid cancer incidence in relation to thyroid dose, adjusted for sex, ethnicity and interval since irradiation. The vertical bars denote the 90% confidence limits (from Shore *et al.*, 1985).

6.1.2.3. *Risk estimates for skin.* Lifetime risk estimates for radiation-induced skin cancer, based primarily on patients exposed to therapeutic x-radiation, are estimated to approximate 1000 per 10^4 per Gy, with a lethality fraction of about 0.2% (Fry *et al.*, 1990). Since these estimates are evaluated at length in another Task Group report (Fry *et al.*, 1991), they will not be discussed further herein.

6.1.3. *Loss of life expectancy*

To the extent that the total impact of a given cancer death depends on the age at which the affected person dies, it is important to express the risks of radiation-induced cancer in terms of the years of life lost due to the cancer as well as in terms of the numbers of deaths from the disease. The loss of life expectancy in individuals receiving a dose D at age a_0 may be calculated by the expression:

$$\sum_{a;a_0}^{a_{max}} L(a) - L(a;a_0,D) \qquad (4)$$

where the notations are the same as those in equations 1 and 2 (in Section 6.1.1.1), and the difference between the life expectancy of the irradiated individuals and that of an unirradiated population represents the loss of life expectancy resulting from the dose in question (UNSCEAR, 1988).

On average, the loss of life expectancy per person in a population of all ages that is attributable to the carcinogenic effects of 1 Gy rapid whole-body low-LET radiation is estimated to be about 1 year, depending on whether the estimate is derived by the use of a multiplicative risk projection model or an additive risk projection model, among other factors (Table 16). In those irradiated late in life, the loss of life expectancy is estimated to be less, on average, than in those irradiated at younger ages, particularly when the estimates are based on the additive risk projection model (Table 17). In a population exposed continuously to whole-body radiation from age 18 to age 65, at a rate of 0.01 Sv

per year, the loss of life expectancy from cancer is estimated to average slightly less than one half year per person, or about 16 years per excess cancer death (Table 18).

Table 16. Projected loss of life expectancy from specific cancers per person after exposure to 1 Gy of organ absorbed dose of low-LET radiation at high dose rate (from UNSCEAR, 1988). (Based on the population of Japan. 90% confidence intervals in parentheses.)

Malignancy	Multiplicative risk projection model	Additive risk projection model
	(yr/Gy)	
Red bone marrow	0.22 (0.16–0.27)	0.30 (0.25–0.36)
All cancers except leukaemia	0.73 (0.57–0.90)	0.91 (0.71–1.10)
Bladder	0.03 (0.01–0.06)	0.04 (0.02–0.07)
Breast[a]	0.11 (0.05–1.90)	0.11 (0.05–0.17)
Colon	0.09 (0.04–0.15)	0.07 (0.04–0.12)
Lung	0.17 (0.09–0.25)	0.15 (0.09–0.22)
Multiple myeloma	0.03 (0.00–0.06)	0.02 (0.01–0.04)
Ovary[a]	0.06 (0.02–0.12)	0.07 (0.02–0.12)
Oesophagus	0.04 (0.01–0.08)	0.04 (0.01–0.08)
Stomach	0.15 (0.07–0.23)	0.22 (0.11–0.33)
Remainder	0.14[b] 0.14[c]	0.28[b] 0.17[c]
Total	0.95[d] 0.94[e]	1.2[d] 1.1[e]

[a] These values have to be divided by 2 to calculate the total and other organ risks.

[b] This value is derived by subtracting the sum of the risks at the sites specified from the risks for all cancers except leukaemia.

[c] This value is derived by fitting a linear relative risk model to the basic cancer data after the exclusion of those cases of cancer at the specific sites listed. (Coefficient 0.19 excess relative risk per Gy and 1.87 per 10^4 PYGy).

[d] Red bone marrow plus all other cancers.

[e] Red bone marrow plus other individual sites including remainder.

Table 17. Projected loss of life expectancy, as a function of age at exposure for a population of both sexes (500 males and 500 females) exposed to 1 Gy whole-body low-LET radiation at high dose rate, using an age-constant risk coefficient (from UNSCEAR, 1988)

Organ or tissue	Age at exposure							
	0	10	20	30	40	50	60	70
	(yr/10^3/Gy)							
	Additive Model							
Leukaemia	640	530	420	310	210	120	62	24
All cancers except leukaemia	2360	1750	1230	800	470	240	93	22
	Multiplicative Model							
Leukaemia	250	242	250	260	240	190	130	63
All cancers except leukaemia	920	930	920	880	790	620	370	130

Table 18. Projected lifetime cancer mortality and associated loss of life expectancy from continuous whole-body irradiation in a population of both sexes (NAS/BEIR V, 1990)

	Exposure throughout life (1 mSv/yr)	Exposure from age 18 to age 65 (10 mSv/yr)
Excess cancer deaths		
No. per 10^4	56	300
% of normal	3	16
Loss of life expectancy (yr)		
Average per person exposed	0.2	0.5
Average per excess death	17	16

Calculations based on cancer and survival rates for the U.S. population and on use of the risk models presented in Table 11, which include an implicit DREF of about 2.0 for leukaemia and DREF of 1 for solid tumours.

7. COMPARISON OF NEW ESTIMATES WITH THOSE USED IN *ICRP 26*

The cumulative lifetime risks that were projected in *ICRP 26* (1977) (Column 1, Table 20) are appreciably lower than those projected in the most recent UNSCEAR (1988) and NAS/BEIR (1990) reports (Table 19), even if the latter are similarly reduced by a factor of 2–3 to allow for a reduced effectiveness of radiation at the low dose rates characteristic of occupational irradiation (Column 2, Table 20). These estimates, derived from UNSCEAR 1988 and BEIR V 1990, are quite similar to those finally recommended in Annex B, Table B-20 (ICRP, 1991). The latter are based on detailed age-specific information on organ risks from the Japanese data (Shimizu *et al.*, 1988, 1990)

Table 19. Comparative estimates of lifetime cancer risks attributable to 1 Sv acute whole-body irradiation, based on latest UNSCEAR and BEIR projections

	UNSCEAR estimate[a]		BEIR V estimates	
Organ at risk	Additive risk model	Multiplicative risk model	Modified multiplicative risk model[b]	
	(Cancer deaths/10^4/Sv)[c]			
Bone marrow	90	100	190	
Lung	60	150	170	
Breast	20	30	40	
Thyroid	—	—	—	
Colon	30	80		
Stomach	90	130	230	
Oesophagus	20	30		
Urinary tract	20	40		
Ovary	20	20	~250	
Multiple myeloma	10	20		
Remainder	100	110		
Total	460	710	880	

[a] From Table 14, based on age-averaged coefficients (the estimates would be roughly 50 percent higher if based on age-specific coefficients, as indicated in Table 9 and 10).
[b] From Table 11, leukaemia adjusted, × 2.
[c] Values, averaged for both sexes, rounded to nearest 10.

Table 20. Lifetime cancer risk estimates based on UNSCEAR (1988) and NAS/BEIR V (1990) reports, in comparison with those assumed in *ICRP 26* (ICRP, 1977)

Organ at risk	Cancer deaths/10^4/Sv	
	ICRP 26	UNSCEAR/BEIR[a]
Bone marrow	20	85
Bone	5	5
Lung	20	100
Thyroid	5	10
Breast	25	20
Subtotal	75	220
Remainder		
G-I tract	—	150
Ovary	—	15
Bladder	—	30
Multiple myeloma	—	15
Skin	—	2
Other	—	65
Subtotal	50	282
Total	125	500

[a] Rounded values, based on averages of the UNSCEAR and BEIR multiplicative projections derived with age-specific risk coefficients, divided by a DREF of 2.0 for compatibility with the estimates in *ICRP 26*, which were applicable to irradiation at low dose rates.

which has been examined for variations due to sex, age, national population characteristics, and the type of transfer model. Table B-20 in Annex B resulted from an overall averaging process for all the variables considered (see Annex B, ICRP, 1991; Land and Sinclair, 1991).

Although neither the latest UNSCEAR (1988) report nor the BEIR V report (NAS/BEIR, 1990) recommended a specific dose rate effectiveness factor (DREF) for use in adjusting risk estimates for exposures at low doses and low dose rates, both reports cited previous analyses (NCRP, 1980; UNSCEAR, 1986) documenting evidence that the carcinogenic effectiveness of low-LET radiation in laboratory animals is generally lower by a factor of 2–10 at low doses (0.20 Gy) and low dose rates (< 1 mGy min^{-1}) than at high doses (> 3 Gy) and high dose rates (> 100 mGy min^{-1}). On the basis of such data, therefore, both reports suggested that the use of a DREF at the lower end of this range would not be unreasonable. It should be noted, however, that since a linear-quadratic dose–incidence model was used for leukaemia in the BEIR V report, which introduced an implicit DREF of approximately 2.0 for this disease, no further adjustments for dose or dose rate in the risk estimates for leukaemia were deemed to be justifiable (NAS/BEIR, 1990).

8. CONCLUSIONS

On the basis of the latest evidence, as summarised in the reports of the UNSCEAR (1988) and BEIR V Committee (NAS/BEIR, 1990), the Task Group concludes that the

lifetime risk of fatal cancer for a member of the general population exposed to low-level whole-body irradiation can be assumed to average approximately 5 per cent per Sv, thus exceeding that estimated in *ICRP 26* by a factor of about 3–4.

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THE RELATIVE CONTRIBUTIONS OF DIFFERENT ORGAN SITES TO THE TOTAL CANCER MORTALITY ASSOCIATED WITH LOW-DOSE RADIATION EXPOSURE

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1. INTRODUCTION

The ICRP introduced the system of attempting to quantify late-occurring detrimental health effects in relation to low-dose exposure in 1977 (ICRP, 1977) and adapted a set of weighting factors to apportion the total health detriment in the body according to the relative contributions of the effects from the principal body organs involved. Application of this system universally, regardless of age, sex, and population characteristics possibly related to socio-economic, ethnic, or environmental differences, involves the implicit assumption that related differences in detriment between individuals are not sufficiently large to require different sets of weights for different circumstances. Radiation-induced cancer is a most important component of the total detriment and therefore the relative contributions of fatal cancers induced in individual body organs are of great significance. In this paper we attempt to explore the factors involved in the assessment of the relative contributions of mortality from cancer of individual organs and thus to provide a basis for new estimates of weighting factors to be made by the ICRP in assessing the total detriment for a given dose.

Recent evaluations of radiation-induced risk of cancer mortality by expert committees, here referred to as UNSCEAR (UNSCEAR 1988) and BEIR V (NAS, 1990), reflect the

increased information available from the addition of new study populations and longer follow-up of the major exposed populations already under study. This information includes data on dose response and on the distribution of cancer risk by organ site and its dependence on age, sex, and time following exposure. Estimates of total cancer risk per unit equivalent dose have increased, partly due to changes in the dosimetry used to evaluate the Japanese A-bomb survivor experience from Hiroshima and Nagasaki but also because, as the younger age cohorts of the study populations have moved into age ranges of increasing baseline cancer rates, they have been found to have somewhat higher excess risks than cohorts exposed at older ages. In addition, the recent preference for multiplicative models of projection from the period of observation to lifetime risk has been an important factor.

Both UNSCEAR and BEIR V provided models and risk coefficients by which the lifetime mortality risk due to induced cancer could be calculated for an exposed population; these models were applied to various exposure scenarios for contemporary life-table populations with mortality and baseline cancer rates characteristic of Japan (UNSCEAR, 1988) and the United States (NAS, 1990). UNSCEAR used conventional additive and multiplicative projection models for leukaemia and for all non-leukaemia cancers as a group, but also for many single organ sites, with coefficients that did not depend upon age, sex, or time following exposure. The BEIR V Committee (NAS, 1990) developed, for leukaemia, non-leukaemia cancers as a group, digestive cancers as a group, lung cancer, and breast cancer, multiplicative models modified by indicator and spline functions of exposure age, attained age, sex, and time after exposure. The present investigation might have proceeded by using the UNSCEAR and BEIR V models and coefficients but, given the site-specific detail needed for the ICRP weights, and our interest in variation by exposure age and sex as well as in the role of projection and transfer models, it seemed preferable to use the directly available risk coefficients for the UNSCEAR list of organs from the most recent report in the A-bomb survivor mortality series (Shimizu *et al.*, 1988 and 1990).

2. METHODS

The basic data for the study were the coefficients in Table 1, adapted from Table 5 of Shimizu *et al.* (1988) and other parts of that report. These coefficients were obtained by modelling site-specific cancer mortality as a linear function of DS86 organ equivalent dose with an assumed neutron RBE of 10, within subsets defined by age at the time of the bombings (age ATB) and sex. The coefficients for leukaemia and cancers of the stomach, colon, lung, and female breast, and for non-leukaemia cancers considered as a group, are exactly as in the original. They represent the estimated excess mortality at 1 Sv tissue equivalent dose (intestinal equivalent dose in the case of non-leukaemia cancers as a group) over the periods 1950–85 for leukaemia and 1956–85 for other cancers, and are expressed in relative terms (excess relative risk, or excess RR or just RR for short) as the proportion of the corresponding site-specific cancer mortality expected in the absence of exposure, and in absolute terms as the difference between estimated rates at 1 Sv and 0 Sv.

Excess RR coefficients for oesophagus, ovary, and bladder cancer were not specified by Shimizu *et al.* (1988) in the required detail, and we did not at the time of preparation have access to the original data on these organs. The coefficients were therefore calculated from organ-dose-specific values (assuming a neutron RBE of one) for oesophagus,

Table 1. Risk coefficients for a single exposure to 1 Sv organ equivalent dose. From Shimizu *et al.*, LSS Report 11, Part 2, Table 5, and by *ad hoc* calculations based on site-specific results for the oesophagus and bladder (same report)

Site	Excess Deaths per 10^4 PY				
	Exposure Age				
	0-9	10-19	20-29	30-39	40+
			Males		
Oesophagus	.00923	.06281	.22916	.59555	1.3057
Stomach	.26000	1.4700	4.9300	1.7500	3.7200
Colon	.60000	.60000	.36000	1.3200	.63000
Lung	.37000	.37000	.22000	1.6900	3.7900
Bladder	.01428	.08721	.33742	1.0610	3.5636
Leukaemia	3.4600	1.7900	3.8700	5.7200	4.2200
Residual	.09648	2.279900	5.4234	4.1834	2.0906
Non-leukaemia Cancer	1.3500	4.8700	11.500	10.600	15.100
			Females		
Oesophagus	.00816	.05846	.24249	.76221	2.4537
Stomach	.65000	1.7900	4.8700	1.5400	3.6100
Colon	.41000	.41000	.53000	1.5600	.96000
Lung	.53000	.53000	.40000	2.3000	4.9300
Breast	.26000	1.8300	.97000	1.3300	.06000
Ovary	.19334	.46008	.80617	1.0868	1.1775
Bladder	.00553	.02205	.10168	.35956	1.3443
Leukaemia	2.7100	.92000	2.2400	1.7900	2.8800
Residual	1.7329	1.5994	4.9813	4.1613	2.9644
Non-leukaemia Cancer	3.7900	6.7000	12.900	13.100	17.500

	Excess Relative Risk				
	Exposure Age				
	0-9	10-19	20-29	30-39	40+
			Males		
Oesophagus	.22528	.22528	.22528	.22528	.22528
Stomach	.40000	.71000	.65000	.09000	.09000
Colon	2.8200	2.8200	.39000	.67000	.17000
Lung	.78000	.78000	.08000	.22000	.32000
Bladder	1.3395	1.3395	1.3395	1.3395	1.3395
Leukaemia	16.900	3.8000	4.9000	3.5000	2.9000
Residual	.09093	.76160	.68164	.24592	.05160
Non-leukaemia Cancer	.96000	.60000	.52000	.23000	.16000
			Females		
Oesophagus	1.4124	1.4124	1.4124	1.4124	1.4124
Stomach	.83000	1.4700	1.3600	.19000	.20000
Colon	7.0900	7.0900	.97000	1.6700	.42000
Lung	2.9300	2.9300	.31000	.84000	1.1900
Breast	1.5400	1.8900	.96000	1.0900	.03000
Ovary	1.2635	1.2635	1.2635	1.2635	1.2635
Bladder	1.3395	1.3395	1.3395	1.3395	1.3395
Leukaemia	17.800	4.0000	5.2000	3.7000	3.0000
Residual	2.3735	.87587	.96897	.40276	.15081
Non-leukaemia Cancer	1.9200	1.2000	1.0400	.45000	.32000

ovary, and urinary cancer in their Table 4 on the basis of other, kerma-specific information in Table 12 and Appendix Tables 2-6, 2-19, 2-21, 2-26, and 2-27 of the technical report version (Shimizu *et al.*, 1988). Specifically, it was concluded that the RR coefficient for bladder cancer was somewhat greater than that for urinary tract cancers generally. Excess RR did not vary significantly by age ATB or sex, and therefore the identical coefficient was assumed for both sexes and all exposure ages. Similarly, the coefficient for ovarian cancer risk did not vary by age at exposure, and the coefficient for oesophageal cancer did not vary by age ATB but differed 6-fold between men (0.256) and women (1.605). These coefficients correspond to an assumed neutron RBE of one;

they were reduced by 12 percent (to 0.225 and 1.41, respectively) for an RBE of 10, by analogy with the corresponding coefficients given by Shimizu *et al.* for stomach cancer. Similarly, the coefficients for the ovary and urinary bladder were reduced by 5%, to 1.26 and 1.34, respectively, by analogy with the colon cancer coefficients given by Shimizu *et al.* for RBEs of 1 and 10.

Given that baseline rates for cancers of the oesophagus, ovary, and bladder depend heavily on age and sex, it could not be assumed that the corresponding absolute risk (AR) coefficients varied similarly to the coefficients for excess RR, but Shimizu *et al.* gave little direct guidance on these values. Approximate AR values were calculated by applying the relative risk coefficients to Japanese national rates (Segi *et al.*, 1981) and a Japanese lifetable for 1986–87 (Institute of Population Problems, 1988) in order to estimate total excess risk over the period 10–40 years after exposure by sex and age-ATB interval; the estimated totals were then divided by the corresponding lifetable person-years at observation for risk to yield values for the average excess yearly rates.

Additive risk coefficients for a residual class of non-leukaemia cancers were obtained by subtracting site-specific coefficients from those for all non-leukaemia cancers as a group. These residual additive coefficients were converted to excess relative risk coefficients by the inverse of the process just described: for each age-ATB interval the estimated excess risk during the period 10–40 years after exposure was divided by the expected baseline mortality according to Japanese rates, for the same period.

The risk calculations are intended to pertain to low-dose radiation exposure, which means that it was unnecessary to adjust site-specific risk estimates for competing mortality from multiple radiation-induced cancers in the same or other organs. Given that risk levels are low, the precise level of overall risk, which might depend upon assumptions about the shape of the dose–response curve used for low-dose extrapolation of risk, or on an assumed dose rate effectiveness factor, is not crucial to calculations of *relative* detriment. The calculations were made for 1 Sv tissue equivalent dose and the total risks given later (e.g. Table 4) are for high dose acute exposure, i.e. no dose rate effectiveness factor has been applied to these numbers.

Three different projection models were used to estimate lifetime excess cancer risk associated with an acute, 1 Sv equivalent dose to various tissues. Two of them, the simple additive model and the simple multiplicative model, were used in the 1988 UNSCEAR report while the third was used to prepare the 1985 NIH probability of causation tables (NIH, 1985) and, for non-leukaemia cancers as a group, in the BEIR III report (NAS, 1980). The two UNSCEAR models incorporate expression periods from 2–40 years after exposure for radiation-induced leukaemia and from 10 years after exposure until the end of life for other cancers. For an exposure at any particular age, the site-specific projected excess cancer rate during each year of the expression period is given by the appropriate AR coefficient (Table 1) in the case of the additive model and, in the case of the multiplicative model, by the product of the corresponding excess RR coefficient times the population baseline rate for the age attained by the exposed person during that year. The NIH model is, for cancers other than leukaemia, a hybrid of the two UNSCEAR models: the total excess risk over the observation period less the minimal latency period (i.e. from 10 to 40 years after exposure) is that estimated by the additive model, but it is distributed over time after exposure as a multiple of the baseline rate, as in the multiplicative model, and the same multiple is applied to baseline rates for years 41, 42, and so on (Fig. 1). For leukaemia, the total excess from 5–40 years after exposure, obtained using the additive model, is used to calibrate a lognormal time-to-

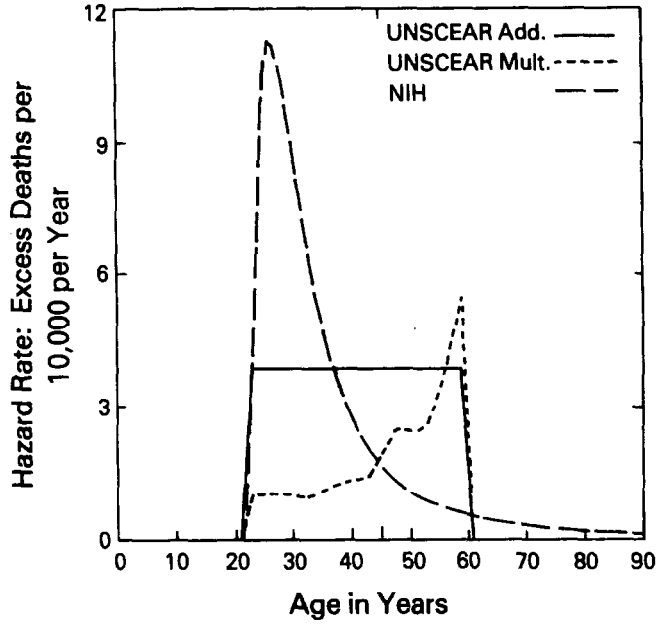

Fig. 1. Projected leukaemia risk over time following an acute radiation exposure giving 1 Sv bone marrow equivalent dose at age 20, by projection model: mortality among U.S. males.

response distribution (NIH, 1985) which determines the excess numbers by year within the observation period and also before and after (Fig. 2).

All three models should project exactly the same total excess risk over the period of observation (i.e. 5–40 years after exposure) for a population having the same baseline mortality rates, for site-specific cancer and competing causes, as the zero-dose portion of the A-bomb survivor population (this was the basis of the calculation of the AR coefficients for oesophagus, ovary, and bladder cancer described earlier). The additive and NIH (but not the multiplicative) model projections should agree for this period for any population, regardless of baseline mortality rates, and the multiplicative and NIH (but not the additive) models should agree for projection of any non-leukaemia cancer risk beyond the period of observation in the case of the A-bomb survivor population or any other for which the two models agree over the period of observation.

The three projection models were applied to five different populations, defined in terms of life tables (Institute of Population Problems, 1988; National Center for Health Statistics, 1988; Estado Libre Asociado de Puerto Rico, 1988; Office of Population Censuses and Surveys, 1989; Tongii Medical U., 1986) (Table 2) and age-specific cancer mortality rates. The populations included the Japanese national population used above to calculate approximate AR coefficients for oesophagus, ovary, and bladder cancer, the United States and Puerto Rico as represented by the 1973–1977 Surveillance, Epidemiology and End Results (SEER) program (National Cancer Institute, 1981), the United Kingdom (Office of Population Censuses and Surveys, 1989) and China, as represented by Tongii Province (Tongii Medical U., 1986) (Table 3).

3. RESULTS

Table 4 gives projected fatal cancer probabilities and loss in years of expected lifetime

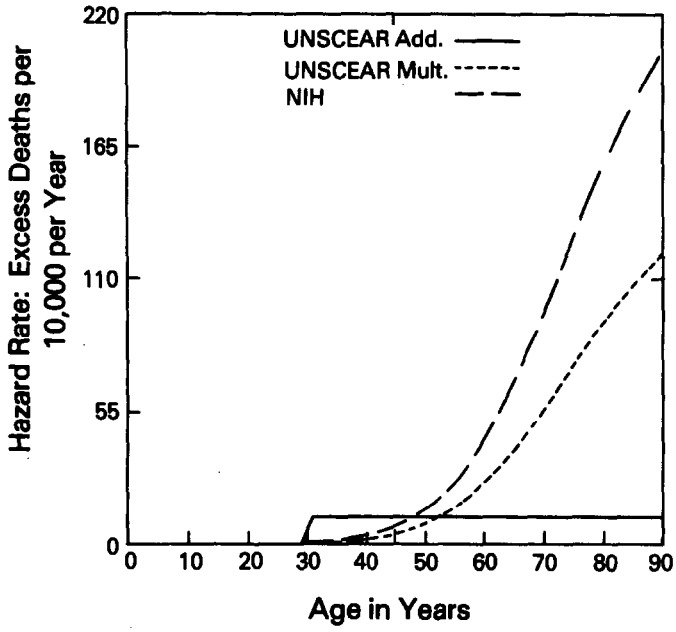

Fig. 2. Projected non-leukaemia cancer risk over time following an acute radiation exposure giving 1 Sv intestinal equivalent dose at age 20, by projection model: mortality among U.S. males.

Table 2. Abbreviated lifetables: survival probabilities by 5-year age intervals, population, and sex

Population:	JAPAN		UNITED STATES		PUERTO RICO		UNITED KINGDOM		CHINA	
Sex:	M	F	M	F	M	F	M	F	M	F
AGE										
0	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000
5	.99232	.99372	.98578	.98892	.98165	.98436	.98750	.99020	.96365	.96890
10	.99116	.99299	.98438	.98787	.98063	.98349	.98640	.98930	.95777	.96382
15	.99020	.99239	.98269	.98687	.97876	.98233	.98510	.98850	.95433	.96155
20	.98687	.99123	.97709	.98458	.97368	.98059	.98170	.98700	.95056	.95860
25	.98296	.98953	.96907	.98198	.96436	.97797	.97760	.98550	.94545	.95415
30	.97913	.98746	.96100	.97904	.96312	.97415	.97370	.98360	.93957	.94812
35	.97468	.98493	.95192	.97519	.94554	.96920	.96920	.98080	.93231	.94041
40	.96820	.98120	.94071	.96979	.92664	.96318	.96290	.97630	.92222	.92997
45	.95790	.97541	.92511	.96137	.90562	.95578	.95250	.96950	.90719	.91497
50	.94128	.96656	.90164	.94773	.87784	.94499	.93410	.95750	.88474	.89287
55	.91343	.95331	.86476	.92604	.84065	.92775	.90230	.93770	.84810	.85904
60	.87307	.93462	.80845	.89317	.78901	.90122	.84800	.90490	.79270	.80991
65	.81751	.90603	.72880	.84434	.71994	.86276	.76160	.85370	.70577	.73427
70	.73642	.86015	.62466	.77633	.63761	.80242	.64070	.77900	.59750	.63842
75	.61715	.78302	.49128	.68088	.52777	.71086	.48560	.67170	.44761	.50413
80	.45244	.65324	.34173	.55320	.41162	.58784	.31300	.52450	.30534	.36081
85	.26525	.46038	.19429	.38763	.26322	.40435	.15870	.34180	.17360	.25282
90	.11195	.24337	.07837	.19250	.14286	.24181	.06402	.16974	.07003	.12555
95	.02970	.08540	.02141	.06521	.06583	.11417	.01748	.05750	.01913	.04253
100	.00401	.01662	.00374	.01424	.02516	.03967	.00306	.01256	.00334	.00929
105	.00050	.00261	.00047	.00224	.00316	.00623	.00038	.00197	.00042	.00146
110	.00000	.00000	.00000	.00000	.00000	.00000	.00000	.00000	.00000	.00000

per Sv organ equivalent dose, according to each of the three projection models as applied to contemporary Japanese, American, Puerto Rican, British, and Chinese populations of 10,000 males and 10,000 females having lifetable distributions of age at exposure within each of the ranges 0–90, 0–19, 20–64, and 65–90. Each block of estimates, corresponding to a population and age group, has two sets of totals. The first is simply the sum of the projected numbers for the individual sites, plus residuals. The second is the sum of the projected values for leukaemia and for non-leukaemia cancer considered as a separate site.

Table 3. Age-specific cancer mortality rates, by population, sex, and site. Deaths per 100,000 per year

JAPAN MALES

Age	OESOPHAGUS	STOMACH	COLON	LUNG	BREAST	OVARY	BLADDER	LEUKAEMIA	RESIDUAL	NON-LEUK.
0 - 4	.0000	.0000	.0000	.0000	.0000	.0000	.0000	2.900	3.800	3.800
5 - 9	.0000	.0000	.0000	.0000	.0000	.0000	.0000	3.600	2.000	2.000
10 -14	.0000	.0000	.1000	.0000	.0000	.0000	.0000	2.200	1.800	1.900
15 -19	.0000	.2000	.2000	.0000	.0000	.0000	.0000	2.800	3.700	4.100
20 -24	.0000	1.000	.3000	.1000	.0000	.0000	.0000	1.700	3.700	5.100
25 -29	.0000	2.600	.7000	.4000	.0000	.0000	.0000	2.700	4.800	8.500
30 -34	.2000	5.800	1.300	1.000	.0000	.0000	.0000	3.200	7.500	15.80
35 -39	.4000	12.10	1.500	1.700	.0000	.0000	.2000	3.200	12.10	28.00
40 -44	1.200	21.10	2.900	4.600	.0000	.0000	.3000	3.800	24.60	54.70
45 -49	4.000	40.40	5.100	11.50	.0000	.0000	.9000	4.600	48.50	110.4
50 -54	9.500	69.60	9.100	22.70	.0000	.0000	2.200	5.000	80.20	193.3
55 -59	17.30	121.3	13.70	45.60	.0000	.0000	3.900	7.900	130.2	332.0
60 -64	27.30	197.2	17.90	90.50	.0000	.0000	7.100	8.500	194.9	534.9
65 -69	47.00	298.0	31.40	154.9	.0000	.0000	13.10	13.80	285.7	830.1
70 -74	67.30	429.6	50.00	241.6	.0000	.0000	23.50	14.30	397.1	1209.
75 -79	80.20	575.6	66.80	287.6	.0000	.0000	37.40	19.20	500.2	1547.
80 -84	89.30	611.0	79.10	276.7	.0000	.0000	50.00	16.00	554.1	1661.
85 -	68.20	543.2	62.80	173.6	.0000	.0000	60.80	14.90	543.4	1452.

JAPAN FEMALES

Age	OESOPHAGUS	STOMACH	COLON	LUNG	BREAST	OVARY	BLADDER	LEUKAEMIA	RESIDUAL	NON-LEUK.
0 - 4	.0000	.0000	.0000	.0000	.0000	.0000	.0000	2.900	2.600	2.600
5 - 9	.0000	.0000	.0000	.0000	.0000	.1000	.0000	2.100	1.600	1.700
10 -14	.0000	.1000	.1000	.0000	.0000	.3000	.0000	2.000	1.500	2.000
15 -19	.0000	.2000	.1000	.0000	.0000	.6000	.0000	1.900	1.900	2.800
20 -24	.0000	1.000	.3000	.1000	.1000	.5000	.0000	1.400	2.300	4.300
25 -29	.0000	4.100	.7000	.4000	.8000	1.000	.0000	1.800	3.800	10.80
30 -34	.0000	9.300	1.200	.9000	2.600	.9000	.0000	2.100	6.500	21.40
35 -39	.1000	14.20	1.700	1.400	4.900	1.900	.1000	2.400	10.70	35.00
40 -44	.2000	19.40	2.900	3.100	8.000	3.800	.1000	2.900	19.70	57.20
45 -49	.4000	27.80	4.400	5.300	12.60	6.200	.3000	3.800	35.50	92.50
50 -54	1.500	38.70	7.400	9.100	16.80	8.000	.4000	3.800	57.70	139.6
55 -59	2.800	56.70	12.70	14.90	18.30	9.400	.8000	4.600	89.60	205.2
60 -64	4.700	83.80	16.50	26.40	17.40	9.700	2.700	5.900	133.9	295.1
65 -69	8.400	126.4	25.00	39.60	17.60	8.900	4.000	6.400	197.9	427.8
70 -74	14.60	191.7	40.50	60.50	15.80	10.20	8.000	8.600	264.7	606.0
75 -79	23.00	262.5	57.80	74.50	17.50	11.10	12.40	9.500	343.8	802.6
80 -84	28.70	312.8	68.20	77.00	19.60	9.100	20.90	6.500	373.5	909.8
85 -	28.20	256.1	65.10	68.90	27.60	6.700	14.70	4.800	363.5	830.8

UNITED STATES MALES

Age	OESOPHAGUS	STOMACH	COLON	LUNG	BREAST	OVARY	BLADDER	LEUKAEMIA	RESIDUAL	NON-LEUK.
0 - 4	.0000	.0000	.0000	.0000	.0000	.0000	.0000	2.200	3.800	3.800
5 - 9	.0000	.0000	.0000	.0000	.0000	.0000	.0000	3.900	3.200	3.200
10 -14	.0000	.0000	.0000	.0000	.0000	.0000	.0000	2.000	2.800	2.800
15 -19	.0000	.0000	.1000	.1000	.0000	.0000	.0000	2.300	5.100	5.300
20 -24	.0000	.1000	.1000	.1000	.0000	.0000	.0000	2.100	7.400	7.700
25 -29	.1000	.3000	.5000	.3000	.0000	.0000	.0000	2.200	9.000	10.20
30 -34	.1000	.3000	.9000	1.700	.0000	.0000	.0000	2.000	10.90	13.90
35 -39	.3000	1.100	2.000	5.700	.0000	.0000	.1000	2.600	17.80	27.00
40 -44	1.300	2.300	4.100	18.20	.0000	.0000	.7000	2.900	27.90	54.50
45 -49	4.100	5.600	9.300	47.40	.0000	.0000	1.300	5.000	54.60	122.3
50 -54	8.500	10.70	17.60	85.50	.0000	.0000	3.700	5.200	93.80	219.8
55 -59	13.90	16.00	31.20	144.9	.0000	.0000	7.500	9.300	160.9	374.4
60 -64	20.20	28.90	53.50	232.5	.0000	.0000	15.30	16.20	254.1	604.5
65 -69	29.10	42.50	89.80	324.8	.0000	.0000	28.20	19.50	384.0	898.4
70 -74	34.20	62.60	132.3	403.2	.0000	.0000	52.60	34.00	556.4	1241.
75 -79	31.50	91.80	189.3	455.4	.0000	.0000	71.20	56.20	772.3	1611.
80 -84	41.20	118.3	232.9	402.8	.0000	.0000	112.5	68.00	997.9	1905.
85 -	43.00	146.8	309.7	323.5	.0000	.0000	138.7	89.10	1218.	2180.

UNITED STATES FEMALES

Age	OESOPHAGUS	STOMACH	COLON	LUNG	BREAST	OVARY	BLADDER	LEUKAEMIA	RESIDUAL	NON-LEUK.
0 - 4	.0000	.0000	.0000	.1000	.0000	.0000	.1000	1.600	2.700	2.900
5 - 9	.0000	.0000	.0000	.0000	.0000	.0000	.0000	2.100	2.200	2.200
10 -14	.0000	.0000	.0000	.0000	.0000	.1000	.0000	1.500	2.400	2.500
15 -19	.0000	.0000	.1000	.1000	.0000	.4000	.0000	1.400	2.300	2.900
20 -24	.0000	.0000	.2000	.1000	.2000	.4000	.0000	1.600	3.800	4.700
25 -29	.0000	.1000	.3000	.2000	1.400	.6000	.0000	1.500	5.400	8.000
30 -34	.0000	.5000	.7000	1.100	6.000	1.100	.0000	1.600	9.100	18.50
35 -39	.1000	1.000	2.300	3.400	13.30	2.400	.1000	2.300	13.70	36.30
40 -44	.5000	1.900	4.400	10.30	22.90	6.200	.2000	2.400	25.10	71.50
45 -49	1.200	3.300	9.400	20.10	42.60	10.30	.4000	3.200	43.30	130.6
50 -54	2.600	4.900	15.60	30.80	61.30	17.50	1.600	5.000	70.40	204.7
55 -59	4.700	7.300	30.30	51.50	77.70	25.00	2.500	6.400	111.6	310.6
60 -64	6.600	11.80	42.80	64.70	91.00	30.20	5.300	8.900	161.8	414.2
65 -69	7.200	18.70	70.10	74.10	102.2	36.50	8.700	14.10	218.0	535.5
70 -74	8.200	25.30	99.50	71.30	110.0	41.20	13.40	16.90	284.1	653.0
75 -79	8.600	43.00	139.2	73.60	128.2	42.80	21.20	25.90	369.0	825.6
80 -84	12.00	58.50	185.4	69.40	143.2	40.10	32.10	36.40	447.7	988.4
85 -	14.50	84.70	239.7	74.80	180.9	42.80	49.40	43.30	520.4	1207.

Table 3—*continued*

PUERTO RICO MALES

Age	OESOPHAGUS	STOMACH	COLON	LUNG	BREAST	OVARY	BLADDER	LEUKAEMIA	RESIDUAL	NON-LEUK.
0 - 4	.0000	.0000	.0000	.1000	.0000	.0000	.0000	2.400	3.000	3.100
5 - 9	.0000	.1000	.0000	.1000	.0000	.0000	.0000	2.400	1.400	1.600
10 -14	.0000	.0000	.0000	.0000	.0000	.0000	.0000	1.300	2.100	2.100
15 -19	.0000	.1000	.0000	.2000	.0000	.0000	.0000	2.500	3.300	3.600
20 -24	.0000	.0000	.3000	.3000	.0000	.0000	.0000	1.700	3.200	3.800
25 -29	.2000	.4000	.4000	.8000	.0000	.0000	.0000	2.000	5.400	7.200
30 -34	.0000	.9000	.9000	1.200	.0000	.0000	.2000	2.800	7.500	10.70
35 -39	2.600	2.000	1.800	3.300	.0000	.0000	.3000	3.600	13.50	23.50
40 -44	3.700	5.600	1.400	5.900	.0000	.0000	.0000	5.900	25.20	41.80
45 -49	9.800	10.10	4.700	12.80	.0000	.0000	.3000	4.500	46.80	84.50
50 -54	24.00	16.80	9.200	23.00	.0000	.0000	2.000	5.900	90.70	165.7
55 -59	36.80	37.60	11.10	38.60	.0000	.0000	3.200	4.300	140.2	267.5
60 -64	64.80	62.20	19.60	63.50	.0000	.0000	8.100	14.10	201.5	419.7
65 -69	79.70	109.8	24.80	88.10	.0000	.0000	14.30	14.20	307.2	623.9
70 -74	110.5	157.3	36.10	123.5	.0000	.0000	29.90	27.70	459.6	916.9
75 -79	95.50	225.2	58.80	128.5	.0000	.0000	28.20	24.50	616.8	1153.
80 -84	132.9	254.9	76.50	132.9	.0000	.0000	54.60	40.00	712.2	1364.
85 -	198.4	368.4	109.0	165.7	.0000	.0000	78.50	32.70	1179.	2099.

PUERTO RICO FEMALES

Age	OESOPHAGUS	STOMACH	COLON	LUNG	BREAST	OVARY	BLADDER	LEUKAEMIA	RESIDUAL	NON-LEUK.
0 - 4	.0000	.1000	.0000	.0000	.0000	.0000	.0000	2.100	1.700	1.800
5 - 9	.0000	.0000	.0000	.0000	.0000	.2000	.0000	1.300	.9000	1.100
10 -14	.0000	.0000	.0000	.1000	.0000	.2000	.0000	1.800	1.400	1.700
15 -19	.0000	.1000	.1000	.1000	.0000	.2000	.0000	2.000	1.400	1.900
20 -24	.0000	.1000	.1000	.1000	.3000	.1000	.0000	1.100	1.900	2.600
25 -29	.2000	.0000	.5000	.2000	1.400	.2000	.0000	1.200	2.700	5.200
30 -34	.0000	.6000	1.200	.8000	4.300	.4000	.0000	2.000	7.000	14.30
35 -39	.9000	2.900	.7000	1.300	7.200	.4000	.0000	2.700	13.50	26.90
40 -44	.3000	5.300	2.300	3.800	13.50	1.500	.3000	3.100	24.30	51.30
45 -49	3.100	7.000	3.300	4.700	17.00	2.500	.0000	4.700	35.10	72.70
50 -54	8.800	12.70	7.500	8.800	30.50	2.900	.6000	4.500	66.20	138.0
55 -59	11.70	17.90	11.70	13.90	29.60	9.900	2.200	5.500	92.90	189.8
60 -64	15.20	27.50	13.10	27.90	28.30	8.000	5.500	11.80	125.9	251.4
65 -69	26.30	42.30	24.20	39.20	40.70	10.30	6.700	9.300	206.1	395.8
70 -74	39.00	59.30	28.50	45.00	37.50	17.30	7.500	10.50	286.8	520.9
75 -79	43.50	102.3	51.70	62.30	50.60	11.80	23.50	25.90	339.7	685.4
80 -84	65.50	130.9	71.80	60.70	47.90	20.80	14.40	23.90	431.0	843.0
85 -	87.30	137.9	105.7	44.40	55.20	6.100	27.60	26.10	563.9	1028.

UNITED KINGDOM MALES

Age	OESOPHAGUS	STOMACH	COLON	LUNG	BREAST	OVARY	BLADDER	LEUKAEMIA	RESIDUAL	NON-LEUK.
0 - 4	.0000	.0000	.0000	.0000	.0000	.0000	.0000	.9071	2.963	2.963
5 - 9	.0000	.0000	.0000	.0000	.0000	.0000	.0000	1.131	2.954	2.954
10 -14	.0000	.0000	.0000	.0635	.0000	.0000	.0000	1.970	2.225	2.288
15 -19	.0000	.0000	.0000	.0510	.0000	.0000	.0000	2.552	4.237	4.288
20 -24	.0000	.0468	.0936	.0936	.0000	.0000	.0000	1.451	5.524	5.758
25 -29	.0515	.3093	.4640	.0515	.0000	.0000	.0000	2.320	7.064	7.940
30 -34	.4111	.7635	.7048	.9985	.0000	.0000	.1174	2.349	11.68	14.68
35 -39	1.251	1.536	1.877	3.527	.0000	.0000	.2844	2.844	17.18	25.66
40 -44	2.142	2.779	3.590	9.382	.0000	.0000	.4633	3.011	28.84	47.19
45 -49	4.581	7.588	6.371	26.27	.0000	.0000	2.076	4.295	51.82	98.71
50 -54	10.26	12.88	14.90	57.53	.0000	.0000	5.244	5.768	94.24	195.0
55 -59	18.80	28.80	25.09	131.1	.0000	.0000	9.931	7.808	163.2	376.9
60 -64	33.52	50.99	43.83	273.5	.0000	.0000	21.40	10.70	261.2	684.6
65 -69	42.38	79.24	70.94	407.3	.0000	.0000	37.92	14.72	397.5	1035.
70 -74	57.42	127.0	100.8	593.5	.0000	.0000	71.00	22.55	599.0	1548.
75 -79	73.43	179.9	149.0	723.2	.0000	.0000	109.2	31.04	872.6	2107.
80 -84	92.37	223.6	212.5	810.5	.0000	.0000	148.7	42.09	1187.	2675.
85 -	92.54	254.2	255.4	695.3	.0000	.0000	215.1	47.47	1573.	3086.

UNITED KINGDOM FEMALES

Age	OESOPHAGUS	STOMACH	COLON	LUNG	BREAST	OVARY	BLADDER	LEUKAEMIA	RESIDUAL	NON-LEUK.
0 - 4	.0000	.0000	.0000	.0000	.0000	.0000	.0000	1.334	3.242	3.242
5 - 9	.0000	.0000	.0000	.0000	.0000	.0000	.0000	.9943	2.717	2.717
10 -14	.0000	.0000	.0000	.0000	.0000	.0000	.0000	1.076	2.556	2.556
15 -19	.0000	.0000	.0000	.0000	.1072	.0536	.0000	.8581	2.413	2.574
20 -24	.0000	.0483	.0000	.0000	.0483	.2418	.0000	.9188	3.820	4.159
25 -29	.1047	.2617	.2094	.1570	1.413	.4712	.0523	.8900	6.073	8.743
30 -34	.0000	.4764	.4168	.6551	7.206	.8337	.1191	1.310	13.22	22.92
35 -39	.2842	.8526	1.648	2.387	14.21	2.614	.2273	2.728	18.35	40.58
40 -44	.5866	1.290	3.989	6.746	27.27	5.573	.1759	2.581	26.98	72.62
45 -49	1.658	2.739	7.787	13.48	52.20	12.04	1.153	3.677	40.73	131.8
50 -54	3.524	5.399	14.69	24.74	74.99	22.94	1.424	5.324	71.99	219.7
55 -59	6.394	10.06	23.59	56.22	91.87	34.83	3.748	6.541	109.5	336.2
60 -64	10.75	20.05	38.65	109.6	115.3	37.49	7.847	7.047	167.1	506.9
65 -69	16.79	29.81	48.87	139.3	125.8	43.90	10.76	9.789	230.4	645.8
70 -74	26.90	44.49	79.76	162.9	145.6	52.69	21.43	13.83	313.1	846.9
75 -79	39.35	77.73	109.3	168.6	174.4	47.42	29.02	21.25	407.2	1053.
80 -84	50.11	105.3	156.3	162.1	217.6	52.52	43.86	24.41	525.1	1313.
85 -	58.65	146.7	241.3	140.5	315.5	45.76	54.80	27.69	705.1	1708.

Table 3—*continued*

CHINA MALES

Age	OESOPHAGUS	STOMACH	COLON	LUNG	BREAST	OVARY	BLADDER	LEUKAEMIA	RESIDUAL	NON-LEUK.
0 - 4	.0000	.0000	.0250	.0100	.0000	.0000	.0100	3.210	2.685	2.730
5 - 9	.0100	.0100	.0250	.0200	.0000	.0000	.0100	2.400	2.065	2.140
10 -14	.0100	.0200	.0300	.0200	.0000	.0000	.0000	2.230	2.170	2.250
15 -19	.0900	.1300	.1800	.1500	.0000	.0000	.0200	2.980	4.030	4.600
20 -24	.2500	.4600	.3550	.3500	.0000	.0000	.0300	2.830	5.385	6.830
25 -29	.6600	1.160	.5350	.7400	.0100	.0000	.0600	2.390	8.555	11.72
30 -34	1.750	3.240	.8900	1.540	.0100	.0000	.1100	2.440	15.20	22.74
35 -39	4.980	7.980	1.530	3.570	.0200	.0000	.2700	2.660	30.14	48.49
40 -44	12.52	18.19	2.320	7.060	.0600	.0000	.4600	2.920	46.27	86.88
45 -49	28.63	37.37	3.565	13.98	.0900	.0000	.8400	3.100	68.38	152.8
50 -54	56.37	68.59	5.475	23.06	.1400	.0000	1.480	3.320	90.88	246.0
55 -59	95.68	109.4	7.890	35.41	.2500	.0000	2.570	3.470	112.7	363.9
60 -64	148.3	154.9	14.41	49.24	.3700	.0000	4.760	3.670	131.2	503.2
65 -69	199.7	194.0	16.23	60.56	.4800	.0000	7.800	3.350	151.3	630.0
70 -74	261.1	226.2	23.10	64.18	.8100	.0000	13.39	3.760	176.3	765.2
75 -79	248.5	208.1	25.75	53.65	.8700	.0000	17.47	3.520	172.2	726.6
80 -84	242.3	177.7	30.79	40.27	1.280	.0000	25.71	3.080	182.0	700.2
85 -	242.3	177.7	30.79	40.27	1.280	.0000	25.71	3.080	182.0	700.2

CHINA FEMALES

Age	OESOPHAGUS	STOMACH	COLON	LUNG	BREAST	OVARY	BLADDER	LEUKAEMIA	RESIDUAL	NON-LEUK.
0 - 4	.0000	.0000	.0150	.0000	.0000	.1916	.0000	2.510	1.973	2.180
5 - 9	.0100	.0100	.0200	.0100	.0000	.0000	.0000	1.770	1.480	1.530
10 -14	.0100	.0200	.0250	.0200	.0300	.0638	.0000	1.800	1.411	1.580
15 -19	.0600	.1700	.1250	.0800	.2200	1.022	.0000	1.820	2.212	3.890
20 -24	.1600	.4400	.2600	.2500	.1200	1.022	.0200	2.300	3.177	5.450
25 -29	.4900	1.140	.4050	.5700	.4300	2.044	.0400	1.940	4.700	9.820
30 -34	1.180	2.530	.6600	1.090	1.220	1.597	.0600	2.020	9.442	17.78
35 -39	3.010	5.170	1.165	2.280	2.910	2.683	.1200	2.280	17.44	34.78
40 -44	7.080	10.32	1.775	4.040	4.930	4.408	.2500	2.530	29.76	62.57
45 -49	15.39	18.16	2.700	7.140	7.630	6.644	.3100	2.580	50.98	108.9
50 -54	29.10	31.96	4.195	11.32	9.860	8.177	.6000	2.870	76.51	171.7
55 -59	47.03	45.96	5.820	15.44	11.60	9.647	1.060	2.800	99.77	236.3
60 -64	69.86	67.43	8.575	20.40	13.25	9.327	1.750	2.670	125.4	316.0
65 -69	93.67	89.38	12.02	25.32	15.23	11.88	2.380	2.750	142.8	392.7
70 -74	125.7	114.5	16.96	27.96	17.77	10.03	3.910	2.530	172.7	489.6
75 -79	131.4	122.5	19.27	26.31	19.04	11.43	4.770	2.620	170.9	505.7
80 -84	149.6	128.8	23.05	21.96	22.85	7.538	5.460	2.430	195.1	554.5
85 -	149.6	128.8	23.05	21.96	22.85	8.561	5.460	2.430	194.0	554.5

4. DISCUSSION

4.1. Review of the Results

One would expect the different models to give approximately the same fatal cancer probabilities and years of life lost for the oldest cohort in the Japanese population, since no projection is required beyond the observation period for the A-bomb survivors and since baseline rates should be reasonably comparable to those of that population. That is in fact what is seen in Table 4. The somewhat greater effects projected using the multiplicative and NIH models probably reflect both temporal changes in Japanese cancer rates and the fact that baseline rates (which are multiplied by the identical RR coefficients given in Table 1 or derived from the AR coefficients) are generally higher after age 65 than from ages 40 to 64 (Table 3).

For the multiplicative and NIH models, both of which incorporate the assumption of a constant relative risk over time following exposure for non-leukaemia cancers, there is often a considerable difference between the total of projected, site-specific numbers of deaths or years of life lost, including residual, and the sum of the projected numbers of non-leukaemia cancers, considered as a group, and leukaemias. When the first value is much larger than the second, the projected number in the residual class also tends to be large. To the extent that constancy of relative risks over time corresponds to radiation as a cancer initiator and the variation of age-specific baseline rates to the action of cancer promoters which are assumed to operate equally on cancers previously initiated by

Table 4. Projected excess mortality and loss of expected lifetime from radiation-induced cancer to a population of 10,000 people having a lifetable age distribution within a specified age range, and exposed to 1 Sv of acute radiation: by population, projection model, sex, age at exposure, and cancer site

Population:	JAPAN											
	UNTIMELY DEATHS						YEARS OF EXPECTED LIFE LOST					
Model:	ADDITIVE		MULTIPLICATIVE		NIH		ADDITIVE		MULTIPLICATIVE		NIH	
Sex:	M	F	M	F	M	F	M	F	M	F	M	F
						Exposure Ages 0-90						
Oesophagus	11.82	23.37	21.71	46.66	21.71	46.66	175.2	348.3	245.1	492.6	245.1	492.6
Stomach	67.96	79.88	224.1	276.9	204.1	223.8	1341.	1748.	2786.	3933.	2510.	3160.
Colon	20.06	23.58	89.39	245.2	100.8	92.88	456.7	514.4	1131.	3333.	1287.	1251.
Lung	35.77	57.15	129.3	173.3	178.8	173.2	579.2	994.0	1485.	2255.	2125.	2302.
Breast	.0000	27.26	.0000	49.08	.0000	43.96	.0000	728.7	.0000	1025.	.0000	921.9
Ovary	.0000	23.16	.0000	30.56	.0000	30.56	.0000	480.1	.0000	581.5	.0000	581.5
Bladder	27.68	12.29	56.61	25.07	56.61	25.07	383.8	179.3	525.9	254.2	525.9	254.2
Leukaemia	106.3	64.91	85.89	58.72	115.7	66.88	2965.	1971.	2374.	1920.	4009.	2580.
Residual	75.57	95.50	195.1	442.1	187.9	365.5	1588.	2222.	2534.	6379.	2449.	5311.
Total	345.2	407.1	802.2	1347.	865.9	1068.	7490.	9187.	11084	20175	13153	16857
Proj. L+NL	345.2	407.1	882.4	1152.	823.9	1036.	7488.	9193.	12200	17523	12743	16407
						Exposure Ages 0-19						
Oesophagus	1.904	1.950	26.67	56.50	26.67	56.50	50.97	58.79	329.8	652.7	329.8	652.7
Stomach	45.92	73.17	464.7	604.2	368.9	447.3	1294.	2274.	5976.	9027.	4746.	6688.
Colon	33.94	25.54	272.7	795.3	318.8	262.0	1021.	823.7	3541.	11090	4149.	3660.
Lung	20.93	33.02	299.4	420.4	545.8	463.0	630.2	1064.	3657.	5950.	6668.	6554.
Breast	.0000	61.19	.0000	127.4	.0000	122.7	.0000	1862.	.0000	2755.	.0000	2654.
Ovary	.0000	19.69	.0000	46.69	.0000	46.69	.0000	617.6	.0000	1040.	.0000	1040.
Bladder	2.689	.8183	65.41	30.02	65.41	30.02	78.04	27.26	664.5	331.1	664.5	331.1
Leukaemia	98.19	68.46	116.0	90.25	125.1	87.52	4669.	3677.	5456.	4708.	6995.	5432.
Residual	61.78	104.1	338.9	1176.	331.7	1006.	1707.	3377.	4551.	17542	4456.	15018
Total	265.3	388.0	1584.	3347.	1782.	2522.	9452.	13783	24177	53100	28011	42032
Proj. L+NL	265.3	388.0	1904.	2701.	1619.	2367.	9445.	13784	28524	44178	26260	39889
						Exposure Ages 20-64						
Oesophagus	18.85	38.17	24.45	53.95	24.45	53.95	280.8	592.9	272.4	575.1	272.4	575.1
Stomach	95.68	108.3	176.4	228.4	184.2	202.3	1758.	2164.	2135.	3116.	2210.	2756.
Colon	19.21	30.39	30.50	87.40	29.65	50.29	331.3	568.0	353.6	1096.	347.1	636.4
Lung	50.12	82.31	83.19	114.7	58.97	99.21	714.7	1305.	892.6	1376.	642.1	1213.
Breast	.0000	22.51	.0000	32.77	.0000	25.40	.0000	501.2	.0000	643.8	.0000	498.3
Ovary	.0000	31.89	.0000	33.61	.0000	33.61	.0000	596.1	.0000	592.5	.0000	592.5
Bladder	44.46	20.08	63.16	29.02	63.16	29.02	626.2	306.4	587.7	297.3	587.7	297.3
Leukaemia	131.9	77.34	86.13	59.39	140.8	77.53	3009.	1883.	1584.	1341.	3812.	2251.
Residual	103.3	124.3	185.9	273.3	177.1	212.8	2013.	2546.	2365.	3768.	2261.	2964.
Total	463.7	535.4	649.8	912.7	678.5	784.2	8734.	10464	8192.	12808	10134	11786
Proj. L+NL	463.7	535.4	643.5	849.0	681.4	793.8	8734.	10470	8150.	11979	10229	11919
						Exposure Ages 65-90						
Oesophagus	4.049	10.64	5.398	16.98	5.398	16.98	21.36	63.50	28.96	100.6	28.96	100.6
Stomach	11.53	15.66	15.94	23.68	20.02	21.37	63.72	94.15	89.64	144.0	111.5	130.0
Colon	1.953	4.164	3.635	11.86	2.908	6.115	11.36	23.97	19.62	70.50	16.22	35.44
Lung	11.75	21.38	22.51	37.10	13.96	27.40	64.80	128.0	130.7	227.1	80.73	167.0
Breast	.0000	.2603	.0000	.3139	.0000	.3284	.0000	1.433	.0000	1.433	.0000	1.488
Ovary	.0000	5.108	.0000	4.334	.0000	4.334	.0000	29.21	.0000	26.45	.0000	26.45
Bladder	11.05	5.832	22.17	9.406	22.17	9.406	60.68	33.29	117.4	57.10	117.4	57.10
Leukaemia	35.73	29.47	39.67	20.79	20.40	16.30	259.0	234.8	288.5	181.4	152.8	136.7
Residual	6.484	12.86	8.293	24.80	6.521	14.53	34.61	76.95	44.24	148.7	34.39	86.98
Total	82.56	105.3	117.6	149.2	91.40	116.7	515.6	685.4	719.2	957.5	542.1	742.0
Proj. L+NL	82.56	105.3	115.9	138.7	86.23	119.1	515.7	696.7	711.5	903.3	516.8	765.0

Table 4—*continued*

Population:	UNITED STATES											
	UNTIMELY DEATHS						YEARS OF EXPECTED LIFE LOST					
Model:	ADDITIVE		MULTIPLICATIVE		NIH		ADDITIVE		MULTIPLICATIVE		NIH	
Sex:	M	F	M	F	M	F	M	F	M	F	M	F
						Exposure Ages 0-90						
Oesophagus	10.63	21.56	10.62	24.97	15.83	28.25	152.5	316.1	127.0	328.9	184.3	341.5
Stomach	63.32	76.13	32.06	44.81	221.4	333.2	1208.	1631.	355.9	519.9	2459.	3922.
Colon	18.99	22.47	222.6	601.9	177.7	143.1	418.7	480.7	2441.	7328.	1972.	1749.
Lung	32.34	53.29	220.2	233.3	102.9	106.0	511.2	912.9	2758.	3744.	1309.	1657.
Breast	.0000	26.54	.0000	244.1	.0000	63.46	.0000	688.6	.0000	4199.	.0000	1102.
Ovary	.0000	21.96	.0000	100.6	.0000	43.79	.0000	446.1	.0000	1537.	.0000	705.8
Bladder	24.64	11.32	101.1	46.86	55.84	24.21	331.6	162.3	907.2	446.7	503.7	231.2
Leukaemia	103.3	63.43	132.1	100.6	114.4	66.38	2766.	1880.	2490.	2128.	3789.	2490.
Residual	71.29	91.56	256.8	482.7	201.6	319.1	1439.	2080.	2991.	6799.	2358.	4519.
Total	324.5	388.2	975.8	1880.	889.9	1127.	6828.	8599.	12072	27034	12578	16720
Proj. L+NL	324.5	388.2	912.1	1329.	766.7	957.4	6828.	8597.	11688	19727	11480	15224
						Exposure Ages 0-19						
Oesophagus	1.768	1.853	13.07	31.89	13.89	15.48	42.17	54.31	171.3	470.8	182.5	229.1
Stomach	42.65	69.61	62.91	92.84	424.7	771.9	1148.	2095.	721.4	1123.	4860.	9354.
Colon	31.67	24.35	643.0	1879.	581.2	448.7	913.0	761.8	7179.	23340	6495.	5577.
Lung	19.53	31.47	506.8	588.7	265.7	229.3	562.9	982.8	6793.	10274	3563.	4006.
Breast	.0000	58.15	.0000	604.1	.0000	186.7	.0000	1712.	.0000	10655	.0000	3292.
Ovary	.0000	18.73	.0000	136.7	.0000	90.71	.0000	568.7	.0000	2384.	.0000	1580.
Bladder	2.498	.7781	111.8	53.88	72.88	30.14	68.89	25.13	1089.	564.3	706.8	315.0
Leukaemia	96.96	68.17	99.85	78.77	123.4	87.02	4306.	3479.	4420.	3851.	6488.	5172.
Residual	57.30	99.28	423.8	1244.	341.0	823.9	1510.	3120.	5124.	18181	4122.	12041
Total	252.3	372.4	1861.	4711.	1823.	2684.	8553.	12801	25500	70845	26419	41569
Proj. L+NL	252.3	372.4	1771.	2934.	1446.	2184.	8548.	12797	25051	47078	22806	36929
						Exposure Ages 20-64						
Oesophagus	16.69	34.76	11.55	27.95	19.57	38.99	239.6	527.9	134.9	364.7	225.7	484.8
Stomach	86.99	100.8	24.75	36.42	176.1	238.3	1537.	1962.	268.1	413.7	1919.	2744.
Colon	17.39	28.17	75.56	212.4	29.46	50.19	287.7	513.0	784.4	2455.	309.7	587.6
Lung	44.12	75.10	131.2	139.2	48.37	79.17	603.9	1160.	1490.	1979.	550.5	1114.
Breast	.0000	21.25	.0000	163.5	.0000	28.89	.0000	458.8	.0000	2700.	.0000	479.9
Ovary	.0000	29.52	.0000	111.8	.0000	35.73	.0000	537.4	.0000	1644.	.0000	540.7
Bladder	39.06	18.26	110.7	52.33	56.35	26.01	529.4	271.9	995.0	506.7	506.2	252.1
Leukaemia	124.5	73.66	144.3	111.4	134.8	74.77	2684.	1727.	1972.	1841.	3442.	2087.
Residual	95.02	116.0	239.5	290.7	184.8	193.4	1770.	2311.	2724.	3885.	2112.	2612.
Total	423.8	497.6	737.8	1145.	649.6	765.5	7653.	9472.	8370.	15793	9066.	10904
Proj. L+NL	423.8	497.6	676.0	974.0	615.9	686.1	7656.	9465.	7950.	13536	8893.	10320
						Exposure Ages 65-90						
Oesophagus	3.679	9.981	2.566	7.488	5.064	14.55	21.43	58.53	14.73	42.08	28.76	82.66
Stomach	10.48	14.68	3.239	5.844	20.54	28.59	58.86	87.39	18.84	31.75	110.0	160.4
Colon	1.775	3.905	12.60	36.09	3.499	6.891	9.914	21.99	66.99	206.3	20.36	38.43
Lung	10.67	20.05	33.62	35.37	12.03	21.21	59.84	120.0	191.6	210.6	68.95	126.3
Breast	.0000	.2440	.0000	1.992	.0000	.3304	.0000	1.134	.0000	10.58	.0000	1.386
Ovary	.0000	4.790	.0000	21.59	.0000	5.330	.0000	27.34	.0000	128.8	.0000	30.37
Bladder	10.04	5.468	44.65	22.24	22.42	11.38	56.54	31.56	234.0	123.1	119.1	62.56
Leukaemia	33.62	28.26	144.7	98.32	19.21	15.69	238.9	223.3	922.3	691.3	144.2	130.1
Residual	5.890	12.05	14.88	30.68	9.232	15.60	33.76	71.45	79.76	178.5	50.73	90.29
Total	76.17	99.45	256.3	259.6	92.01	119.6	479.2	642.8	1528.	1623.	542.2	722.7
Proj. L+NL	76.17	99.45	234.4	240.9	91.34	123.2	473.7	651.8	1402.	1520.	531.8	754.7

Table 4—*continued*

Population:	PUERTO RICO											
	UNTIMELY DEATHS						YEARS OF EXPECTED LIFE LOST					
Model:	ADDITIVE		MULTIPLICATIVE		NIH		ADDITIVE		MULTIPLICATIVE		NIH	
Sex:	M	F	M	F	M	F	M	F	M	F	M	F
						Exposure Ages 0-90						
Oesophagus	11.71	23.00	39.67	123.4	19.08	36.42	180.2	350.7	490.9	1448.	230.9	411.6
Stomach	67.04	79.04	89.57	103.4	297.5	319.9	1344.	1735.	1052.	1335.	3522.	4168.
Colon	19.79	23.32	87.15	248.8	124.2	121.2	454.9	512.2	1090.	3118.	1569.	1515.
Lung	35.48	56.35	76.19	138.5	99.94	148.4	591.6	992.2	999.7	1975.	1327.	2137.
Breast	.0000	27.06	.0000	96.26	.0000	52.56	.0000	722.5	.0000	1849.	.0000	1016.
Ovary	.0000	22.88	.0000	32.46	.0000	51.69	.0000	478.0	.0000	510.9	.0000	860.1
Bladder	27.48	12.09	64.88	34.75	66.67	26.27	397.3	181.5	636.1	374.2	663.1	284.8
Leukaemia	104.9	64.53	106.8	91.28	114.7	66.82	2933.	1957.	2500.	2234.	3942.	2561.
Residual	74.25	94.56	249.9	493.8	230.1	378.0	1582.	2203.	3129.	6915.	2896.	5338.
Total	340.7	402.8	714.2	1362.	952.4	1201.	7485.	9133.	9899.	19762	14153	18294
Proj. L+NL	340.7	402.8	792.0	1106.	887.2	1135.	7486.	9122.	10991	16366	13555	17527
						Exposure Ages 0-19						
Oesophagus	1.810	1.901	46.46	148.2	16.82	25.84	49.66	61.04	640.6	1947.	232.0	339.3
Stomach	43.67	71.37	175.1	217.1	609.2	741.3	1228.	2204.	2118.	2909.	7370.	9938.
Colon	32.37	24.93	253.3	783.3	383.6	351.4	971.3	800.8	3246.	10059	4923.	4512.
Lung	19.96	32.23	170.3	334.1	236.6	369.3	598.5	1032.	2421.	5149.	3367.	5701.
Breast	.0000	59.65	.0000	242.8	.0000	147.5	.0000	1806.	.0000	4817.	.0000	2923.
Ovary	.0000	19.20	.0000	43.78	.0000	117.0	.0000	601.0	.0000	771.1	.0000	2062.
Bladder	2.557	.7979	69.56	40.57	85.67	38.49	74.13	29.40	738.8	473.8	914.1	451.5
Leukaemia	96.47	68.13	109.9	86.71	123.2	87.07	4428.	3583.	4765.	4284.	6638.	5298.
Residual	58.69	101.6	412.6	1278.	391.2	1001.	1621.	3275.	5331.	18511	5055.	14498
Total	255.5	379.9	1237.	3175.	1846.	2879.	8972.	13394	19263	48924	28501	45728
Proj. L+NL	255.5	379.9	1563.	2436.	1686.	2653.	8960.	13373	23643	38838	26919	43032
						Exposure Ages 20-64						
Oesophagus	18.38	36.89	43.39	138.4	23.15	47.22	287.0	584.8	533.9	1632.	282.4	549.2
Stomach	93.49	105.5	70.70	84.91	224.7	234.1	1764.	2120.	820.4	1076.	2630.	2990.
Colon	18.71	29.54	29.95	88.34	32.94	56.96	332.7	557.3	350.5	1037.	390.5	678.1
Lung	48.83	79.61	46.85	89.34	56.19	91.85	731.9	1283.	564.1	1172.	683.2	1220.
Breast	.0000	22.01	.0000	64.24	.0000	28.22	.0000	490.7	.0000	1168.	.0000	514.8
Ovary	.0000	30.98	.0000	36.98	.0000	39.00	.0000	584.1	.0000	562.6	.0000	611.8
Bladder	43.33	19.40	70.90	39.28	67.53	26.24	642.7	302.3	706.4	431.1	677.2	286.9
Leukaemia	127.6	75.38	110.6	99.49	137.4	76.11	2965.	1837.	1923.	1895.	3726.	2195.
Residual	100.9	121.1	238.0	301.7	215.1	224.4	2009.	2492.	2937.	4054.	2668.	3057.
Total	451.3	520.5	610.4	942.8	757.2	824.2	8734.	10253	7835.	13031	11059	12104
Proj. L+NL	451.3	520.5	588.1	823.7	718.0	803.6	8736.	10244	7633.	11524	10752	11917
						Exposure Ages 65-90						
Oesophagus	5.370	11.76	15.62	52.27	8.910	20.44	31.35	79.67	94.63	335.1	52.93	130.5
Stomach	15.30	17.30	11.88	12.68	28.51	28.59	97.54	115.8	72.33	84.29	177.3	189.4
Colon	2.591	4.601	6.596	18.42	5.200	8.882	14.22	33.32	38.14	116.7	28.36	57.33
Lung	15.58	23.63	20.07	28.72	22.24	26.72	99.56	159.8	126.3	201.1	141.0	187.6
Breast	.0000	.2875	.0000	.7605	.0000	.3543	.0000	3.722	.0000	5.343	.0000	4.022
Ovary	.0000	5.644	.0000	6.277	.0000	4.819	.0000	39.98	.0000	49.29	.0000	38.36
Bladder	14.65	6.443	36.42	15.33	32.11	11.21	94.07	44.90	224.3	97.56	196.9	72.64
Leukaemia	41.00	30.87	88.59	74.82	22.36	16.71	337.5	265.5	707.2	604.8	193.3	154.7
Residual	8.599	14.20	20.09	38.17	13.76	19.32	53.66	96.00	123.1	246.8	82.99	124.5
Total	103.1	114.7	199.3	247.4	133.1	137.0	727.9	838.8	1386.	1741.	872.9	959.2
Proj. L+NL	103.1	114.7	206.3	219.8	137.3	149.0	745.6	832.5	1443.	1551.	912.9	1018.

Table 4—*continued*

Population:	UNITED KINGDOM											
	UNTIMELY DEATHS						YEARS OF EXPECTED LIFE LOST					
Model:	ADDITIVE		MULTIPLICATIVE		NIH		ADDITIVE		MULTIPLICATIVE		NIH	
Sex:	M	F	M	F	M	F	M	F	M	F	M	F
	Exposure Ages 0-90											
Oesophagus	10.42	20.96	18.21	75.86	16.72	35.40	146.8	302.6	197.7	803.2	177.3	365.2
Stomach	62.88	75.06	56.10	71.69	256.6	497.9	1181.	1589.	585.0	766.0	2695.	5431.
Colon	18.94	22.16	172.1	489.3	166.0	145.3	411.6	467.7	1833.	5723.	1789.	1706.
Lung	31.74	52.04	296.5	408.5	198.1	192.9	493.2	880.2	3110.	5538.	2160.	2682.
Breast	.0000	26.41	.0000	320.6	.0000	69.43	.0000	674.2	.0000	5123.	.0000	1118.
Ovary	.0000	21.62	.0000	119.5	.0000	46.59	.0000	433.6	.0000	1807.	.0000	743.7
Bladder	24.06	10.99	133.5	57.53	53.94	20.21	315.7	155.1	1151.	566.1	467.0	194.9
Leukaemia	103.6	63.08	94.55	78.65	115.4	66.40	2742.	1851.	2025.	1727.	3794.	2468.
Residual	71.18	90.53	270.9	527.2	210.2	315.7	1412.	2031.	2973.	7044.	2318.	4238.
Total	322.9	382.9	1041.	2149.	1017.	1390.	6704.	8385.	11878	29099	13403	18950
Proj. L+NL	322.9	382.9	1007.	1574.	899.5	1043.	6704.	8388.	11799	21815	12263	15658
	Exposure Ages 0-19											
Oesophagus	1.793	1.843	22.20	90.85	15.38	29.59	44.35	55.87	266.7	1063.	183.1	347.5
Stomach	43.25	69.26	111.3	147.6	544.7	1343.	1151.	2060.	1192.	1633.	5850.	14883
Colon	32.09	24.23	503.0	1523.	546.5	456.6	917.6	750.2	5463.	18188	5937.	5456.
Lung	19.79	31.32	667.3	990.0	611.3	564.1	565.7	966.3	7430.	14350	6808.	8180.
Breast	.0000	57.84	.0000	789.7	.0000	205.4	.0000	1683.	.0000	12931	.0000	3361.
Ovary	.0000	18.64	.0000	163.5	.0000	104.8	.0000	561.1	.0000	2786.	.0000	1784.
Bladder	2.533	.7741	150.3	67.38	71.04	19.39	69.09	26.10	1406.	729.9	664.8	210.5
Leukaemia	98.11	68.38	94.74	67.49	124.6	87.23	4362.	3459.	4039.	3055.	6602.	5152.
Residual	58.12	98.80	451.5	1355.	366.1	789.6	1515.	3070.	5139.	18835	4166.	10981
Total	255.7	371.1	2000.	5195.	2279.	3600.	8627.	12632	24939	73574	30212	50358
Proj. L+NL	255.7	371.1	2060.	3520.	1870.	2470.	8620.	12624	26007	52031	26100	38970
	Exposure Ages 20-64											
Oesophagus	16.25	33.71	19.63	85.06	20.17	44.55	227.3	500.6	208.0	901.2	211.6	466.6
Stomach	85.42	98.61	42.88	58.04	180.9	270.4	1477.	1886.	439.1	611.7	1862.	2892.
Colon	17.09	27.52	57.43	170.9	28.19	49.49	275.0	490.6	576.4	1895.	286.5	554.7
Lung	42.89	72.90	181.7	257.8	50.26	81.52	569.0	1103.	1780.	3240.	500.1	1032.
Breast	.0000	20.91	.0000	213.5	.0000	30.57	.0000	440.8	.0000	3279.	.0000	470.4
Ovary	.0000	28.82	.0000	132.1	.0000	34.15	.0000	514.2	.0000	1927.	.0000	510.6
Bladder	37.94	17.69	144.6	64.29	54.05	24.10	497.8	257.4	1247.	637.4	463.7	235.9
Leukaemia	124.2	72.88	99.04	88.55	135.1	74.28	2610.	1673.	1465.	1549.	3389.	2035.
Residual	93.70	113.7	249.7	314.5	187.1	200.3	1708.	2224.	2677.	3963.	2016.	2558.
Total	417.5	486.8	795.0	1385.	655.9	809.4	7365.	9091.	8393.	18006	8730.	10757
Proj. L+NL	417.5	486.8	717.2	1133.	645.7	702.4	7368.	9094.	7811.	14870	8701.	10043
	Exposure Ages 65-90											
Oesophagus	3.232	9.289	4.957	28.62	5.362	16.31	16.04	53.24	26.07	163.4	28.62	91.10
Stomach	9.209	13.66	5.116	9.479	17.86	27.43	50.32	78.70	26.89	50.39	92.25	152.0
Colon	1.559	3.634	9.280	31.54	3.298	7.252	7.201	19.87	48.49	172.8	15.95	37.79
Lung	9.382	18.66	58.67	67.91	14.11	20.22	51.41	108.9	314.4	412.4	75.57	121.0
Breast	.0000	.2271	.0000	3.039	.0000	.3604	.0000	.1948	.0000	15.52	.0000	.1948
Ovary	.0000	4.458	.0000	22.96	.0000	4.702	.0000	24.67	.0000	135.7	.0000	26.55
Bladder	8.821	5.089	57.09	24.39	21.25	9.891	47.67	28.70	286.8	135.6	106.8	53.24
Leukaemia	31.36	27.09	76.09	64.61	18.20	15.17	215.1	207.7	477.0	461.3	130.2	122.2
Residual	5.175	11.22	16.02	36.38	9.150	16.32	27.43	64.15	81.31	204.8	47.13	89.93
Total	68.74	93.35	227.2	288.9	89.25	117.6	415.2	586.2	1261.	1752.	496.6	694.1
Proj. L+NL	68.74	93.35	185.4	246.7	89.34	122.8	413.0	601.5	1043.	1499.	498.5	734.7

Table 4—*continued*

Population:	CHINA											
	UNTIMELY DEATHS						YEARS OF EXPECTED LIFE LOST					
Model:	ADDITIVE		MULTIPLICATIVE		NIH		ADDITIVE		MULTIPLICATIVE		NIH	
Sex:	M	F	M	F	M	F	M	F	M	F	M	F
						Exposure Ages 0-90						
Oesophagus	10.35	18.38	71.78	259.9	14.62	23.60	144.7	258.8	869.8	3290.	169.3	275.3
Stomach	62.37	69.42	106.1	124.1	123.9	176.2	1175.	1421.	1498.	1784.	1710.	2518.
Colon	18.78	20.48	38.78	77.78	60.59	53.91	407.6	419.0	531.8	1123.	830.2	758.9
Lung	31.55	46.47	37.78	70.08	58.23	78.19	492.4	769.7	544.2	1092.	808.5	1157.
Breast	.0000	25.23	.0000	33.52	.0000	48.79	.0000	613.5	.0000	575.6	.0000	842.9
Ovary	.0000	19.83	.0000	28.05	.0000	24.73	.0000	385.8	.0000	502.6	.0000	436.5
Bladder	23.93	9.615	23.68	7.577	37.57	12.80	315.9	131.9	231.5	89.01	355.0	138.2
Leukaemia	102.8	60.73	48.05	40.22	114.4	65.38	2721.	1714.	1680.	1453.	3751.	2323.
Residual	70.49	84.49	98.24	258.3	94.79	176.0	1403.	1826.	1614.	4239.	1506.	2848.
Total	320.3	354.6	424.5	899.5	504.2	659.8	6662.	7541.	6971.	14151	9131.	11299
Proj. L+NL	320.3	354.6	529.0	744.9	504.4	697.2	6671.	7540.	8598.	12129	9158.	11729
						Exposure Ages 0-19						
Oesophagus	1.750	1.681	89.13	319.5	11.40	10.82	41.19	46.12	1189.	4501.	152.0	150.1
Stomach	42.22	63.30	213.2	249.7	205.3	365.0	1122.	1786.	3099.	3727.	2983.	5454.
Colon	31.36	22.22	113.2	231.8	170.7	125.5	893.0	652.9	1602.	3443.	2425.	1873.
Lung	19.34	28.72	91.10	170.6	113.1	139.0	549.5	842.8	1414.	2890.	1756.	2355.
Breast	.0000	52.75	.0000	78.64	.0000	129.0	.0000	1455.	.0000	1394.	.0000	2281.
Ovary	.0000	17.04	.0000	41.64	.0000	32.76	.0000	485.3	.0000	878.9	.0000	687.3
Bladder	2.472	.7067	27.21	9.054	24.30	5.355	65.65	20.38	296.8	119.0	264.6	69.41
Leukaemia	96.85	67.26	102.0	85.76	123.0	85.66	4256.	3132.	4582.	3946.	6430.	4703.
Residual	56.72	90.63	168.1	640.3	115.1	383.4	1476.	2676.	2915.	10906	1993.	6529.
Total	250.7	344.3	804.2	1827.	763.2	1276.	8404.	11098	15100	31809	16005	24104
Proj. L+NL	250.7	344.3	1163.	1663.	750.6	1388.	8406.	11101	20615	29151	15897	25517
						Exposure Ages 20-64						
Oesophagus	16.17	29.06	77.56	283.5	18.74	33.00	226.0	417.6	912.2	3510.	214.4	391.8
Stomach	84.98	88.20	79.99	96.42	113.0	131.0	1479.	1622.	1095.	1343.	1508.	1795.
Colon	16.98	24.45	12.32	25.18	22.13	33.45	273.9	418.7	148.6	326.5	268.0	431.2
Lung	42.67	63.05	20.65	39.09	44.18	66.32	573.3	920.6	257.1	524.9	542.5	881.8
Breast	.0000	19.11	.0000	21.34	.0000	24.12	.0000	383.3	.0000	345.7	.0000	392.6
Ovary	.0000	25.55	.0000	28.34	.0000	26.80	.0000	438.9	.0000	456.7	.0000	432.4
Bladder	37.75	15.21	25.67	8.280	48.53	17.87	501.4	213.4	246.3	94.67	461.7	197.1
Leukaemia	123.1	67.41	32.18	27.89	133.9	70.01	2603.	1462.	692.7	656.8	3361.	1805.
Residual	93.15	102.3	88.43	145.5	107.1	123.5	1708.	1915.	1387.	2229.	1638.	1872.
Total	414.8	434.3	336.8	675.6	487.7	526.1	7365.	7794.	4740.	9489.	7996.	8200.
Proj. L+NL	414.8	434.3	346.3	496.3	495.2	536.9	7379.	7793.	4910.	7291.	8098.	8275.
						Exposure Ages 65-90						
Oesophagus	3.535	8.721	14.85	73.90	4.237	11.80	16.88	54.02	79.93	441.9	20.72	72.28
Stomach	10.07	12.83	4.458	9.097	10.21	16.50	54.02	78.98	22.06	55.70	55.27	100.4
Colon	1.706	3.412	1.377	3.367	2.537	5.025	7.004	22.44	4.989	21.69	11.13	32.16
Lung	10.26	17.52	3.687	9.529	8.576	17.03	54.98	106.6	18.13	59.63	46.15	105.0
Breast	.0000	.2132	.0000	.2383	.0000	.2760	.0000	1.758	.0000	1.842	.0000	1.926
Ovary	.0000	4.185	.0000	3.880	.0000	3.642	.0000	27.39	.0000	26.04	.0000	24.29
Bladder	9.650	4.778	8.815	2.556	18.98	7.368	51.62	30.99	45.19	17.67	99.21	45.31
Leukaemia	32.72	25.78	7.495	6.711	18.75	14.37	228.4	202.2	49.80	55.28	134.3	120.4
Residual	5.661	10.53	2.417	10.68	5.412	10.87	29.26	64.83	10.45	65.16	27.53	65.92
Total	73.61	87.99	43.10	119.9	68.71	86.89	442.2	589.3	230.5	744.9	394.3	567.8
Proj. L+NL	73.61	87.99	38.03	69.05	64.98	92.99	448.8	578.0	214.8	429.6	383.4	591.4

radiation or other factors, it seems more reasonable to project different sites separately, and then to sum them. It is easy to show that, when constant-relative-risk projections over time are made for grouped cancers with markedly different patterns of site-specific baseline rates, the projection for group as a whole is likely to disagree with the sum of the projected values for the separate sites (see, e.g. Land and Pierce, 1983). In the case of the residual class, however, which consists of many organs of uncertain and variable sensitivity to radiation carcinogenesis, the same objection applies. Thus we are left with the choice of two unsatisfactory projections of total excess cancer risk.

There is considerably more variation by projection model for the younger Japanese cohorts. The maximum age at observation (in 1985) was 40 for an A-bomb survivor exposed during the first year of life, and 60 for exposure at age 19. This leaves between

15 and 40 more years of expected lifetime during which baseline rates for most sites increase steeply. The behaviour of the baseline rates is immaterial to the additive model, but the other two models are affected strongly. For most sites, the projected fatal cancer probabilities and years of life lost according to the multiplicative and NIH models are similar, and far greater than those projected by the additive model. For leukaemia, all three model projections are fairly similar because almost all the expression of risk is assumed to occur during the first 40 years after exposure, but there is more loss of expected life span for the NIH model which assigns most of the excess deaths to the early part of that period (Fig. 2).

The non-Japanese populations represented in Table 3 are different from the Japanese population and from each other mainly because the five populations have different site-specific baseline cancer rates (Table 3), but also to some extent because all-cause mortality rates, age distributions, and expected life spans also differ. The latter (i.e. life-table) factors are responsible for the relatively minor variations in the additive model projections.

For exposure after age 65, the additive and NIH projections are similar to each other and among populations, because there is no need for extrapolation beyond the observation period. The multiplicative model projections differ considerably among populations, however, reflecting differences in site-specific cancer mortality rates. For example, baseline stomach cancer mortality is much higher in Japan than in the U.S., while the reverse is true of colon cancer. Consequently, the projected excess of stomach cancer mortality is much higher in Japan than in the U.S. and that for colon cancer is higher in the U.S. than in Japan. The projections for both cancers according to the additive and NIH models are somewhat higher for Japan than the U.S., but this merely reflects the longer expected lifetime of the Japanese population.

The greatest variation in projected cancer risk results from exposure before age 20. This is true among models within populations, and among populations within models. Continuing the comparison of the preceding paragraph between Japan and the U.S., the multiplicative projection of stomach cancer is higher for Japan, which has the higher baseline rates, whereas the same projection for colon cancer is higher for the U.S., for which the colon cancer baseline is higher. The additive projections of both cancers are about the same for the two countries. The NIH projection for colon cancer is higher for the U.S. than for Japan; baseline rates are similar during the first 50 years or so of life, but the U.S. rate climbs faster at older ages (Table 3). But for the U.S., the NIH model projection of stomach cancer is about ten times as high as the multiplicative projection, and it is higher than the NIH model projection for Japan. This seeming paradox is explainable in terms of Table 3: U.S. baseline rates are far lower than Japanese rates at young ages, whereas at older ages the rates become proportionally less different because the U.S. rates increase more steeply with age. Thus in calculations for the U.S. population, the absolute risks in Table 1 are converted to very high relative risks which yield high numbers of deaths and lost years of life when multiplied by the higher rates of later life.

It is not surprising that there is a high level of consistency among the site-specific cancers, the non-leukaemia group, and the residual class for the Japanese population, since the "residual" relative risk coefficients were constructed using Japanese rates. But for the other populations there is general consistency only in the cases of the additive projection model. As expected, inconsistent results are the norm when projections based on relative risk are made for summed sites with markedly different patterns of site-specific baseline rates (see, e.g. Land and Pierce, 1983).

4.2. Appropriateness of Projection Models

The three projection models used in this examination are extremely simple, reflecting a general ignorance about variation of radiation-related risk over time following exposure and by characteristics of the exposed population other than age and sex. We know a little about time dependence, mainly from observations of populations following a single, acute exposure; it has been shown fairly conclusively for several cancer sites that the additive model's treatment of time does not hold and that the multiplicative model's treatment is a usable approximation for many purposes (Shimizu *et al.*, 1990; Land, 1987; Muirhead and Darby, 1987). Other analyses, however, suggest that relative risks may decline over time following exposure (NAS, 1988; Darby *et al.*, 1987; NAS, 1990). The multiplicative time-to-response model seems generally plausible if we consider that cancer latency is typically long, and that in order for exposure to carcinogens like radiation to result in cancer, other subsequent events may also be necessary. Thus, the well-known variation in baseline rates with age may correspond to age-related events that similarly promote the occurrence of cancer initiated by any number of causes, including radiation exposure. The NIH model for leukaemia is mainly empirical, but lognormal distributions are used to describe tumour growth (Steel, 1977) and they seem to fit at least two radiation-induced cancers with typically short latent periods (Land, 1987; Chmelevsky *et al.*, 1988).

Our ignorance about variation of radiation-induced cancer by population is abysmal given that extrapolation is such an essential part of risk analysis, but the fact is that general populations, for which reliable baseline rates are available, are not exposed to enough radiation to allow useful estimation of excess risk except in extraordinary circumstances like the atomic bombings of Hiroshima and Nagasaki or the Chernobyl nuclear power plant accident. Comparison of, for example, breast cancer risk among Japanese A-bomb survivors, U.S. and Canadian tuberculosis patients given multiple chest fluoroscopies, and U.S. mastitis patients given X-ray therapy is complicated by the possibility that underlying differences related to the reasons for and circumstances of exposure, and not just national differences, may influence the expression of radiation-related excess risk. It is of some interest that analyses of data from the populations just mentioned, but at different follow-up periods and with somewhat different methods, have been used to justify both the additive and multiplicative approaches to projection between populations (Land *et al.*, 1980; NIH, 1985; NAS, 1990). If baseline rates differ between two populations because of differential exposure to carcinogens that act in the same way as radiation, then additivity has a certain plausibility; if they differ because of promoting factors that influence the expression of cancers caused by radiation and other carcinogens, on the other hand, then multiplicativity might be more appropriate. Epidemiological studies of cancer risk among migrants, and their descendants, between countries having markedly different site-specific baseline cancer rates suggest that differences in exposure to both cancer promoters and initiators other than radiation may be involved, and that there may be considerable variation by site. This question, and related observations, are discussed in more detail by Land (1990).

4.3. Implications for Site-Specific Weighting

The projected deaths and lost years of life in Table 4 were converted into site-specific weights by dividing each of them by the total of all single-site values plus residual. For the

additive projection model and exposure ages 0–90, the residual class corresponded to 21% and 22% of the total projected early mortality for males and females, respectively, for all populations. For the other two projection models higher, and more variable, residual values were obtained; this reflects variation with increasing age at death of baseline mortality rates for many organ sites of doubtful sensitivity to radiation carcinogenesis, as well as of those specifically considered here. A comparison of autopsy findings with death certificate diagnoses among Japanese A-bomb survivors (Steer *et al.*, 1976) found that about 15% of deaths due to the specific non-leukaemia sites considered here were incorrectly assigned to sites included in the "residual" category. This correction was applied to the projected values, i.e. by multiplying each of the site-specific values by 1.15 and subtracting the additional 15% from the residual class. After this had been done the average residual percentage for period of observation, as inferred from the additive model projections for the Japanese population, was about 15% for both males and females. Given that there is very little information on which to base projected risks for a residual class of radiation-induced cancers, it was decided to set the weight for this class uniformly equal to 15%, for both sexes and all exposure ages, populations, and projection models. The weights obtained with this convention are given in Table 5.

Table 5. Percentage weights obtained after standardisation of the residual weights at 15 percent for both males and females: by population, projection model, sex, cancer site, and exposure age

Population:	JAPAN											
	UNTIMELY DEATHS						YEARS OF EXPECTED LIFE LOST					
Model:	ADDITIVE		MULTIPLICATIVE		NIH		ADDITIVE		MULTIPLICATIVE		NIH	
Sex:	M	F	M	F	M	F	M	F	M	F	M	F
						Exposure Ages 0-90						
Oesophagus	3.93	6.55	3.09	4.41	2.78	5.71	2.70	4.41	2.52	3.09	2.04	3.73
Stomach	22.5	22.3	31.9	26.2	26.1	27.4	20.6	22.1	28.7	24.6	20.9	23.9
Colon	6.66	6.61	12.7	23.2	12.9	11.3	7.03	6.51	11.6	20.9	10.7	9.48
Lung	11.8	16.0	18.4	16.4	22.9	21.2	8.92	12.5	15.3	14.1	17.7	17.4
Breast	.000	7.64	.000	4.64	.000	5.38	.000	9.23	.000	6.43	.000	6.99
Ovary	.000	6.49	.000	2.89	.000	3.74	.000	6.08	.000	3.64	.000	4.40
Bladder	9.19	3.44	8.07	2.37	7.25	3.06	5.91	2.27	5.42	1.59	4.39	1.92
Leukaemia	30.7	15.8	10.6	4.83	12.9	7.11	39.7	21.7	21.3	10.4	29.1	17.0
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 0-19						
Oesophagus	.848	.603	1.84	2.22	1.58	3.19	.607	.503	1.48	1.58	1.23	2.10
Stomach	20.4	22.6	32.1	23.7	21.8	25.2	15.4	19.4	26.8	21.9	17.8	21.6
Colon	15.1	7.89	18.8	31.3	18.8	14.8	12.1	7.05	15.9	26.9	15.5	11.8
Lung	9.32	10.2	20.6	16.5	32.3	26.1	7.50	9.11	16.4	14.4	25.0	21.1
Breast	.000	18.9	.000	5.01	.000	6.93	.000	15.9	.000	6.70	.000	8.57
Ovary	.000	6.08	.000	1.83	.000	2.63	.000	5.28	.000	2.53	.000	3.36
Bladder	1.19	.253	4.52	1.18	3.87	1.69	.929	.233	2.98	.805	2.49	1.07
Leukaemia	38.0	18.4	6.97	3.08	6.44	4.29	48.3	27.3	21.3	9.95	22.8	15.2
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 20-64						
Oesophagus	4.67	8.09	4.59	7.26	4.30	8.17	3.77	6.56	4.12	5.51	3.14	5.73
Stomach	23.7	22.9	33.1	30.7	32.4	30.6	23.6	23.9	32.2	29.8	25.4	27.4
Colon	4.75	6.44	5.72	11.7	5.21	7.61	4.45	6.29	5.34	10.5	4.00	6.34
Lung	12.4	17.4	15.6	15.4	10.3	15.0	9.59	14.4	13.5	13.2	7.40	12.0
Breast	.000	4.77	.000	4.41	.000	3.84	.000	5.55	.000	6.17	.000	4.96
Ovary	.000	6.75	.000	4.52	.000	5.09	.000	6.60	.000	5.68	.000	5.90
Bladder	11.0	4.25	11.8	3.90	11.1	4.39	8.41	3.39	8.88	2.85	6.77	2.96
Leukaemia	28.4	14.2	14.0	6.95	21.5	10.2	35.1	18.1	20.8	11.1	38.2	19.5
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 65-90						
Oesophagus	4.81	10.2	4.40	11.8	5.58	14.4	4.05	9.34	3.86	10.8	5.04	13.4
Stomach	13.7	15.0	13.0	16.5	20.7	18.1	12.1	13.8	11.9	15.5	19.4	17.3
Colon	2.32	3.99	2.96	8.28	3.00	5.19	2.16	3.52	2.61	7.63	2.82	4.72
Lung	13.9	20.4	18.3	25.8	14.4	23.2	12.3	18.8	17.4	24.5	14.0	22.2
Breast	.000	.249	.000	.219	.000	.278	.000	.210	.000	.155	.000	.198
Ovary	.000	4.89	.000	3.02	.000	3.67	.000	4.29	.000	2.86	.000	3.52
Bladder	13.1	5.58	18.0	6.56	22.9	7.98	11.5	4.89	15.6	6.18	20.4	7.61
Leukaemia	36.9	24.5	28.1	12.6	18.3	12.0	42.8	30.0	33.4	17.0	23.1	15.8
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.

Table 5—*continued*

Population:	UNITED STATES											
	UNTIMELY DEATHS						YEARS OF EXPECTED LIFE LOST					
Model:	ADDITIVE		MULTIPLICATIVE		NIH		ADDITIVE		MULTIPLICATIVE		NIH	
Sex:	M	F	M	F	M	F	M	F	M	F	M	F
	Exposure Ages 0-90											
Oesophagus	3.76	6.35	1.28	1.53	1.99	3.00	2.57	4.28	1.23	1.40	1.61	2.44
Stomach	22.4	22.4	3.88	2.75	27.9	35.4	20.4	22.1	3.45	2.21	21.4	28.0
Colon	6.73	6.62	26.9	36.9	22.4	15.2	7.07	6.51	23.6	31.2	17.2	12.5
Lung	11.4	15.7	26.6	14.3	12.9	11.2	8.64	12.3	26.7	15.9	11.4	11.8
Breast	.000	7.82	.000	14.9	.000	6.74	.000	9.33	.000	17.8	.000	7.88
Ovary	.000	6.47	.000	6.18	.000	4.65	.000	6.04	.000	6.54	.000	5.05
Bladder	8.73	3.33	12.2	2.87	7.04	2.57	5.60	2.20	8.80	1.90	4.40	1.65
Leukaemia	31.8	16.2	13.9	5.37	12.5	6.13	40.6	22.1	21.0	7.88	28.8	15.5
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
	Exposure Ages 0-19											
Oesophagus	.823	.596	.780	.784	.805	.711	.553	.500	.735	.767	.723	.675
Stomach	19.8	22.3	3.75	2.28	24.6	35.4	15.0	19.3	3.09	1.83	19.2	27.5
Colon	14.7	7.83	38.3	46.2	33.7	20.6	11.9	7.01	30.8	38.0	25.7	16.4
Lung	9.09	10.1	30.2	14.4	15.4	10.5	7.38	9.05	29.1	16.7	14.1	11.8
Breast	.000	18.7	.000	14.8	.000	8.58	.000	15.7	.000	17.3	.000	9.69
Ovary	.000	6.02	.000	3.36	.000	4.17	.000	5.23	.000	3.88	.000	4.65
Bladder	1.16	.250	6.67	1.32	4.22	1.38	.903	.231	4.67	.919	2.80	.927
Leukaemia	39.2	19.0	5.18	1.68	6.22	3.47	49.1	27.8	16.5	5.45	22.3	13.2
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
	Exposure Ages 20-64											
Oesophagus	4.53	7.94	2.04	2.82	3.72	5.89	3.68	6.47	2.12	2.65	2.94	5.13
Stomach	23.6	23.0	4.38	3.68	33.4	36.0	23.6	24.0	4.22	3.01	25.0	29.0
Colon	4.73	6.43	13.3	21.4	5.60	7.58	4.42	6.28	12.3	17.8	4.04	6.22
Lung	11.9	17.1	23.2	14.0	9.19	11.9	9.27	14.2	23.5	14.4	7.19	11.8
Breast	.000	4.85	.000	16.5	.000	4.36	.000	5.62	.000	19.6	.000	5.08
Ovary	.000	6.74	.000	11.3	.000	5.40	.000	6.58	.000	11.9	.000	5.73
Bladder	10.6	4.17	19.6	5.29	10.7	3.93	8.13	3.33	15.6	3.69	6.61	2.67
Leukaemia	29.4	14.6	22.2	9.80	22.2	9.82	35.8	18.4	27.0	11.6	39.1	19.2
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
	Exposure Ages 65-90											
Oesophagus	4.74	10.1	.980	2.94	5.36	12.1	4.39	9.17	.943	2.64	5.17	11.4
Stomach	13.5	14.9	1.23	2.29	21.7	23.8	12.0	13.6	1.20	1.99	19.7	22.1
Colon	2.28	3.96	4.81	14.1	3.70	5.74	2.03	3.44	4.28	12.9	3.66	5.30
Lung	13.7	20.3	12.8	13.9	12.7	17.6	12.2	18.8	12.2	13.2	12.3	17.4
Breast	.000	.247	.000	.783	.000	.275	.000	.177	.000	.664	.000	.191
Ovary	.000	4.86	.000	8.49	.000	4.44	.000	4.28	.000	8.08	.000	4.19
Bladder	12.9	5.55	17.0	8.74	23.7	9.49	11.5	4.94	14.9	7.72	21.4	8.64
Leukaemia	37.7	24.9	48.0	33.6	17.6	11.3	42.6	30.4	51.3	37.7	22.5	15.6
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.

Table 5—*continued*

Population:	PUERTO RICO											
	UNTIMELY DEATHS						YEARS OF EXPECTED LIFE LOST					
Model:	ADDITIVE		MULTIPLICATIVE		NIH		ADDITIVE		MULTIPLICATIVE		NIH	
Sex:	M	F	M	F	M	F	M	F	M	F	M	F
						Exposure Ages 0-90						
Oesophagus	3.94	6.52	7.48	12.2	2.29	3.80	2.77	4.46	6.47	9.80	1.82	2.77
Stomach	22.5	22.4	16.9	10.2	35.7	33.3	20.7	22.0	13.8	9.04	27.8	28.0
Colon	6.65	6.61	16.4	24.6	14.9	12.6	7.00	6.52	14.3	21.1	12.4	10.2
Lung	11.9	15.9	14.3	13.7	12.0	15.4	9.11	12.6	13.1	13.3	10.5	14.3
Breast	.000	7.67	.000	9.54	.000	5.48	.000	9.20	.000	12.5	.000	6.84
Ovary	.000	6.48	.000	3.21	.000	5.39	.000	6.08	.000	3.45	.000	5.79
Bladder	9.24	3.42	12.2	3.44	8.01	2.74	6.11	2.31	8.39	2.53	5.24	1.91
Leukaemia	30.6	15.9	17.5	7.87	11.9	6.06	39.2	21.6	28.6	13.1	27.1	14.9
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 0-19						
Oesophagus	.835	.599	4.87	6.68	.993	1.17	.623	.537	4.09	5.54	.873	.944
Stomach	20.1	22.5	18.3	9.78	35.9	33.7	15.4	19.4	13.5	8.28	27.7	27.6
Colon	14.9	7.86	26.5	35.3	22.6	16.0	12.1	7.05	20.7	28.6	18.5	12.5
Lung	9.20	10.1	17.8	15.0	13.9	16.8	7.51	9.09	15.4	14.6	12.6	15.8
Breast	.000	18.8	.000	10.9	.000	6.71	.000	15.9	.000	13.7	.000	8.13
Ovary	.000	6.06	.000	1.97	.000	5.33	.000	5.29	.000	2.19	.000	5.74
Bladder	1.17	.251	7.29	1.82	5.05	1.75	.930	.258	4.71	1.34	3.44	1.25
Leukaemia	38.6	18.6	10.0	3.39	6.33	3.44	48.3	27.4	26.4	10.6	21.7	12.8
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 20-64						
Oesophagus	4.68	8.05	10.3	18.7	3.75	6.80	3.84	6.61	9.76	15.8	3.03	5.32
Stomach	23.8	23.0	16.7	11.4	36.4	33.7	23.6	23.9	15.0	10.4	28.2	29.0
Colon	4.76	6.44	7.11	11.9	5.34	8.20	4.46	6.29	6.41	10.1	4.19	6.57
Lung	12.4	17.3	11.1	12.0	9.11	13.2	9.81	14.5	10.3	11.4	7.34	11.8
Breast	.000	4.80	.000	8.69	.000	4.06	.000	5.54	.000	11.3	.000	4.99
Ovary	.000	6.76	.000	5.00	.000	5.62	.000	6.60	.000	5.47	.000	5.93
Bladder	11.0	4.23	16.8	5.31	10.9	3.78	8.62	3.41	12.9	4.19	7.28	2.78
Leukaemia	28.2	14.3	22.8	11.7	19.3	9.53	34.5	18.0	30.5	16.0	34.8	18.5
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 65-90						
Oesophagus	5.11	10.3	7.92	22.2	6.50	15.0	4.22	9.56	6.87	20.1	5.88	13.6
Stomach	14.5	15.2	6.02	5.40	20.8	21.0	13.1	13.9	5.25	5.06	19.7	19.7
Colon	2.47	4.05	3.34	7.84	3.79	6.53	1.91	3.99	2.76	7.00	3.15	5.98
Lung	14.8	20.8	10.1	12.2	16.2	19.6	13.4	19.1	9.17	12.0	15.6	19.5
Breast	.000	.253	.000	.323	.000	.260	.000	.446	.000	.320	.000	.419
Ovary	.000	4.97	.000	2.67	.000	3.54	.000	4.79	.000	2.95	.000	4.00
Bladder	13.9	5.67	18.4	6.53	23.4	8.25	12.6	5.39	16.2	5.85	21.8	7.58
Leukaemia	33.9	23.6	39.0	27.7	14.1	10.6	39.5	27.7	44.6	31.5	18.6	14.0
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.

Table 5—*continued*

Population:	UNITED KINGDOM											
	UNTIMELY DEATHS						YEARS OF EXPECTED LIFE LOST					
Model:	ADDITIVE		MULTIPLICATIVE		NIH		ADDITIVE		MULTIPLICATIVE		NIH	
Sex:	M	F	M	F	M	F	M	F	M	F	M	F
						Exposure Ages 0-90						
Oesophagus	3.72	6.27	2.04	4.00	1.79	2.82	2.52	4.20	1.94	3.12	1.42	2.15
Stomach	22.4	22.4	6.28	3.78	27.5	39.7	20.3	22.0	5.75	2.98	21.6	32.0
Colon	6.75	6.63	19.2	25.8	17.8	11.5	7.09	6.50	18.0	22.2	14.3	10.0
Lung	11.3	15.5	33.2	21.5	21.2	15.3	8.49	12.2	30.6	21.5	17.3	15.8
Breast	.000	7.90	.000	16.9	.000	5.53	.000	9.37	.000	19.9	.000	6.60
Ovary	.000	6.46	.000	6.30	.000	3.71	.000	6.02	.000	7.03	.000	4.39
Bladder	8.58	3.29	14.9	3.03	5.79	1.61	5.43	2.15	11.3	2.20	3.74	1.15
Leukaemia	32.1	16.4	9.21	3.60	10.7	4.60	41.0	22.3	17.3	5.84	26.4	12.6
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 0-19						
Oesophagus	.825	.594	1.22	2.01	.689	.898	.576	.521	1.17	1.66	.618	.763
Stomach	19.8	22.3	6.15	3.27	24.4	40.7	14.9	19.2	5.25	2.55	19.7	32.6
Colon	14.7	7.81	27.8	33.7	24.4	13.8	11.9	6.99	24.0	28.4	20.0	11.9
Lung	9.10	10.1	36.9	21.9	27.3	17.1	7.34	9.01	32.7	22.4	22.9	17.9
Breast	.000	18.6	.000	17.5	.000	6.23	.000	15.7	.000	20.2	.000	7.38
Ovary	.000	6.01	.000	3.62	.000	3.18	.000	5.23	.000	4.35	.000	3.91
Bladder	1.16	.249	8.31	1.49	3.18	.588	.897	.243	6.20	1.14	2.24	.462
Leukaemia	39.2	19.1	4.55	1.30	4.85	2.30	49.2	28.0	15.4	4.15	19.3	9.83
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 20-64						
Oesophagus	4.49	7.88	3.13	6.82	3.80	6.31	3.63	6.40	3.20	5.53	2.86	4.99
Stomach	23.6	23.0	6.84	4.65	34.0	38.3	23.6	24.1	6.75	3.75	25.2	30.9
Colon	4.72	6.43	9.16	13.7	5.31	7.01	4.39	6.27	8.86	11.6	3.88	5.94
Lung	11.8	17.0	29.0	20.6	9.46	11.5	9.09	14.1	27.3	19.9	6.77	11.0
Breast	.000	4.88	.000	17.1	.000	4.33	.000	5.63	.000	20.1	.000	5.04
Ovary	.000	6.73	.000	10.6	.000	4.84	.000	6.57	.000	11.8	.000	5.47
Bladder	10.4	4.13	23.0	5.16	10.1	3.41	7.96	3.29	19.1	3.91	6.28	2.52
Leukaemia	29.8	14.8	13.7	6.18	22.1	9.15	36.2	18.6	19.6	8.27	39.9	18.9
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 65-90						
Oesophagus	4.61	10.0	2.09	9.96	5.86	13.9	3.79	9.14	1.98	9.34	5.62	13.1
Stomach	13.1	14.7	2.16	3.30	19.5	23.4	11.8	13.5	2.04	2.88	18.1	21.9
Colon	2.22	3.93	3.91	10.9	3.60	6.20	1.70	3.41	3.68	9.88	3.13	5.46
Lung	13.4	20.1	24.7	23.6	15.4	17.2	12.1	18.7	23.9	23.5	14.8	17.4
Breast	.000	.245	.000	1.05	.000	.308	.000	.033	.000	.887	.000	.028
Ovary	.000	4.82	.000	7.99	.000	4.02	.000	4.23	.000	7.75	.000	3.83
Bladder	12.6	5.50	24.1	8.49	23.2	8.46	11.2	4.92	21.8	7.75	20.9	7.69
Leukaemia	38.9	25.4	27.9	19.5	17.3	11.2	44.2	31.0	31.5	22.9	22.2	15.3
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.

Table 5—*continued*

Population:	CHINA											
	UNTIMELY DEATHS						YEARS OF EXPECTED LIFE LOST					
Model:	ADDITIVE		MULTIPLICATIVE		NIH		ADDITIVE		MULTIPLICATIVE		NIH	
Sex:	M	F	M	F	M	F	M	F	M	F	M	F
						Exposure Ages 0-90						
Oesophagus	3.72	5.95	19.0	34.7	3.15	4.22	2.50	4.00	14.3	28.7	2.01	2.87
Stomach	22.4	22.5	28.2	16.5	26.7	31.5	20.3	21.9	24.7	15.6	20.3	26.2
Colon	6.75	6.64	10.3	10.3	13.0	9.64	7.06	6.48	8.79	9.82	9.88	7.91
Lung	11.3	15.0	10.0	9.36	12.5	13.9	8.53	11.9	9.00	9.55	9.63	12.0
Breast	.000	8.17	.000	4.48	.000	8.72	.000	9.49	.000	5.03	.000	8.79
Ovary	.000	6.42	.000	3.74	.000	4.42	.000	5.97	.000	4.39	.000	4.55
Bladder	8.60	3.11	6.29	1.01	8.09	2.28	5.47	2.04	3.83	.778	4.22	1.44
Leukaemia	32.1	17.1	11.0	4.67	21.4	10.1	41.0	23.0	24.1	11.0	38.8	21.0
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 0-19						
Oesophagus	.820	.583	12.1	23.1	1.53	1.04	.549	.489	8.72	18.7	.980	.752
Stomach	19.7	21.9	29.1	18.0	27.6	35.1	14.9	18.9	22.7	15.5	19.2	27.3
Colon	14.6	7.71	15.4	16.7	22.9	12.0	11.9	6.92	11.7	14.3	15.6	9.38
Lung	9.06	9.96	12.4	12.3	15.2	13.3	7.32	8.94	10.3	12.0	11.3	11.8
Breast	.000	18.3	.000	5.68	.000	12.4	.000	15.4	.000	5.81	.000	11.4
Ovary	.000	5.91	.000	3.01	.000	3.15	.000	5.14	.000	3.66	.000	3.44
Bladder	1.15	.245	3.71	.654	3.26	.516	.875	.216	2.17	.496	1.70	.347
Leukaemia	39.4	20.2	12.1	5.39	14.3	7.17	49.3	28.8	29.2	14.3	36.0	20.4
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 20-64						
Oesophagus	4.49	7.64	26.9	45.7	4.38	7.12	3.61	6.24	23.7	41.5	3.07	5.46
Stomach	23.6	23.1	27.8	15.5	26.4	28.3	23.6	24.2	28.5	15.9	21.6	25.0
Colon	4.72	6.42	4.29	4.06	5.18	7.22	4.37	6.25	3.87	3.86	3.84	6.01
Lung	11.8	16.5	7.18	6.31	10.3	14.3	9.16	13.7	6.69	6.22	7.79	12.3
Breast	.000	5.02	.000	3.44	.000	5.21	.000	5.72	.000	4.09	.000	5.47
Ovary	.000	6.71	.000	4.57	.000	5.79	.000	6.55	.000	5.41	.000	6.03
Bladder	10.5	4.00	8.93	1.33	11.3	3.86	8.01	3.19	6.41	1.12	6.63	2.75
Leukaemia	29.7	15.4	9.74	3.91	27.2	13.1	36.1	19.0	15.6	6.76	41.9	21.9
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
						Exposure Ages 65-90						
Oesophagus	4.71	10.0	31.7	57.9	5.91	13.5	3.74	9.21	31.8	55.8	5.04	12.6
Stomach	13.4	14.7	9.54	7.13	14.2	18.9	11.9	13.4	8.78	7.03	13.4	17.5
Colon	2.27	3.91	2.94	2.63	3.54	5.76	1.55	3.83	1.98	2.74	2.70	5.62
Lung	13.6	20.1	7.89	7.47	11.9	19.5	12.1	18.1	7.21	7.53	11.2	18.3
Breast	.000	.244	.000	.186	.000	.316	.000	.300	.000	.232	.000	.336
Ovary	.000	4.80	.000	3.04	.000	4.17	.000	4.67	.000	3.29	.000	4.24
Bladder	12.8	5.48	18.8	2.00	26.5	8.44	11.4	5.28	17.9	2.23	24.1	7.92
Leukaemia	37.9	25.7	13.9	4.57	22.7	14.3	44.0	30.0	17.2	6.07	28.4	18.3
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.

Because the weights in each column of Table 5, within exposure-age intervals, sum to 100, the extreme variations among models and exposure ages, in particular, found in Table 4 are absent from Table 5; the weights indicate how important each site is in relation to the others in the same grouping by model, sex, exposure age, and/or population. The weighting system based on loss of expected life span differs from that based on numbers of untimely deaths mainly in that the former system gives more weight to leukaemia, for which the expression period is relatively early. For the NIH model in particular, the life span-based leukaemia weights are about twice the corresponding values based on numbers of deaths; the disparity is greatest for exposure at young ages and least for exposure after age 65.

The influence of the choice of projection model can be evaluated from Table 6, in which the tabulated values have been averaged over population and sex, but more insight can be obtained from Table 5. First, there is hardly any difference among populations with respect to the weights obtained using the additive model. This is to be expected since the projected mortality and loss of expected life span, and the resulting weights, depend only upon the absolute risk coefficients in Table 1 and the lifetables in Table 3. Second, there is somewhat more variation by population for the NIH model, which

Table 6. Percentage weights, obtained by averaging over populations and sexes: by projection model, exposure age, and site

	UNTIMELY DEATHS			YRS. EXP. LIFE LOST		
Model:	ADD.	MULT.	NIH	ADD.	MULT.	NIH
			Exposure Ages 0-90			
Oesophagus	5.07	8.99	3.15	3.44	7.27	2.29
Stomach	22.4	14.6	31.1	21.3	13.1	25.0
Colon	6.66	20.6	14.1	6.78	18.1	11.4
Lung	13.6	17.8	15.9	10.5	16.9	13.8
Breast	3.92	5.05	3.18	4.66	6.18	3.71
Ovary	3.23	2.23	2.19	3.02	2.50	2.42
Bladder	6.09	6.65	4.84	3.95	4.68	3.01
Leukaemia	23.9	8.87	10.3	31.2	16.0	23.1
Residual	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.
			Exposure Ages 0-19			
Oesophagus	.713	5.57	1.26	.546	4.45	.967
Stomach	21.2	14.6	30.4	17.2	12.1	24.0
Colon	11.3	29.0	20.0	9.52	23.9	15.7
Lung	9.63	19.8	18.8	8.22	18.4	16.4
Breast	9.34	5.40	4.09	7.87	6.38	4.52
Ovary	3.01	1.38	1.84	2.62	1.66	2.11
Bladder	.711	3.70	2.55	.572	2.54	1.67
Leukaemia	29.0	5.37	5.89	38.4	15.3	19.4
Residual	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.
			Exposure Ages 20-64			
Oesophagus	6.24	12.8	5.42	5.08	11.4	4.17
Stomach	23.3	15.5	32.9	23.8	14.9	26.7
Colon	5.58	10.2	6.43	5.35	9.08	5.10
Lung	14.6	15.4	11.4	11.8	14.6	9.56
Breast	2.43	5.02	2.18	2.80	6.14	2.55
Ovary	3.37	3.60	2.67	3.29	4.03	2.90
Bladder	7.44	10.1	7.37	5.77	7.88	4.72
Leukaemia	21.9	12.1	16.4	27.0	16.7	29.2
Residual	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.
			Exposure Ages 65-90			
Oesophagus	7.47	15.2	9.83	6.66	14.4	9.10
Stomach	14.3	6.66	20.2	12.9	6.18	18.9
Colon	3.14	6.19	4.70	2.75	5.55	4.25
Lung	17.1	15.7	16.8	15.6	15.1	16.3
Breast	.124	.257	.143	.116	.226	.117
Ovary	2.43	2.52	1.98	2.22	2.49	1.98
Bladder	9.33	12.8	16.2	8.39	11.6	14.8
Leukaemia	31.0	25.5	15.0	36.2	29.3	19.4
Residual	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.

depends additionally upon the population-specific baseline rates in Table 3, in terms of their average level at ages 10–40 years after exposure, and their relative variation afterward. Far more variation is obtained using the multiplicative model, which directly reflects population variation with respect to baseline rate integrated over age at observation.

The stability of the additive projection model over populations is not an advantage if, as it appears, that stability merely reflects a lack of attention to factors that affect both baseline and radiation-induced cancer risk and their variation over time following exposure. The possibility that additive projection may be appropriate from one population to another, on the other hand, is covered by the NIH model. Therefore, in the remainder of this paper consideration of the additive model is dropped, and in the following tables weights have been averaged over the multiplicative and NIH models in addition to sex (Table 7), population (Table 8), and both sex and population (Table 9).

Only for oesophageal cancer is there remarkable variation among populations for the weights after averaging over the multiplicative and NIH models (Table 7); the high oesophageal cancer weight for China reflects the influence on the multiplicative model

Table 7. Percentage weights obtained by averaging over sex and over the UNSCEAR multiplicative model and the NIH model: by population, exposure age, and site

	UNTIMELY DEATHS					YEARS OF EXPECTED LIFE LOST				
Popn:	JAPAN	US	PR	UK	CHINA	JAPAN	US	PR	UK	CHINA
					Exposure Ages 0-90					
Oesophagus	4.00	1.95	6.45	2.66	15.2	2.85	1.67	5.22	2.16	12.0
Stomach	27.9	17.5	24.0	19.3	25.7	24.5	13.8	19.7	15.6	21.7
Colon	15.0	25.3	17.1	18.6	10.8	13.2	21.1	14.5	16.1	9.10
Lung	19.7	16.3	13.9	22.8	11.4	16.1	16.5	12.8	21.3	10.0
Breast	2.50	5.43	3.75	5.61	3.30	3.35	6.44	4.84	6.63	3.45
Ovary	1.65	2.70	2.15	2.50	2.04	2.01	2.90	2.31	2.85	2.23
Bladder	5.19	6.18	6.61	6.34	4.42	3.33	4.19	4.52	4.60	2.57
Leukaemia	8.87	9.49	10.8	7.04	11.8	19.4	18.3	20.9	15.5	23.7
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
					Exposure Ages 0-19					
Oesophagus	2.21	.770	3.43	1.20	9.46	1.60	.725	2.86	1.05	7.30
Stomach	25.7	16.5	24.4	18.6	27.4	22.0	12.9	19.3	15.0	21.2
Colon	20.9	34.7	25.1	24.9	16.8	17.5	27.7	20.1	21.1	12.7
Lung	23.9	17.6	15.9	25.8	13.3	19.2	17.9	14.6	24.0	11.3
Breast	2.98	5.86	4.41	5.93	4.52	3.82	6.76	5.46	6.90	4.31
Ovary	1.11	1.88	1.82	1.70	1.54	1.47	2.13	1.98	2.06	1.77
Bladder	2.81	3.40	3.98	3.39	2.03	1.83	2.33	2.69	2.51	1.18
Leukaemia	5.20	4.14	5.80	3.25	9.76	17.3	14.3	17.9	12.2	25.0
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
					Exposure Ages 20-64					
Oesophagus	6.08	3.62	9.90	5.02	21.0	4.62	3.21	8.50	4.15	18.4
Stomach	31.7	19.3	24.6	20.9	24.5	28.7	15.3	20.6	16.6	22.7
Colon	7.58	12.0	8.15	8.80	5.19	6.55	10.1	6.82	7.58	4.40
Lung	14.1	14.6	11.3	17.6	9.54	11.5	14.2	10.2	16.2	8.25
Breast	2.06	5.22	3.19	5.36	2.16	2.78	6.19	4.09	6.29	2.39
Ovary	2.40	4.17	2.65	3.86	2.59	2.89	4.42	2.85	4.32	2.86
Bladder	7.81	9.89	9.22	10.4	6.37	5.36	7.16	6.79	7.97	4.23
Leukaemia	13.1	16.0	15.8	12.8	13.5	22.4	24.2	25.0	21.6	21.5
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.
					Exposure Ages 65-90					
Oesophagus	9.06	5.35	12.9	7.97	27.2	8.30	5.04	11.6	7.52	26.3
Stomach	17.0	12.2	13.3	12.1	12.4	16.0	11.2	12.4	11.2	11.7
Colon	4.86	7.11	5.38	6.17	3.72	4.45	6.55	4.72	5.54	3.26
Lung	20.4	14.2	14.5	20.2	11.7	19.5	13.8	14.1	19.9	11.0
Breast	.124	.264	.146	.341	.125	.088	.213	.185	.228	.142
Ovary	1.67	3.23	1.55	3.00	1.80	1.59	3.06	1.74	2.89	1.88
Bladder	13.8	14.7	14.1	16.0	13.9	12.4	13.1	12.9	14.5	13.0
Leukaemia	17.7	27.6	22.9	19.0	13.9	22.3	31.8	27.2	23.0	17.5
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.	100.	100.

estimate of baseline rates for that site that are very high relative to other organs (Tables 3 and 4). The two sexes differ, of course, with respect to mammary and ovarian cancer, but also for leukaemia and for cancers of the oesophagus and bladder (Table 8). For leukaemia and oesophageal cancer these differences reflect the original risk coefficients, while for bladder cancer they reflect differences in baseline rates that are shared by all five populations.

There is substantial variability among the three discrete ranges of age at exposure (Table 9). Leukaemia weights increase with increasing age at exposure mainly because the projected contribution from other cancers decreases more rapidly than that from leukaemia, and because the multiplicative risk projection increases for the United States, United Kingdom, and Puerto Rico, reflecting their increasing baseline rates. The decreasing weights for stomach, colon, lung, and breast cancer reflect decreasing risk coefficients, and it should be remembered that the uniformity of the excess RR coefficients in Table 1 for cancers of the oesophagus, ovary, and bladder reflect an insufficiency of information rather than positive information that relative risks are constant over age at exposure.

Table 8. Percentage weights obtained by averaging over populations and over the UNSCEAR multiplicative model and the NIH model: by sex, exposure age, and site

Sex:	Deaths M	Deaths F	Exp. Life Span M	Exp. Life Span F
	Exposure Ages 0-90			
Oesophagus	4.50	7.64	3.55	6.01
Stomach	23.1	22.7	18.8	19.2
Colon	16.6	18.1	14.1	15.5
Lung	18.4	15.2	16.1	14.6
Breast	.000	8.24	.000	9.89
Ovary	.000	4.42	.000	4.92
Bladder	9.00	2.50	5.98	1.71
Leukaemia	13.2	6.04	26.2	12.9
Residual	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.
	Exposure Ages 0-19			
Oesophagus	2.64	4.18	2.06	3.35
Stomach	22.4	22.7	17.5	18.7
Colon	24.9	24.0	19.8	19.8
Lung	22.2	16.4	19.0	15.8
Breast	.000	9.49	.000	10.9
Ovary	.000	3.22	.000	3.77
Bladder	5.01	1.24	3.34	.877
Leukaemia	7.71	3.55	23.1	11.6
Residual	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.
	Exposure Ages 20-64			
Oesophagus	6.70	11.5	5.80	9.78
Stomach	25.1	23.3	21.2	20.4
Colon	6.63	10.0	5.68	8.51
Lung	13.4	13.4	11.7	12.4
Breast	.000	7.20	.000	8.70
Ovary	.000	6.27	.000	6.94
Bladder	13.4	4.03	9.66	2.94
Leukaemia	19.5	9.04	30.7	15.2
Residual	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.
	Exposure Ages 65-90			
Oesophagus	7.64	17.4	7.22	16.3
Stomach	12.9	14.0	11.9	13.1
Colon	3.56	7.33	3.08	6.73
Lung	14.4	18.0	13.8	17.6
Breast	.000	.401	.000	.343
Ovary	.000	4.50	.000	4.47
Bladder	21.6	7.49	19.5	6.92
Leukaemia	24.7	15.7	29.3	19.4
Residual	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.

4.4. Some Possible Weighting Systems

A central consideration in the foregoing discussion is that we do not know why baseline cancer rates vary from one population to another, and we have little direct information on variations in radiation-related excess risk. It is difficult, therefore, to choose between the multiplicative and the NIH projection models, and it seems not unreasonable to suppose that the truth may lie somewhere in between. If we had to rely solely on the multiplicative model it would be very difficult to conclude that a single set of weights might serve all populations, but in fact the weights in Table 7 do not differ very much among the five populations considered and therefore a system based on averages over these populations cannot be rejected on the basis of current information.

On the other hand, there definitely is variation by sex and age at exposure, and the evidence is based on observed dose–response relationships. Also, it is clear that, mainly because radiation-induced leukaemia has a generally shorter latent period than other cancers, different weights are obtained depending upon whether the calculation is based

Table 9. Percentage weights obtained by averaging over populations, sexes, and projection models: by age at exposure and site

	UNTIMELY DEATHS				YEARS EXP. LIFETIME LOST			
Exposure Age:	0-90	0-19	20-64	65-90	0-90	0-19	20-64	65-90
Oesophagus	6.07	3.41	9.13	12.5	4.78	2.71	7.79	11.7
Stomach	22.9	22.5	24.2	13.4	19.0	18.1	20.8	12.5
Colon	17.4	24.5	8.34	5.45	14.8	19.8	7.09	4.90
Lung	16.8	19.3	13.4	16.2	15.3	17.4	12.1	15.7
Breast	4.12	4.74	3.60	.200	4.94	5.45	4.35	.171
Ovary	2.21	1.61	3.13	2.25	2.46	1.88	3.47	2.23
Bladder	5.75	3.12	8.75	14.5	3.84	2.11	6.30	13.2
Leukaemia	9.62	5.63	14.2	20.2	19.6	17.3	22.9	24.3
Residual	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Total	100.	100.	100.	100.	100.	100.	100.	100.

upon numbers of untimely deaths or years of expected life lost. The information in Table 8 suggests the range of variation in the possible systems of weights associated with different treatments of sex, age at exposure, and measure of health effect.

4.5. Average Years of Life Lost for a Specific Cancer

The data in Table 4 provide estimates of the average years of life lost for a specific cancer in each organ site listed, which can be calculated simply by dividing the total years of expected life lost by the number of fatal cancers induced in that organ. Thus a further set of tables similar to those in Table 4 could be derived for average years of life lost per specific cancer as a function of sex, age, population, and model. These values could then be averaged over parameters to produce a table similar to Table 9. There is one important difference. In those cancers (e.g. breast and ovary) occurring only in females, the length of life lost per specific cancer is based on the female data only and is not averaged for males and females. The relevant data are shown in Table 10, first for males and females and then averaged, for specific cancers. The average for all cancers is derived from the expected years of life lost for all cancers divided by the total number of fatal cancers given as a group in Table 4. The results vary slightly with age, and for a working population (20–64 y) the average number of years of life lost from all cancers is 14.1 vs. 15.0 for the general population.

Table 10. Average years of life lost for a specific cancer: all populations, 0–90 y

	Males	Females	Average for a specific cancer
Oesophagus	11.6	11.5	11.5
Stomach	11.9	12.8	12.4
Colon	12.1	12.8	12.5
Lung	12.5	14.4	13.5
Breast	—	18.2	18.2
Ovary	—	16.8	16.8
Bladder	9.3	10.3	9.8
Bone Marrow	29.4	32.4	30.9
Remainder	12.9	14.5	13.7
All cancers	14.6	15.4	15.0

5. CONCLUSIONS

Systems of site-specific relative weights for cancer mortality risk due to radiation exposure have been examined with respect to the effects of age, sex, projection model, population characteristics as represented by baseline, cause-specific mortality rates, and choice between probability of untimely death and expected loss of life span as a measure of health detriment. Sources of major variation include the projection model used, sex, and age at exposure, each of which can cause substantial variations in the relative contributions assigned to the individual organs. The effect of the different population characteristics is much greater for the multiplicative model than it is for the NIH model.

It could be argued that the variations caused by all these factors are large enough that account should be taken of them by providing different weights for different circumstances (such as for different age groups). Some of these factors, however, such as the choice of model for transfer between populations, involve uncertainties simply not resolvable at this time. Furthermore, among the various factors to be considered in the weighting process for radiation protection purposes it is virtually inevitable that the results for individual organs will be averaged between the sexes, especially since the total risk does not differ greatly between males and females. Since the other factors involved do not, broadly speaking, cause greater variations than those attributable to sex, it is not unreasonable to average over all these factors, i.e. over sex, age, projection model, and population characteristics, to provide a single set of weights based on either excess probability of cancer death or expected years of life lost. These are available for exposure ages 0–90 in Table 9.

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LOW-DOSE RADIATION EPIDEMIOLOGICAL STUDIES: AN ASSESSMENT OF METHODOLOGICAL PROBLEMS

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1. INTRODUCTION

Estimates of radiation induced cancer that form the basis of the main considerations for dose limits in radiation protection are derived mainly from studies of human populations exposed to doses in the range of 0.5 to 10 Gy (Darby *et al.*, 1985; Boice *et al.*, 1987; Darby *et al.*, 1987; Bithell and Stiller, 1988; Hrubec *et al.*, 1989; Hildreth *et al.*, 1989; Preston and Pierce, 1988; Shimizu *et al.*, 1989). For some cancer sites the data may extend down to 0.2 Gy or even 0.1 Gy. The protection recommendations apply to doses of the order of 0.02 Gy or lower, annually. However, the estimates of cancer risk implied by some studies of populations exposed to low dose radiation (Stewart and Kneale, 1970; Lyon *et al.*, 1979; Gilbert and Marks, 1979; Caldwell *et al.*, 1983; Monson and MacMahon, 1984; Beral *et al.*, 1985, 1988; Harvey *et al.*, 1985; Machado *et al.*, 1987; Darby *et al.*, 1988; Cook-Mozaffari *et al.*, 1989a; Gilbert *et al.*, 1989; Holm *et al.*, 1989; Modan *et al.*, 1989; Preston-Martin *et al.*, 1989; Ron *et al.*, 1989) are apparently higher

than the estimates derived from high doses. In some cases the excess risk per Gy may differ by as much as two orders of magnitude.

Any comparison of this kind is complicated by a multitude of methodological problems and uncertainties. For example, the differences between risk estimates derived from different human populations may reflect biases from non-random selection; e.g. comparison of groups with specific diseases (Boice *et al.*, 1987; Darby *et al.*, 1987) versus essentially normal individuals, such as soldiers on sites of nuclear testings (Caldwell *et al.*, 1983; Darby *et al.*, 1988), employees of the nuclear industry (Beral *et al.*, 1985, 1988; Gilbert *et al.*, 1989), healthy individuals exposed to fallout (Lyon *et al.*, 1979; Machado *et al.*, 1987), or children irradiated for benign conditions (Albert and Omran, 1968; Modan *et al.*, 1974).

The present report attempts to assess the problems inherent in the analysis of low dose radiation studies, with emphasis on possible sources of methodological errors in the published data, and the consequent relevance to risk estimates.

2. POTENTIAL SOURCES OF ERROR

Several sources of bias may confound the interpretation of low dose radiation studies. These include, among others, inadequate dosimetry, selective samples, lack of adequate control population, additive extraneous factors, and socio-demographic parameters.

2.1. Inadequate Dosimetry

In only a few of the reported low dose radiation studies has the dose delivered to an individual subject been precisely determined in retrospect. First, there may be a difference between the exposure situation assumed during the retrospective dosimetry assessment and that in the previous real life experience. For instance, tilting of the subjects' head, neck, or chest, among children who received scalp irradiation, would have exposed them to much higher radiation levels than estimated *a posteriori*. Likewise, inconsistently or inadequately used individual dosimeters or environmental measurements among x-ray technicians, or technical personnel at nuclear installations, preclude true estimates of the doses to workers and to the surrounding population. Finally, one cannot exclude the possibility that actual discharges from nuclear reactors may have been, occasionally, much higher than those defined by regulatory boards (Black, 1987; Darby and Doll, 1987).

2.2. Samples Studied

On the basis of currently accepted estimates, the level of excess risk at low-dose radiation exposure is small relative to baseline rates. Therefore, exceedingly large populations are needed to demonstrate a true effect at a low dose. Such study populations are either non-existent, unmanageable for a prolonged follow up, or irretrievable for administrative reasons. Studies based on small numbers are more likely to yield chance associations (Land, 1980; Pochin, 1988).

Assessment of a large number of individual cancer categories adds further complexity to the issue. Thus, with the exception of *in utero* exposure, none of the excess risk data apply to total cancer risk, but rather to specific, albeit those considered as radiosensitive, sites, like the breast or the bone marrow.

The tendency to report positive findings, and undervalue negative ones, complicates the assessment of the true rate of events even further, since it is likely that the literature is weighted by low dose radiation studies where an excess risk was found, as compared to those that yielded negative results.

2.3. Lack of Adequate Controls

Quite frequently the risk of cancer in low dose radiation studies is derived on the basis of expected rates in the total population. Such a comparison may be misleading, in view of selective factors inherent in the specific irradiated population under study. "The healthy worker effect", a term that represents a better physical status of industry workers is of particular concern in this respect.

2.4. Extraneous Effects

It is virtually impossible to discriminate between a true radiation effect, and a combined effect of radiation with other established carcinogens, by which subjects exposed to low dose radiation might have been contaminated. Chemicals in the workplace of nuclear industry employees, or the variety of substances used for cooling at nuclear testing sites may serve as examples. Moreover, irradiated subjects under observation continue to lead a normal life, and are exposed to a variety of deleterious factors that may affect and/or shorten their life, years before the carcinogenic effect materialises. This is particularly a problem with low-dose studies, in which the effects of other carcinogens can easily outweigh radiation effects without the investigator being aware of it.

2.5. Socio-Geographical Confounders

Social strata, lifestyle, the type of house construction, or consanguinity, cannot be disentangled from radiation exposure factors. The susceptibility of people residing in a disrupted society may also vary from that of normal persons. Similarly, individually reported "clusters" of excess cancer may result from selective criteria for inclusion. Pochin (1988), quoted a selective reporting of increased mortality from leukaemia, observed in Aberdeen, a city which is not only built on radioactive granite, but is also the site of an important haematological clinic, to which patients with leukaemia are commonly sent for treatment.

3. SUMMARY OF EVIDENCE

Direct estimates of cancer risk following low dose radiation exposure, are derived primarily from the following sets of observations:

(1) Populations exposed to nuclear sources such as fallout, weapons' tests, or in the vicinity of nuclear reactors.
(2) Occupational exposure.
(3) Intra-uterine diagnostic x rays.
(4) Scattered radiation following x-ray therapy.
(5) Background irradiation.

3.1. Nuclear Sources

The most extensive source of data for the understanding of delayed radiation effects is the ongoing survey of atom bomb survivors in Hiroshima and Nagasaki (Beebe, 1981; Darby *et al.*, 1985; Preston and Pierce, 1988; Pierce, 1989; Shimizu *et al.*, 1989). With the exception of a claim of a higher incidence of leukaemia among early entrants to Hiroshima (Rotblat, 1977) in the 1960s, which was not borne out by RERF analysis, and some incidental pieces of information in reports focused on high dose exposure (Darby *et al.*, 1987), no increase in risk has been detectable at doses of less than 0.1 Gy (Shimizu *et al.*, 1989). The more recent comparison with non-exposed survivors in Hiroshima (34 000 in zero dose, 19 000 in the 10–50 mGy range and 4 000 exposed to 60–90 mGy), will most probably yield more information in the future. In the meantime, the two single observations of significantly increased risk of lung cancer (RR = 1.36) and of leukaemia (RR = 1.8), in the under 0.1 Gy category (Darby *et al.*, 1985; Shimizu *et al.*, 1989), could be still construed as random events, when multiple categories are assessed individually. A similar explanation might be valid for the significantly decreased risk (RR = 0.53) reported for colon cancer in the same population, at the very low radiation category (Shimizu *et al.*, 1990a,b).

Data from studies on experimental testings of nuclear weapons, which exposed large populations to low dose radiation, are equivocal. The data pertain primarily to civilian populations in the Utah–Nevada area (Lyon *et al.*, 1979; Machado *et al.*, 1987), and military participants in tests undertaken in the Southwestern US (Caldwell *et al.*, 1980, 1983) and the South Pacific (Darby *et al.*, 1988).

Lyon *et al.* (1979) reported an apparent two-fold increase (RR = 2.44; 95% CI—1.18–5.03) in the rate of leukaemia mortality among Utah residents born between 1951 and 1958; (the later period represents the time span of the heaviest concentration of atmospheric nuclear weapon testing in Nevada) as compared to two "low exposure cohorts", i.e. individuals born between 1944 through 1950 or after 1958. An excess of this kind was also reported in 17 "high exposure counties", representing 10% of the Utah population that received an estimated bone marrow dose of 6 cGy. These findings are problematic, due to a possible misinterpretation of dose distribution, and the fact that the rates of cancer at other anatomical sites were lower in the "high exposure" areas.

Beck and Krey (1983) reconstructed the exposures of the Utah population to external gamma radiation from nuclear weaponry tests, based on more recent measurements of residual caesium-137 and plutonium-239 in soil. They found that the southwest corner of Utah did get a substantially higher exposure than the rest of the state, and that residents of the northern counties received a higher mean dose than did those residing in counties closer to the Nevada test site; i.e. the average weighted fallout dose in Lyon's "high dose area" is actually less than that of Northern Utah—"his low dose area". Land *et al.* (1984), who replicated the study with two more years of follow-up, conjectured that the apparent leukaemia excess reported reflected comparison rates that were anomalously low due to undiagnosed cases in the earlier years in Southern Utah, rather than higher rates after exposure.

Machado *et al.* (1987) recorded a significant excess of childhood leukaemia deaths (RR = 2.84) in three "high-exposure" southwestern Utah counties, among individuals younger than 15 years of age who were born before the tests ended, relative to the corresponding population of the rest of Utah. Since apparently most of the fallout was deposited during 1957, comparisons were made for leukaemia and bone cancer deaths

that occurred between 1955 and 1980, and for other cancer between 1964–1980. They suggested the possibility that a temporal wave of radiation-induced childhood leukaemia mortality occurred in southwestern Utah following the fallout depositions of 1953–57.

Johnson (1984, 1987) claimed to have identified radiation-related cancers in Mormon families in southwestern Utah exposed to radioactive fallout between 1951–62, and to venting of underground nuclear detonations between 1962 and 1979. His contention was based on a comparison of the ratio between what he defined as "cancer of more radiosensitive organs" with all other types of cancer, and on an interview of residents who reported "post-irradiation-like" symptoms. This study was, however, hampered by severe methodological deficiencies: (i) the interviewees were selected from the 1951 telephone directory if they were still listed in 1962 and were located in 1981 (only 60% of the individuals could be located), (ii) the cancer diagnosis was based on personal reports without verification, and (iii) the so-called "high effect" group was constituted of retrospective self-determined acute radiation symptomatology, at a time when an intensive litigation process involving the population residing in this area was going on. Furthermore, in 18 percent of those who reported cancer the year of diagnosis was not recorded, and they were randomly distributed between the 1958–66, 1967–71, and 1972–80 cohorts. Finally, Johnson's definition of "radiosensitive sites" is incorrect for some of the sites and questionable for others.

Caldwell *et al.* (1980, 1983) noted a significant excess incidence of leukaemia, but not of overall cancer, among 3224 participants of the Smoky nuclear test in 1952, who had a recorded average gamma exposure of 0.52 rem. In contrast, Robinette and Jablon (1983) found no excess of leukaemia among 5000 participants following 24 detonations at other tests. Bross and Bross (1987), who re-analysed these data, claimed an apparent leukaemia excess of 62% when correcting the findings for "the healthy soldier effect" and for radiogenic leukaemia. However, as pointed out by Jablon (1987), this analysis seems highly circular, in the sense that it reflects one selective set of observations, using an arbitrary correction factor.

Darby *et al.* (1988) followed 22 000 British veterans who took part in experimental nuclear weapons tests in Australia and the South Pacific, between 1952 and 1967, through the end of 1983, and a similar size control group. There was a significant excess mortality from leukaemia, multiple myeloma, and accidents, and a deficit in prostatic, bladder, and kidney cancer, as well as of bronchitis. The study group did not differ from the control in total mortality, and both groups exhibited the healthy soldier effect. For all leukaemia related conditions, the RR was 1.65. The rates of incidence of leukaemia and multiple myeloma were also increased. No dose–effect relationship was noted. Increased mortality was not concentrated in the groups selected *a priori* for special examination, being pre-identified as liable to be exposed to excess radiation. Also, very low rates were noted in the controls (SMR for leukaemia and multiple myeloma 113 and 111 for the cases, 32 and 0 for the controls, respectively). Differences in social class between the groups could have played a role. On the other hand, since the leukaemia types observed were of the "radiogenic" variety, a true effect cannot be ruled out. In contrast, no excess risk was noted in a follow-up of Canadian military personnel exposed in the Pacific Ocean testing (Raman *et al.*, 1987).

Archer (1987) correlated chronic myeloid and acute leukaemia mortality rates in the US with fallout events in 1951, 1953, and 1957, and elsewhere in 1962. He suggested that the US had experienced higher leukaemia rates during, and subsequent to, open air testing that levelled off subsequently. The strongest association was claimed for acute

and myeloid leukaemia in the 5–9 age group, that peaked 5.5 years following the fallout peak, and fell sharply in 1976–77. Individual states were classified into high, low, and intermediate exposure, according to three indices based on ^{90}Sr in: (a) cow's milk, (b) the diet of institutionalised children, and (c) children's bones. The periodicity following nuclear testing claimed by Archer may be questioned, since one would expect an overlap. Also, no account was made of the general decline in leukaemia mortality rates (not of incidence), since the 1970s, due to improved treatment and survival.

More puzzling are the slowly accumulating data on excess leukaemia near nuclear installations in the UK. Roman *et al.* (1987), demonstrated a significantly increased incidence of leukaemia among children younger than 5 years of age in the immediate vicinity of nuclear installations in three specific districts in the UK, compared to neighbouring areas and the rest of England and Wales (RR = 1.7). The study was based on children under 15, first diagnosed to have leukaemia between 1971 and 1985. Radiation doses were not specified, and the excess incidence was limited to less than 10 km from the nuclear establishments (RR = 2.3; 95% CI 1.1–4.4). Completeness of registration was checked against the national registry, ruling out a methodological bias.

Subsequently, Gardner *et al.* (1987a,b), presented a follow-up through mid-1986, of 1068 children born to mothers in the Seascale parish during 1950–83, and those born elsewhere but attending school there. RR for leukaemia was 9.36 (5 vs. 0.55 expected; 95% CI 3.0–21.8) and for other cancer 3.76 (4 vs. 1.06; 95% CI 1.02–9.63). Both total mortality (RR = 0.84) and infant mortality (RR = 0.56) were significantly lower. In comparison, there was no excess of leukaemia or other cancer among 1546 children attending schools at Seascale but born elsewhere; their total mortality was similar to that of the native children. Again, lack of actual dose data precluded a definitive risk assessment.

These figures may point to a risk factor affecting children early in life, especially since close to 20% of the "school children" were between 2–5 years of age at entry. Still, the main drawback of both cohorts studied is reliance on national data for comparison. Thus, a higher social class among Seascale residents could provide at least a partial explanation. An ingestion of soil dust by infants is another possible factor.

A more recent case control comparison by Gardner *et al.* (1990a,b; Abrahamson, 1990; Beral, 1990; Dunster, 1990) showed the excess of leukaemia in this population to be apparently associated with paternal exposure (RR = 6.42; 95% CI 1.57–26.3). The comparison is based essentially on 4 cases of leukaemia (out of 46), and 3 controls (out of approximately 300), whose fathers had been exposed to over 10 mSv in the 6 months preceding conception, and to over 100 mSv in total. This observation is confounded by maternal age (> 40 years), proximity of residence to the nuclear installation, and possibly by the patients' age at diagnosis. Such parameters should have been assessed jointly, rather than singly. Also, the possibility of residential exposure, for instance through contamination of paternal clothing, cannot be ruled out.

Cook-Mozaffari *et al.* (1987) assessed the data on cancer incidence near nuclear establishments in the UK more comprehensively. Taking into consideration the individual sites of cancer covered in this study, the proportion of statistically significant deviations was similar for installation areas and for their controls—around 7% to 8% for incidence and about 4% for mortality. The somewhat higher proportion of significant incidence rates was thought to reflect local and temporal variations in the efficiency of cancer registration. Shortly afterward, she and her associates (Cook-Mozaffari *et al.*, 1989a), reported that in districts near nuclear installations there were significantly

increased rates of mortality from leukaemia (RR = 1.15), particularly of the lymphoid type (RR = 1.21), and from Hodgkin's disease (RR = 1.24). Yet, almost simultaneously, the same group showed that a significant increase for these two sites was also noted in sites where nuclear installations were only planned, but not really established (Cook-Mozaffari *et al.*, 1989b). Obviously, a finding of this kind casts a shadow of doubt on causal significance of the previous apparently positive findings. There was also one report of excess haematological malignancies in five Massachusetts towns in the vicinity of a nuclear reactor (Clapp *et al.*, 1987) but not in two other locations evaluated in the US (Enstrom, 1983; Crump *et al.*, 1987).

An alternate explanation, that of a lower herd immunity in populations migrating to the vicinity of nuclear plants was suggested by Kinlen (1988). Kinlen showed that a non-nuclear new community of Glenrothes, in Scotland, also showed an increase in childhood leukaemia. This is a challenging explanation but, as of yet, requires further substantiation.

A most recent comprehensive assessment of cancer, particularly leukaemia, in US populations living near nuclear facilities (Jablon *et al.*, 1990), confirms within the limits of the study itself, the lack of true excess in the proximity of nuclear power stations. (RR for leukaemia = 1.08 as compared to 1.03 at start of study.)

3.2. Occupational Exposure

The simultaneous exposure to a multitude of chemical substances and "the healthy worker effect" constitute two principal confounders for a conclusive evaluation of atomic industry employees. Industrial workers constitute a selected group, which would inevitably have a superior survivorship relating to that of the general population to which their fate is usually compared. This is particularly pertinent for radiation workers, who require special qualifications and skills (Tolley *et al.*, 1983).

Mancuso *et al.* (1977) reported an increased rate of cancer mortality among 25 000 employees at the Hanford atomic plant in the state of Washington, from which the doubling dose for cancer was interpreted to be as low as 28 mGy for bone and RES neoplasms. Yet their original observations lacked systematic follow up, adequate dosimetry, and a suitable control population. Re-analysis of the data by Hutchinson *et al.* (1979), Gilbert and her associates (Gilbert *et al.*, 1979, 1989; Peterson *et al.*, 1990), and Tolley *et al.* (1983), suggests that the observed excess can at best be valid only for multiple myeloma, and is limited to persons who have had a cumulative exposure above 0.15 Gy.

Evaluation of several other occupational groups poses similar methodological difficulties. Najarian and Colton (1978), reported a twofold increase of proportional mortality rate for cancer, and a fivefold excess for leukaemia, among nuclear workers with cumulative doses under 0.1 Gy. No data on dose monitoring were given. Reporting was by next of kin, and exposure to chemicals was not ruled out. Again, the effect has practically vanished when a more substantial study was undertaken. Thus, Rinsky *et al.* (1981), analysed the mortality patterns of 24 545 US white male naval shipyard workers employed between 1951 and 1977. Their study was based on 7 615 workers, with a mean radiation exposure of 0.5 rem (range 0.01–91.4). No excess of leukaemia or other cancer was noted, compared to the expected number, based on rates for total US white population or plant workers without radiation exposure. On the contrary, lower mortality rates for all causes, including leukaemia, were observed, in line with the "healthy worker effect". A subsequent matched case-control study (Stern *et al.*, 1986), of 53 leukaemia

deaths and 212 controls, did not show an association with radiation, except for a higher risk of lymphatic leukaemia among electricians (RR = 3.0; 95% CI 1.29–6.50), and of myeloid leukaemia (RR = 3.8; 95% CI 1.28–11.46) among welders. Unfortunately, no distinction was made between the acute and chronic variety of leukaemia. Nevertheless, these findings could easily be ascribed to the additive or confounding effects with exposure to chemical substances. A more comprehensive prospective study of this group is still in progress.

Beral and her associates (1985, 1988), reported two follow-up studies of the British Atomic Energy employees, covering the period of 1951–1982. They showed a significantly increased mortality ratio for prostatic cancer, particularly in young employees with single dosimeter readings exceeding 10 mSv (RR = 2.23; 95% CI 1.13–4.4). Mortality for total neoplasms showed a significant increase of 7.6% per 10 mSv (95% CI 0.4%–15.3%), but stemmed primarily from increased rates of prostatic and possibly of lung cancer. The "healthy worker effect" was illustrated here as well, and contamination by tritium and radon daughters could not be ruled out. It must be noted that a diagnosis of prostatic cancer is rarely looked for in young subjects unless they are routinely followed up, and is therefore highly dependent on the frequency of screening.

Cancer incidence, examined on a subset of the same data, showed an excess of skin and bladder cancer, two sites that could have easily been missed on mortality data. The inexact dosimetry for exposure to inhaled nuclides, and the better chance of diagnosis among people who are in a regular follow-up framework, preclude the derivation of a true risk estimate.

Prostate cancer was also noted in excess among employees of the Sellafield plant (Smith and Douglas, 1986) and in Oak Ridge National Laboratory (Checkoway *et al.*, 1985); although the excess was not significant statistically. There was also a suggestion of increased risk for lung cancer, possibly due to alpha radiation, in the Oak Ridge Y-12 plant employee population (Checkoway *et al.*, 1988).

3.3. Fetal Exposure

Studies of *in utero* exposed subjects have not yielded consistent results. Some of the data have been criticised for selection bias, faulty methodology, lack of comparable experimental animal evidence, and the lack of noticeable effect among A-bomb survivors (Jablon and Kato, 1970). Only very recently did Yoshimoto *et al.* (1988), show that subjects exposed to the A-bomb *in utero* had a risk of cancer comparable in adult life to that observed in survivors exposed during childhood, amounting to an excess RR of about 0.03 per 10 mGy.

The Oxford childhood survey, first utilised in this context by Alice Stewart and her associates in 1956 (Stewart *et al.*, 1956) was interpreted to show about twofold increase in risk of childhood cancer from radio-diagnostic exposure to approximately 0.02 Gy during intra-uterine life. Further support for an effect of this kind was provided by the Tri-State study (Gibson *et al.*, 1972; Bross and Natarajan, 1972; Gibson *et al.*, 1972) and by the study of Shiono *et al.* (1980). It should be noted that in the latter two studies a strong component of preconceptual exposure to radiation was observed among mothers. Retrospective cohort studies by MacMahon and his associates (MacMahon, 1962; Monson and MacMahon, 1984), also demonstrated an increased risk of 1.4, that was later found to be valid only for leukaemia (RR = 1.52), and not for solid tumours (RR = 1.27; 95% CI 1.18–1.95). Their extended study was based on 1342 cancer deaths among

1429400 children, born between 1947 and 1960 in 42 maternity hospitals in New England. An interview survey, directed at the parents of 555 childhood cancer cases diagnosed in the UK over a three year period, and two control groups (Hopton *et al.*, 1985), also showed a significant excess of pelvic and x ray examinations in other parts of the body among mothers of children diagnosed to have leukaemia below 2 years of age. This was not true for solid tumours.

While other investigators (Court Brown *et al.*, 1960; Oppenheim *et al.*, 1974), failed to duplicate these findings, Diamond *et al.* (1973), found the association to exist for leukaemia (RR = 3) among white children only, and not for other sites of cancer. A subsequent case control study by Harvey *et al.* (1985), based on 31 twins who developed cancer and 124 matched controls, out of 32000 twins born in Connecticut between 1930–1969, showed a pre-natal x-ray exposure risk ratio of 2.4 (95% CI 1.0–5.9) for cancer and leukaemia together. The separate risks for leukaemia and other cancer did not really show significance, possibly due to the small numbers included. The mean estimated fetal dose was 0.01 Gy. The wide confidence intervals of the increased risk weaken the results.

Two potential sources of bias in both the Oxford and the Tri State surveys, centre on the chance that mothers of children who died of cancer would have better recall of their x-ray history, and that certain characteristics of either the mother or the child would result in diagnostic x-ray examinations, and in turn correlate with childhood cancer development (Burch, 1981; Totter and MacPherson, 1981). MacMahon's surveys removed the first potential source of bias. The exclusion of multiple pregnancies that have a higher probability of being exposed to diagnostic examinations from the analysis was also supportive. Mole (1974), who pointed out that although twins were about five times more likely to be exposed to diagnostic x rays *in utero*, their risk of radiation-associated cancer was about the same as of singleton births, took care of the other reservation.

More recent reassessments, by Stewart and her associates (Knox *et al.*, 1987; Gilman *et al.*, 1988), support the contention of a higher susceptibility of fetal tissue to carcinogenic effects of radiation than adult risk. Bithell and Stiller (1988), who co-worked with Stewart, attempted to show that, in fact, the fetal risk consisting of 175 excess cases during the first 15 years of life per million fetuses exposed to 1 mGy, computed by them, is not inconsistent with other currently acceptable estimates. Mole (1990), who has reassessed the *in utero* studies, emphasised the parallel decline of cancer risk with decreasing pelvimetry and increased protection standards. He supports the interpretation of a causal role for fetal radiation exposure.

3.4. Therapeutically Irradiated Populations

Follow up of subjects who received radiation therapy in the process of applying a therapeutic measure, has inadvertently contributed to a better understanding of low-dose radiation effects. One example is the cohort of 10834 children below age 15 y irradiated for tinea capitis in Israel between 1949 and 1960 (Modan *et al.*, 1974, 1989). An updated follow up through 1986 showed a relative risk of 4.12 (90% CI 2.65–6.45) of thyroid cancer, following an estimated average thyroid dose of 0.09 Gy. Recently, a significant excess of female breast cancer also appears to have developed in this cohort (Modan *et al.*, 1989), after the study subjects reached the age in which spontaneous cancer becomes prevalent. The relative risk of breast cancer for the most recent 5-year

follow-up period was 2.11 (90% CI 1.05–4.24), and for the total period 1.35 (90% CI 0.86–2.13). Dose to the breast was estimated at 0.016 Gy. However, a combined breast, thyroidal and hypophyseal effect could not be ruled out.

3.5. Background Radiation

The role of background irradiation is now being more intensively evaluated on the basis of two major sources of data: high background radiation, particularly in China (Tao and Wei, 1986; Wei *et al.*, 1988, 1990), and exposure to radon in the US and elsewhere (Clarke and Southwood, 1989; Samet, 1989; Lubin *et al.*, 1990).

With the possible exception of a correlation study conducted by Knox *et al.* (1988), in Great Britain, from which no risk estimate can be derived, no excess cancer risk has been demonstrated in high background radiation areas. Moreover, Frigerio and Stowe (1976), as well as Jacobson *et al.* (1976), noted an inverse correlation in high background areas in the US, with cancer or leukaemia mortality.

An epidemiological investigation of radiological effects in high-background radiation areas of Yangjiang, China, on the basis of one million person years, showed that between 1972 and 1986 no increase of cancer mortality has been found. On the contrary, there was a tendency for the cancer mortality in the high background radiation areas to be lower. The prevalence of hereditary disease and congenital defects was similar in both areas, but the frequency of Down's syndrome was higher in the high background radiation areas (though within the normal range), possibly due to a difference in maternal age between the two areas. The radiation doses were about 2.1 mGy per year in the high background and 0.77 mGy per year in the controls. Several confounding factors, including age, remain to be investigated before a more definite conclusion can be reached.

A multitude of radon studies, that are being carried out at present, will probably yield valuable findings in the near future. Epidemiological surveys have demonstrated a high incidence of lung cancer among heavily exposed uranium miners in the US and elsewhere (Morrison *et al.*, 1988; Sevc *et al.*, 1988; Roscoe *et al.*, 1989; Samet, 1989; Samet *et al.*, 1989). These follow-up studies indicate an association between a prolonged exposure to high radon levels and the risk of lung cancer. Recently, a number of studies suggested that a prolonged exposure to low doses of radon in domestic facilities, does also contribute to lung cancer development (Samet and Nero, 1988; Svensson *et al.*, 1989; Biberman *et al.*, 1990). Small cell carcinoma of the lung has been implicated in particular (Archer *et al.*, 1974; Svensson *et al.*, 1989; Biberman *et al.*, 1990).

Several studies conducted in Sweden (Svensson *et al.*, 1987, 1989; Axelson *et al.*, 1988), reported an approximately 2-fold increased risk for lung cancer, among persons who have resided for a prolonged period in houses where radon levels were above the average. However, in one of these studies (Svensson *et al.*, 1989) radon levels were measured in only 50% of the houses, in the second (Axelson *et al.*, 1988) measurements were determined in 80% of the houses of lung cancer patients but only in 36% of the controls, while in the third study (Svensson *et al.*, 1987) only 10% of the houses were sampled.

Other studies have not been successful in demonstrating an association of this kind, but, again, in one of these, no measurements were conducted within the houses themselves (Klotz *et al.*, 1989), and in another one the sample size was extremely small (Lees *et al.*, 1987). An extensive survey in a number of selected areas in the US is underway.

Early results seem to support an association between chronic exposure to radon and lung cancer for dwellers at the upper boundary of residential limits (Schoenberg *et al.*, 1990).

Still, at this point the data on chronic low-dose exposure to radon do not suffice for a definitive support of low dose radiation effects.

4. PROSPECTS

The results of low dose radiation studies discussed in the preceding paragraphs, can be divided into 5 groups:

(1) An apparently true effect—*in utero* exposure.
(2) A potential interaction with extraneous factors—UK nuclear industry workers, children in the vicinity of UK nuclear installments, medical irradiation.
(3) Spurious associations due to an inadequate methodology—the early findings among Hanford workers and Johnson's fallout study.
(4) Uncertain—follow up of residents and military personnel exposed to nuclear testing.
(5) Established lack of a higher yield—background radiation.

Thus, at the present time, with the possible exception of the studies of prenatal x-irradiation, methodological limitations detailed above preclude the use of data coming from low-dose radiation epidemiological studies for risk estimation.

The recently published information of a higher than originally assumed radiation exposure of the population in the surroundings of Hanford, highlights the futility of extending risk estimates based on population that have been only apparently exposed to low-dose radiation. It will probably take at least another decade before more refined data might emerge from the follow-up of such modern major nuclear accidents as that at Chernobyl. Such data, in either direction, would hopefully shed more light on the complexity of this issue.

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GENETIC EFFECTS OF IONISING RADIATION IN MAN

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1. INTRODUCTION

Among the adverse biological effects of exposure of human beings to ionising radiation are "genetic effects", namely those associated with gene mutations and chromosomal aberrations induced in parental germ cells and transmitted to the progeny. Since spontaneously-occurring gene mutations and chromosomal aberrations are known to result in genetic disorders, it is inferred that radiation exposure may increase the risk of such effects in the descendants of those exposed.

The estimation of genetic risks is an important scientific endeavour within the framework of radiation protection, one which several national and international scientific bodies have been actively pursuing since the mid-1950s. These estimates are arrived at through extrapolation from data obtained in experimental mammalian species, chiefly the mouse. Such extrapolation inevitably involves a number of uncertainties and their nature and magnitude are dependent on the strengths and weaknesses of the data used and the assumptions made. The term "genetic risks" as used in this paper denotes the probability of harmful genetic effects manifest in the descendants, both close and remote, of those exposed to irradiation.

2. METHODS FOR GENETIC RISK ESTIMATION

The methods that are used in quantitative genetic risk estimation can be broadly grouped under two headings; the "doubling dose method" or the "relative mutation risk method" and the "direct method". These are roughly comparable respectively, to the "relative risk method" and "absolute risk method" used in cancer risk estimation.

2.1. The Doubling Dose Method

The doubling dose method enables one to provide an estimate of risks in terms of the additional number of cases of genetic disorders due to radiation exposures, relative to the prevalence of those occurring naturally in the population. The doubling dose is the amount of radiation necessary to produce as many mutations as those occurring naturally in a generation and is obtained by dividing the spontaneous rate by the rate of induction. Thus, for instance, if the average spontaneous rate of a set of representative gene loci is m_1 per locus and the average rate of induction at the same set of loci is m_2 per locus per unit dose, then the doubling dose $c = m_1/m_2$. The reciprocal of the doubling dose, $1/c$ is the relative mutation risk (RMR) per unit dose. It is easy to see that the lower the doubling dose, the higher the RMR and vice versa.

The doubling dose method is generally used to estimate risks to a population under continuous irradiation and is based on the following equation:

$$\text{Risk at equilibrium per unit dose} = p \times \text{RMR} \qquad (1)$$

where p = prevalence of spontaneously-arising genetic disorders and RMR = relative mutation risk defined earlier. The assumption is that, under normal conditions, there is an equilibrium in the population between those mutations that arise spontaneously and those that are eliminated by selection every generation. With continuous irradiation (and the influx of new mutations that it entails), the population will eventually reach a new equilibrium, and it is the expected additional risk at the new equilibrium that the method allows one to estimate. The increased risk to the first generation progeny is then estimated from that at equilibrium by using certain assumptions.

When the population is exposed to radiation only once, new mutant genes will be added to the gene pool, but their frequencies will gradually (over a number of generations) decay back to the old equilibrium value. Population genetic theory predicts that, numerically, the integrated risk over all future generations following a single radiation exposure will be the same as that at equilibrium under conditions of continuous irradiation with the same dose in every generation (see Crow and Denniston, 1985, for detailed discussions). Thus the estimate of risk for equilibrium conditions can be taken to represent the total risk following a single generation radiation exposure.

Implicit in the use of equation (1) is the reasoning that there is an approximately one-to-one relationship between mutation and the disorder as can be assumed for instance, for autosomal dominant disorders (i.e. for these, it is assumed that the equilibrium frequencies of the responsible mutant genes are directly proportional to the mutation rate; the assumption is almost as good for X-linked conditions). However, for congenital abnormalities and other multifactorial disorders (see later), such a simple relationship between mutation and disorder cannot be assumed and consequently equation (1) needs to be modified. In the terminology first used in the BEIR I report (NAS, 1972), the "mutational component" (MC) of these disorders, namely the fraction of their incidence that is proportional to mutation rate, needs to be taken into account (see Crow and Denniston, 1981, 1985 and NAS, 1990, for a detailed discussion of the concept and its implications). What this means here is that for the examples used above, autosomal dominant disorders can be assumed to have MCs of 1 whilst the multifactorial disorders have MCs of less than 1. Equation (1) can therefore be rewritten in a more general form as follows:

$$\text{Risk at equilibrium per unit dose} = p \times RMR \times MC \qquad (2)$$

Other considerations that need to be borne in mind in using the doubling dose method are the following. An increase in mutation rate of autosomal recessive genes will not lead to a corresponding increase in the frequency of recessive disorders because (i) when recessive mutations first arise (or are induced), they are present in heterozygous condition and their fate depends on the way selection acts and (ii) a recessive mutation has to become homozygous or to have a "partnership" with a defective allele already established in the population to manifest the disease; this may take from many to hundreds of generations depending on a number of factors.

Evidence for the radiation induction of numerical chromosomal anomalies resulting in livebirths either in experimental mammals or in humans is insufficient and equivocal (reviewed in UNSCEAR, 1977, 1982, 1986; Sankaranarayanan, 1979; Kline and Stein, 1985). Consequently, the use of the doubling dose method to estimate risks for this group of disorders is subject to considerable uncertainty. However, there is definite evidence for the induction of structural chromosomal anomalies, particularly reciprocal translocations (but not Robertsonian translocations) in mammalian and human germ cells. With certain assumptions therefore, the doubling dose method can be used to estimate the risk associated with the induction of at least one kind of structural chromosomal abnormality.

2.2. Direct Method

With the direct method, the rates of induction of mutations and of chromosomal aberrations obtained in animal studies are converted, using a number of correction factors, into risk of genetic disorders to the first generation progeny of an irradiated

human population. These correction factors include (i) those to take into account dose-rate effects, sex differences in genetic radiosensitivity etc., and (ii) those to convert the estimated rates of induction of specific kinds of damage in a given bodily system in the test animals to an overall estimate of risk of genetic disorders in the first generation progeny of irradiated humans. For details, see UNSCEAR (1977, 1982, 1986) and Sankaranarayanan (1991d).

3. GERM CELL STAGES AND RADIATION CONDITIONS RELEVANT FOR GENETIC RISK ESTIMATION

From the standpoint of genetic risk estimation, the effects of radiation on two germ cell stages are particularly important. In the male, these are the stem cell spermatogonia which constitute a permanent germ cell population in the testes and which continue to multiply throughout the reproductive lifespan of the individual. In the female, the corresponding stages are the oocytes, primarily the immature ones. Female mammals are born with a finite number of oocytes already formed during fetal development, but they are arrested at a particular stage until ovulation. The oocytes are not replenished by mitosis during adult life.

The radiation exposures received by human populations are usually delivered as small doses at high dose rate (e.g. diagnostic radiology) or are greatly protracted (e.g. continuous exposures from natural and man-made sources). In therapeutic radiology, high doses of the order of several Gy may be delivered (and at high dose rates); however, such exposures, warranted on medical grounds, are given only to limited volumes of tissue in selected individuals for treatment of specific cancers. Genetic risks to the population as a whole therefore, are generally estimated for low dose and chronic (or low dose-rate) low LET radiation exposure conditions. It should however be borne in mind that with the increasing number of childhood cancers successfully treated with high dose, high dose-rate irradiation, this issue may become one of potential relevance in the coming years.

4. ESTIMATES OF DOUBLING DOSES

The doubling dose estimate of 1 Gy (for low dose, chronic, low LET irradiation) used by UNSCEAR in its 1977, 1982, 1986 and 1988 reports is based entirely on mouse data for genetically well-defined endpoints. However, using the same mouse data for low dose rate low LET radiation, the BEIR Committee obtained estimates of doubling dose ranges of 0.2–2 Gy in its 1972 (NAS, 1972) and of 0.5–2.5 Gy in its 1980 (NAS, 1980) reports. In its 1990 report (NAS, 1990) however, the above Committee accepted a doubling dose estimate of 1 Sv and justified its use for risk estimation as follows: "... A doubling dose of 100 rem approximates the lower 95% confidence limit for the human data from Japan and it is also consistent with the range of doubling doses observed in the mouse. While somewhat arbitrary, the number has the advantage of arithmetic simplicity and is a round number that does not invite an unwarranted assumption of high accuracy. To the extent to which the risks (given in its Table 2-1) may be inaccurate, they are to be regarded as probably too high rather than too low. For purposes of setting radiation standards, it is wiser to estimate risks that we hope might be too large rather than risks that we fear might be too small."

Recently, all the data from genetic studies in the offspring of A-bomb survivors in Hiroshima and Nagasaki have been summarised and re-evaluated, taking into account the

new dosimetric (DS 86) analysis (Otake *et al.*, 1990; Neel *et al.*, 1988, 1990; Yoshimoto *et al.*, 1990). The indicator traits chosen for these studies were: untoward pregnancy outcomes (which include congenital malformations, stillbirths and mortality within the first two weeks after birth), survival of liveborn children through an average of 26 years, malignant tumours in the first generation progeny with onset before the age of 20 years, mutations altering protein charge or function, chromosomal abnormalities, sex-ratio among children of exposed mothers and growth and development of the first generation progeny.

These re-evaluations have not shown any significant radiation-related increases in any of the measures of genetic damage employed, as was also the case in earlier ones (e.g. Awa *et al.*, 1987; Schull *et al.*, 1982). The data are consistent with minimal doubling dose estimates of between 1.7 and 2.2 Sv for acute radiation conditions obtained during the bombings and of between 3.4 and 4.4 Sv for chronic radiation (Neel *et al.*, 1990). It is important to note here that, given the uncertainties in dose estimates in the Japanese investigations, and differences in end-points used in these and in mouse experiments, the use of a doubling dose estimate of 1 Gy of low dose rate low LET radiation for estimating genetic risks in man is conservative and is unlikely to underestimate the risk.

5. CLASSIFICATION AND PREVALENCE OF NATURALLY-OCCURRING GENETIC DISORDERS

5.1. Classification

Nearly all disorders are to some extent genetic and to some extent environmental and, with regard to the relative importance of genetic and environmental factors in pathogenesis, they can be considered as falling on a spectrum. Towards one end of the spectrum, genetic factors dominate and towards the other, environmental factors dominate. Close to the "genetic end" lie conditions which are relatively simple in their formal genetics and which tend to be rare (i.e. Mendelian disorders) and constitutional chromosomal anomalies. Towards the other end are infectious diseases.

Occurring between these two ends are conditions which are common, which do not follow any clear-cut pattern of inheritance but which tend to "cluster" in families. These are referred to as "multifactorial" or "irregularly-inherited" or "partially genetic" disorders. One major view that has dominated the thinking in this field is that these conditions result from the joint action of numerous genetic ("polygenic") and environmental factors which could also be multiple.

Based on transmission patterns, Mendelian conditions are divided into three groups: autosomal dominants, autosomal recessives and X-linked. The commoner forms of autosomal dominants first appear in adult life (e.g. Huntington disease, polycystic kidney disease, multiple polyposis, cerebellar ataxia, myotonic dystrophy, etc). Other dominants identified through and associated with congenital abnormality syndromes (these have been referred to as "sentinel phenotypes"; see Czeizel, 1989) appear in infancy or childhood (e.g. achondroplasia, Apert syndrome, bilateral aniridia, Crouzon syndrome, osteogenesis imperfecta type I, etc).

Most autosomal recessive disorders (e.g. cystic fibrosis, phenylketonuria, adrenal hyperplasia, etc), X-linked disorders (e.g. Duchenne and Becker muscular dystrophy, haemophilia A, fragile-X associated mental retardation, X-linked retinitis pigmentosa, etc.) and chromosomal anomalies (e.g. Down syndrome, cri du chat syndrome due to

deletion of short arm of chromosome 5, those due to unbalanced chromosomal aberrations, etc.) have onset at birth or childhood.

The multifactorial category can be divided into two groups of conditions, namely congenital abnormalities and common disorders of adult life. Congenital abnormalities (e.g. neural tube defects, congenital heart defects, pyloric stenosis, cleft lip with or without cleft palate, undescended testes, etc.) result from errors in morphogenesis i.e. they are gross or microscopic structural defects present at birth whether detected at that time or not. Congenital abnormalities are aetiologically heterogeneous i.e. they have different origins (see Czeizel and Tusnady, 1984, for a discussion). The relative proportions attributable to the different aetiological categories have varied between different studies (e.g. Kalter and Warkany, 1983; Baird *et al.*, 1988; Brent, 1986; Nelson and Holmes, 1989) and UNSCEAR's (1986). Approximate estimates are the following: mutant genes, 6% of the total prevalence; chromosomal anomalies, 5%; multifactorial, 50%, environmental (including maternal factors), 6% and unknown, the remainder.

The other multifactorial disorders are, as already mentioned, common conditions of adult life. These include (Table 1) clinically serious conditions such as schizophrenia, multiple sclerosis, epilepsy, acute myocardial infarction, systemic lupus erythematosus; moderately serious and/or episodal or seasonal ones such as affective psychoses, glaucoma, diabetes mellitus, rheumatoid arthritis and asthma. Conditions such as varicose veins of lower extremities, allergic rhinitis, atopic dermatitis, can be deemed to be less severe than those belonging to the first two groups. These are clinical designations and each condition is aetiologically complex and includes an unknown proportion of sub-entities that follow Mendelian patterns of inheritance.

5.2. Prevalences

Data on the natural prevalence of genetic disorders pertinent in the context of the doubling dose method of risk evaluation are those collected in epidemiological studies of defined populations (Stevenson, 1959; Trimble and Doughty, 1974; Czeizel and Sankaranarayanan, 1984; Czeizel *et al.*, 1988; Baird *et al.*, 1988), in several *ad hoc* studies of specific Mendelian conditions (reviewed in Carter, 1977, 1982; NAS, 1990; Sankaranarayanan, 1991a) and in cytogenetic studies of newborns (reviewed in UNSCEAR, 1977, 1982, 1986).

The estimates of birth prevalence for Mendelian and chromosomal disorders have remained essentially unchanged over the past 10 years. These are: 1.0% (autosomal dominant and X-linked), 0.25% (autosomal recessives, including those disorders for which the responsible mutant genes are maintained through heterozygous advantage), and 0.38% (chromosomal, including 0.34% due to numerical anomalies and the remainder, due to structural anomalies).

For congenital abnormalities and other multifactorial disorders, on the basis of results of the British Columbia study (Trimble and Doughty, 1974), UNSCEAR (1977, 1982), accepted birth prevalence values are 4.3% and 4.7%, respectively. The period of follow-up in the British Columbia study was from birth to age 21 years. Subsequently, when the results of Hungarian studies (Czeizel and Sankaranarayanan, 1984; Czeizel *et al.*, 1988) became available, UNSCEAR (1986, 1988) revised the birth prevalence of congenital abnormalities from 4.3% to 6.0% (see also Baird *et al.*, 1988) and that of other multifactorial disorders from 4.7% to about 65%. One should hasten to stress here that the revised figure for the "other multifactorial disorders" does not pertain to prevalence at

Table 1. Lifetime prevalence (i.e. through 70 years of age) of selected multifactorial diseases (excluding congenital abnormalities) in Hungary (Czeizel *et al.*, 1988)

Disease		Prevalence per 10^4 individuals
Group I (Clinically very serious)		
Schizophrenic psychoses		85
Multiple sclerosis		4
Epilepsy		60
Acute myocardial infarction, other forms of acute and sub-acute forms of ischaemic heart disease		359
Systemic lupus erythematosus		4
	Sub-total	512
Group II (Moderately severe and/or episodal or seasonal)		
Graves' disease		65
Diabetes mellitus		427
Gout		18
Affective psychoses		600
Glaucoma		160
Essential hypertension		850
Asthma		249
Peptic ulcers		460
Idiopathic proctocolitis		3
Cholelithiasis		94
Coeliac disease		13
Calculus of the kidney		90
Psoriasis		39
Rheumatoid arthritis		131
Ankylosing spondylitis		19
	Sub-total	3218
Group III (Less severe than those of Groups I and II)		
Varicose veins of lower extremities		1250 (125)[a]
Allergic rhinitis		360 (120)[a]
Atopic dermatitis		60 (20)[a]
Scheuermann disease		1100 (55)[a]
Adolescent idiopathic scoliosis		41 (8)[a]
	Sub-totals	2811 (328)[a]
	Grand total	6541

[a] Estimates adjusted to take into account the proportion of cases that needs medical treatment; for Scheuermann disease, the figure of 1100 per 10^4 is based on radiological screening.

birth but refers to lifetime prevalence in the population (including all age groups up to age 70 years).

6. SOURCE OF DATA USED IN THE DIRECT METHOD OF RISK ESTIMATION

Data on rates of induction of mutations used in the direct method of risk estimation are those collected in studies with male mice and pertain to dominant mutations affecting the skeleton or causing cataracts in the first generation progeny. Most of these experiments involved x or gamma irradiation with high doses and at high dose-rates. The rates estimated for these conditions are "transformed" into risk(s) of dominant genetic

disorders in humans using an array of correction factors, primarily derived from the extensive studies on the induction of recessive specific locus mutations in male mice. At present, there are no data on the induction of dominant skeletal and cataract mutations in female mice. Therefore, the rates used in risk estimation for females are derived from those available for males, using the known differences in the response of stem cell spermatogonia in males and oocytes in females as a rough guide.

The estimates of risk of congenital abnormalities due to chromosomal aberrations are derived from cytogenetic data on the induction of reciprocal translocations in males of a number of non-human primate species. More specifically, these rates are used to estimate the proportion of unbalanced gametes expected to be generated and from this, the risk of congenital abnormalities in livebirths. Again, since there are no data on translocation induction in female primates, the procedure followed for risk estimation in females is similar to that used for mutations outlined in the preceding paragraph.

7. GENETIC RISK ESTIMATES FROM THE MID-1970s TO THE PRESENT

7.1. Doubling Dose Method

The similarities and differences in genetic risk estimates arrived at using the doubling dose method during the last 10–15 years have recently been discussed in the UNSCEAR (1988) and the BEIR V (NAS, 1990) reports and by Sankaranarayanan (1988). Table 2 presents a summary of these. Considering first the UNSCEAR estimates, the following points are worthy of note: (i) the estimate of doubling dose used in risk evaluations presented in the 1977, 1982, 1986 and 1988 reports is the same, namely, 1 Gy of low dose rate low LET radiation; (ii) the prevalence estimates for Mendelian and chromosomal disorders have remained essentially unchanged whereas those for congenital abnormalities and other multifactorial disorders have been revised upwards in 1988; (iii) the estimates of risk for autosomal dominant and X-linked conditions and those due to structural chromosomal anomalies have remained unchanged through 1988; for multifactorial disorders, although new prevalence data have become available, it was not considered prudent to apply the *ad hoc* mutation component estimate of 5% (this figure was used by UNSCEAR in 1977 and 1982) to these new data for risk estimation, in the absence of a definitive analysis; therefore, no risk estimates are presented for these disorders.

The differences between the estimates of UNSCEAR and those of the BEIR Committee are due to the following reasons. First, in its 1980 report (NAS, 1980), the BEIR III Committee used a range of doubling doses (0.5 to 2.5 Gy) and a range of values for the mutational component (0.05 to 0.5) of multifactorial disorders. Second, in its 1990 report, the BEIR V Committee adopted 1 Gy of low dose rate low LET radiation as the best doubling dose estimate, subclassified the autosomal dominant disorders into those which are clinically serious and clinically mild, and also derived a range of selection coefficients applicable to these (from published data on naturally-occurring disorders), to estimate first generation effects. Third, for congenital abnormalities, on the basis of the same data discussed in the 1986 and 1988 UNSCEAR reports, the BEIR V Committee (NAS, 1990) adopted a prevalence range of 2–3% (taking into account the aetiological heterogeneity mentioned earlier) and a mutation component range of 5–35%.

Table 2. Genetic effects estimated using the doubling dose method for an average genetically significant dose of 0.01 Gy of low LET, low dose-rate (chronic) irradiation per generation on a population of one million livebirths

Report	Doubling dose (Gy)	Type of genetic disease	Natural prevalence per 10^6 livebirths	Expected increase (per 10^6 livebirths) in		
				First generation	Second generation	Equilibrium
UNSCEAR (1977)	1	Autosomal dominant and X-linked	10 000	20	not given	100
		Autosomal recessive	1100[b]	slight	not given	slow
		Chromosomal	4000	38[c]	not given	40
		Multifactorial	90 000	5	not given	45
		Total	105 100	63		185
UNSCEAR (1982)	1	Autosomal dominant and X-linked	10 000	15	not given	100
		Autosomal recessive	2500[b]	slight	not given	slow
		Chromosomal, due to:				
		Numerical anomalies	3400	very small	not given	very small
		Structural anomalies	400	2.4	not given	4
		Multifactorial	90 000	5	not given	45
		Total	106 300	22	not given	~150
UNSCEAR (1986)	1	Autosomal dominant and X-linked	10 000	15	not given	100
		Autosomal recessive	2500	slight	not given	slow
		Chromosomal, due to:				
		Numerical anomalies	3400	very small	not given	very small
		Structural anomalies	400	2.4	not given	4
		Total (excluding multifactorial)	16 300	18		104
UNSCEAR (1988)	1	Autosomal dominant and X-linked	10 000	15	13	100
		Autosomal recessive, due to:	2500			
		Homozygous effects		no increase	no increase	11
		Partnership effects		negligible	negligible	4[d]
		Chromosomal, due to:				
		Structural anomalies	400	2.4	1	4
		Sub-total	~13 000	~18	14	~120
		Congenital abnormalities	6000		not estimated	
		Other multifactorial	650 000		not estimated	
		Chromosomal, numerical	3400		not estimated	
		Heritable tumours	unknown		not estimated	

Table 2—*continued*

Report	Doubling dose (Gy)	Type of genetic disease	Natural prevalence per 10^6 livebirths	Expected increase (per 10^6 livebirths) in First generation	Second generation	Equilibrium
NAS (1980) (BEIR III)	0.5–2.5	Autosomal dominant and X-linked	10 000	5–65[e]	not given	40–200
		Autosomal recessive	1100	very slight	not given	very slight
		Chromosomal[f]	6000	< 10	not given	slight
		Multifactorial	90 000	not given	not given	20–900
			107 000	15–75		60–1100
NAS (1990) (BEIR V)	1	Autosomal dominant				
		Clinically severe[g]	2500	5–20[h]	not given	25
		Clinically mild[g]	7500	1–15[h]	not given	75
		X-linked	400	< 1	not given	5
		Autosomal recessive	1100	< 1	not given	very slow
		Chromosomal, due to:				
		Unbalanced translocations	600	< 5	not given	very little
		Trisomies	3800	< 1	not given	< 1
		Congenital abnormalities	20 000–30 000	< 10[j]	not given	10–100[i]
		Sub-total	35 900–45 900	15–40		115–215
		Other disorders of complex aetiology[k]				
		Heart disease	600 000		not estimated	
		Cancer	300 000		not estimated	
		Selected others	300 000		not estimated	

[a] Unless otherwise stated, the equilibrium increase is first estimated as a product of prevalence, relative mutation risk and mutation component. The first generation increase is then estimated from that at equilibrium (15 or 20% of that at equilibrium for autosomal dominant and X-linked and 10% of that at equilibrium for multifactorial conditions). The increase in the second generation is calculated similarly as a fraction of the equilibrium value minus the first generation increase. Multifactorial disorders have been assumed to have a mutation component of 5% (UNSCEAR) or between 5 and 50% (NAS 1980).

[b] $1100/10^6$ excludes recessives maintained by heterozygous advantage and $2500/10^6$ includes them.

[c] The first generation increase is assumed to include all the numerical anomalies and 3/5 of the unbalanced translocations.

[d] From partnership between induced mutations and those already present in the population, assuming 2.5% heterozygous disadvantage and, on average, one harmful recessive per gamete (see Searle and Edwards, 1986 for details).

[e] Estimated from first generation effects on the skeleton.

[f] Includes only those aberrations expressed as congenital malformations resulting from unbalanced products of translocations and from numerical aberrations.

[g] Survival and reproduction assumed to be reduced by 20–80% (or $s = 0.2–0.8$; clinically severe) or by 1–20% ($s = 0.01–0.20$; clinically mild) relative to normal.

[h] First generation effect = natural prevalence $\times$ $1/100 \times s$; the s values are those given in footnote g.

[i] A mutation component range of 5–35% has been assumed.

[j] Based on "worst-case assumption" that the mutation component results from dominant genes.

[k] Provided for guidance only to indicate the rough order of magnitude of their prevalences.

7.2. Direct Method

As discussed earlier, the data used by UNSCEAR to estimate absolute risks to the first generation progeny are those from mouse genetic studies on the induction of dominant skeletal and cataract mutations and from primate cytogenetic studies on the induction of balanced reciprocal translocations. Since there have been no major conceptual changes during the past decade, it will suffice to present a summary of the estimates arrived at by UNSCEAR in its 1988 report (Table 3). Worthy of note is that the numerical estimate of risk to the first generation progeny is about the same as that estimated with the doubling dose method.

Table 3. Estimates of genetic risk arrived at by UNSCEAR in its 1988 report using the direct methods (low LET, low dose-rate (chronic) irradiation conditions)

Risk associated with	Expected frequency (per 10^6, per 10^{-2} Gy) of genetically abnormal children in the first generation after irradiation of	
	Males	Females
Induced mutations having dominant effects[a]	~ 10 to ~ 20	0 to ~ 9
Induced recessive mutations	0	0
Unbalanced products of induced reciprocal translocations[b]	~ 1 to ~ 15	0 to ~ 5

[a] Includes risks from the induction of dominant mutations, as well as of deletions and balanced reciprocal translocations with dominant effects; based on data on the induction of dominant skeletal and dominant cataract mutations in male mice; the risk for irradiation of females was derived on the basis of known differences between male and female mice in response to the induction of recessive specific locus mutations for which the data are extensive.

[b] Based on cytogenetic data obtained in male primates; the risk for irradiation of females is derived from that for males. The risk figures pertain to the risk of congenitally malformed births.

The BEIR III Committee's (NAS, 1980) direct estimates of risk to the first generation progeny (see Table 2, and foot-notes *e* and *f*) are somewhat different from those arrived at by UNSCEAR; these are due to the different assumptions used to convert the rates of induction of mutations into risk of genetic disorders from the same data-set. These are fully discussed by BEIR III and BEIR V Committees (NAS, 1980, 1990) and also by UNSCEAR in its 1982 and 1988 reports. In its 1990 report, the BEIR V Committee did not use the skeletal or cataract data to estimate risks. It noted that "... the Committee had little confidence in the reliability of the individual assumptions required by the direct method let alone the product of a long chain of uncertain estimates that follow from these assumptions ... therefore, they did not place heavy reliance on the direct method in making their estimates, but used it only as a test of consistency."

8. ESTIMATES OF GENETIC RISK USED IN *ICRP 26*

At the time of preparation of its recommendations in the mid-1970s, ICRP appointed a Task Group to address the question of genetic risks and to present the quantitative estimates in a manner comparable to that for somatic effects. The conclusions of this Task Group were published by Oftedal and Searle (1980) and are summarised in Table 4. While the basic data and several of the assumptions (including the doubling dose estimate of 1 Sv of low dose rate low LET radiation) used by the Task group were similar to those used by UNSCEAR in 1977, the numerical estimates of risk by the

Table 4. Estimates of the number of cases of serious genetic ill health in offspring (excluding abortions) from parents irradiated with 1 million man-rem in a population of constant size (Oftedal and Searle, 1980; used in *ICRP 26*, 1977). A doubling dose of 100 rem was assumed by these authors

Category of genetic effect	Equilibrium[a]	1 + 2 generation
Unbalanced translocations; risk of malformed liveborn	30	23 + 6 = 29
Trisomics and XO	30	30 + 0 = 30
Simple dominants and sex-linked mutations	100	20 + 16 = 36
Dominants of incomplete penetrance and multifactorial disease maintained by mutation	160[b]	16 + 14 = 30
Multifactorial disease not maintained by mutation	0	0
Recessive disease	[c]	[c]
	320	89 + 36 = 125

[a] Over all generations following the generation exposed.
[b] The sum of the first three entries (i.e. 30 + 30 + 100).
[c] No estimate given.

former were different. The important differences pertain to risk estimates for multifactorial disorders and those stemming from unbalanced products of induced balanced reciprocal translocations. These will now be considered in turn.

Using the doubling dose method, UNSCEAR (1977) estimated the equilibrium risk of multifactorial disorders as 45 cases per 10^6 livebirths (under conditions when the population is continuously exposed at the rate of 0.01 Gy of low dose rate low LET radiation/generation); the first generation increase was assumed to be about one-tenth of this value (i.e. $5/10^6$ livebirths; see Explanatory Note 1; the 9% natural prevalence assumed here was based on the studies of Trimble and Doughty [1974] in the Canadian province of British Columbia). Although an estimate of risk for the second generation (under radiation conditions specified above) was not given, it can be estimated to be about 4 cases per 10^6 livebirths [i.e. 10% of (45–4.5) 10^{-6}]. Thus, for the first two generations, the estimate is about 9 cases/10^6 livebirths.

The Task Group however, did not use any prevalence figure for the above class of disorders to make risk estimates. Instead it split up disorders of complex aetiology into (a) dominants with incomplete penetrance and multifactorial disorders maintained by mutation (i.e. those that will respond to induced mutation) and (b) multifactorial disorders not maintained by mutation (i.e. those that will not respond to induced mutation). Further, it assumed that the expected increase in the frequency of group (a) disorders is unlikely to exceed the sum of expected increments in Mendelian and chromosomal disorders; the Task Group estimated that for a population under continuous low LET irradiation at a rate of 0.01 Gy per generation, the risk amounted to 160 cases per 10^6 livebirths at equilibrium and about 30 cases per 10^6 livebirths in the first two generations. It is clear that the latter of these two figures (30 cases/10^6) is higher than that of UNSCEAR (9 cases/10^6).

In its 1977 report, using the direct method, UNSCEAR estimated the risk of production of unbalanced gametes (arising as a consequence of the induction of balanced reciprocal translocations) leading to congenitally abnormal children, on the basis of cytogenetic data in marmosets and human males. The estimate was 2–10 affected children per 10^6 livebirths in the first generation per 0.01 Gy of paternal irradiation. The lower limit of the above range was for chronic gamma irradiation, and the upper limit, for

low dose-rate x-irradiation conditions. The risk for the irradiation of females was considered to be low, but no quantitative estimate was given.

The Task Group's estimate for the above class of genetic damage was 30 cases per 10^6 livebirths per 0.01 Gy of parental (i.e. both sexes) irradiation with low dose-rate x rays (at equilibrium) and was based on the same set of marmoset and human cytogenetic data but on different assumptions. Furthermore, to be on the conservative side, the Task Group assumed that the risk from translocation induction would be the same in both sexes.

The conclusions of the Task group were stated by Oftedal and Searle (1980) as follows: "... The total genetic risk of serious ill-health after 1 million man-rem to parents adds up to 125 cases in the first two generations after exposure and 320 cases at equilibrium, if the same dose is given in every generation to a stable population. This latter figure will also be the number of extra cases in all succeeding generations from a single generation's dose of 1 million man-rem. Estimates are given for the first two generations after exposure because these generations will be of predominant interest to the radiation worker in his or her own lifetime. It should be emphasized that these estimates apply to genetically significant doses, so have to be modified when, for instance, some part of a lifetime's occupational exposure is given after the age of reproduction. The estimate of 89 extra cases of serious genetic damage in the first generation after 1 million man-rem is not far removed from the corresponding estimate in UNSCEAR (1977) with use of the doubling dose method, namely, 63 cases per million per rad of low LET radiation given at low doses and dose-rates...".

In discussing risk coefficients for genetic effects (based on Table 4), *ICRP 26* (1977) stated that "... The risk of serious genetic ill-health within the first two generations following the irradiation of either parent is taken to be about 10^{-2} Sv^{-1} and the additional damage to later generations to be of the same magnitude ... For the purpose of radiation protection involving individuals, ... the average risk factor for hereditary effects, as expressed in the first two generations ... when account is taken of the proportion of exposures that is likely to be genetically significant ...can be taken as about 4 10^{-3} Sv^{-1}...".

9. ICRP'S CURRENT ASSESSMENT OF GENETIC RISKS

The objectives of ICRP are (i) to gain a perspective of the total genetic risk as well as that for the first two generations, following either a one-time exposure of the parental generation or a continuous exposure of the population generation after generation at a finite rate (the reason for being interested in calculating risks for the first two generations is that genetic injury to children and grandchildren is perceived as important as somatic injury (risk of cancer) to the exposed individual), and (ii) to derive risk coefficients for genetic risks which can be compared with risk coefficients for cancer.

In order to do these, ICRP examined the results that have accumulated since the mid-1970s and the recent conclusions derived from these in UNSCEAR (1988) and BEIR V (NAS, 1990) reports (see Table 2). As may be recalled, the risk estimates presented in the above reports are basically similar, considering the fact that UNSCEAR's figures are for Mendelian and chromosomal disorders only whereas the BEIR Committee's estimate includes congenital abnormalities as well.

9.1. Risk Coefficients for Mendelian and Chromosomal Diseases

ICRP's risk coefficients for Mendelian and chromosomal diseases are summarised in Table 5. In deriving these, it used UNSCEAR's (1988) risk estimates (arrived at using the doubling dose method; see Table 2) as starting points. As may be recalled, the UNSCEAR estimates are for an assumed parental *gonadal dose of 0.01 Gy* (i.e. all the individuals are assumed to receive a genetically significant dose of 0.01 Gy). On a per *Gy* of low dose rate low LET radiation, or per Sv basis, the figures are: 12,000 cases per 10^6 livebirths (risk to all generations) and 3,200 cases per 10^6 livebirths (risk to the first two generations). Therefore, the risk coefficients to the reproductive population are, respectively 1.2×10^{-2} Sv^{-1} (all generations) and 0.3×10^{-2} Sv^{-1} (first two generations).

Table 5. ICRP's current estimates of risk coefficients for serious hereditary effects of ionising radiation (10^{-2} Sv^{-1})

			For gonadal dose equivalent	
Time span	Disease category		Reproductive population	Total population
All generations	Mendelian and chromosomal		1.2	0.5
	Multifactorial[a,b]		1.2	0.5
		Total	2.4	1.0[c]
First two generations	Mendelian and chromosomal		0.3	0.1
	Multifactorial[a,b]		0.23	0.09
		Total	0.53	0.19

[a] Includes congenital abnormalities and common diseases of adults such as those listed in Table 1.
[b] The risk coefficients for this category have been derived using assumptions discussed in the text (Section 9 and in Explanatory Note 1, item 2).
[c] The value used in the current ICRP recommendations.

However, when the total population is considered, the genetically significant dose will be markedly lower than the total dose received over a lifetime. Damage sustained by germ cells of individuals who are beyond the reproductive period or who are not procreating for any reason, poses no genetic risks. If it is assumed that the mean age at reproduction is 30 years and the average life expectancy at birth is of the order of 70 to 75 years, the dose received by 30 years is about 40% of the total dose. The risk coefficients for the total population therefore are: 40% of 1.2×10^{-2} i.e. 0.5×10^{-2} Sv^{-1} (all generations) and 40% of 0.3×10^{-2} or 0.1×10^{-2} Sv^{-1} (first two generations). It is clear that the latter figure is smaller by a factor of 4 relative to that of 0.4×10^{-2} Sv^{-1} used in *ICRP 26*. This is because of the fact that the risk of multifactorial disorders has not been included in the estimate of 0.1×10^{-2} Sv^{-1}.

9.2. Risk Coefficients for Multifactorial Disorders

Although UNSCEAR presented estimates of risk for multifactorial conditions in its 1977 report (with the then considered valid assumptions of 9% prevalence and 5% mutation component; see Explanatory Note 1), it refrained from doing so in its subsequent reports, because of a number of uncertainties. From the standpoint of ICRP however, it is important to have some estimate for these disorders so that risk coefficients for all genetic effects can be estimated. One approach to this problem is to

make some plausible assumptions regarding doubling dose, prevalence, mutation component and severity for these disorders and examine what the risks are likely to be. This has been done and the rationale and details are given in Explanatory Note 1.

9.2.1. *Risk of multifactorial disease and of all severe hereditary effects over all generations*

Under the assumptions that: (i) the multifactorial disorders (including congenital abnormalities) have a natural prevalence of 71%; (ii) the doubling dose is 1 Gy of low dose rate low LET radiation; (iii) the population is continuously exposed to a genetically significant dose of 0.01 Gy low LET radiation per generation; and (iv) the average mutational component is 5%, the estimate of risk of these disorders at equilibrium is:

$$0.71 \times 1/1 \times 0.01 \times 0.05 = 0.000355 \text{ or } 3.55 \times 10^{-2}\,\text{Gy}^{-1} \text{ (or Sv}^{-1}\text{)}$$

Since some of these disorders are less detrimental than others, ICRP is of the view that (i) the above probability estimate should not be added as such to that for Mendelian and chromosomal disorders without some weighting for the severity of the effects, and (ii) the magnitude of the weighting factor, which is necessarily arbitrary, can be taken as about 1/3. With this weighting factor, the risk coefficient for multifactorial disorders (all generations; reproductive population) becomes 1.2×10^{-2} Sv^{-1} (i.e. $1/3 \times 3.55 \times 10^{-2}$). For the total population, the estimate is 40% of 1.2×10^{-2}, namely, about 0.5×10^{-2} Sv^{-1}. The latter can now be combined with the one arrived at for Mendelian and chromosomal disorders (0.5×10^{-2} Sv^{-1}), to obtain an *overall risk coefficient of about* 1×10^{-2} *Sv*$^{-1}$ *for serious hereditary effects for the total population and is the one used in the present ICRP recommendations.* These estimates are summarised in Table 5.

9.2.2. *Risk of multifactorial disease and of all severe hereditary effects in the first two generations*

Under the assumption that for these disorders, about one-tenth of the equilibrium risk will be expressed in each of the first two generations, the coefficients of risk of multifactorial disorders applicable to the first two generations are: about 0.23×10^{-2} Sv^{-1} for the reproductive population and about 0.09×10^{-2} Sv^{-1} for the total population (these estimates take into account the severity correction factor of 1/3). Combined with the corresponding estimates for Mendelian and chromosomal disorders (0.3×10^{-2} Sv^{-1} for the reproductive population and 0.1×10^{-2} Sv^{-1}, for the total population), the risk coefficients for the first two generations can be estimated as about 0.53×10^{-2} Sv^{-1} for the reproductive population and about 0.19×10^{-2} Sv^{-1} for the total population.

It should be noted here that the overall risk coefficient of 0.19×10^{-2} Sv^{-1} (for the first two generations) for the total population appears lower than the one of 0.4×10^{-2} Sv^{-1} assumed in *ICRP 26* (1977). Two primary reasons for this difference are the following: (i) the current estimate of risk for multifactorial disorders has been arrived at differently, and (ii) a "severity correction factor" has now been incorporated into the estimate for multifactorial disorders.

9.2.3. *Consequences of other assumptions on risk estimates for multifactorial disorders*

The estimates of risk for multifactorial disorders discussed in the preceding paragraphs have been arrived at using certain specific assumptions on doubling dose (1 Gy of low dose rate low LET radiation), prevalence (71%), mutation component (5%) and severity correction factor (1/3). It is clear that if any of these assumptions is changed, the risk estimates will also be different.

If, for instance, it is assumed that the prevalence (in terms of affected individuals) is 45% and the other assumptions remain the same, the risk coefficients will be:

$45/71 \times 1.2 \times 10^{-2} = 0.76 \times 10^{-2}\ Sv^{-1}$ (all generations, reproductive population) and
$0.76 \times 0.40 = 0.30 \times 10^{-2}\ Sv^{-1}$ (all generations, total population)

For the first two generations, the comparable figures will be about $0.14 \times 10^{-2}\ Sv^{-1}$ (reproductive population) and $0.06 \times 10^{-2}\ Sv^{-1}$ (total population). If, on the other hand, one assumes that the mutation component is 15% (other assumptions remaining the same as above), then the corresponding risk coefficients will be 3-fold higher.

It is obvious that all these estimates are heavily influenced by the assumptions used; the choice of one or the other of these estimates, therefore, is a matter of informed judgement. At the present state of knowledge, there are no compelling reasons either to assume that genetic risks were underestimated in *ICRP 26* or to advance arguments that these risks are now higher than those estimated in 1977. ICRP is of the view that (i) the use of a risk coefficient of $1 \times 10^{-2}\ Sv^{-1}$ over all generations for severe hereditary effects in the population as a whole is sufficiently conservative and can be used within the framework of radiation protection and (ii) should further studies and analyses reveal that the risk coefficient for severe hereditary effects is likely to be different than the one mentioned above, then, the Commission will review the situation and act accordingly.

10. FUTURE PROSPECTS

10.1. Risk Estimation for Autosomal Dominant and X-linked Disorders

The estimates of risk presented in a preceding section for these disorders (obtained through the use of the doubling dose method of risk estimation) have used a birth prevalence figure of 1%. Two of the assumptions implicit in these calculations are: (i) all autosomal dominant and X-linked disorders are maintained in the population through a balance between mutation and selection, and (ii) induced mutations are similar in their nature to spontaneously-arising ones. There are reasons to question the validity of both these assumptions.

In a series of recent papers, Sankaranarayanan (1990, 1991a, b, c, d) has examined the entire conceptual framework of genetic risk estimation including the assumptions mentioned above. Some of the principal conclusions that emerge from this analysis and their pertinence for genetic risk estimation are briefly outlined below.

The assumption of mutation-selection balance, which is the cornerstone for the doubling dose method of risk evaluation, may be valid for only a small proportion of autosomal dominants, while for the rest, it is debatable; if this view is correct, the use of a prevalence figure of 1% for autosomal dominant + X-linked diseases in the risk equation (see Section 2) will overestimate the risk.

Molecular data currently available on naturally-occurring Mendelian diseases ($n = 76$) support the view that in approximately 50% of them, the changes are point mutations (i.e. base pair changes) while in the remainder they are "length mutations" (i.e. intragenic deletions, multilocus deletions or other gross changes). In contrast, the spectrum of radiation-induced mutations (in mammalian *in vivo* and *in vitro* systems) is dominated by length mutations; ionising radiation is a poor point mutagen. These findings also suggest that the use of the 1% prevalence figure in the risk equation for autosomal dominants and X-linked disorders may need reassessment.

10.2. Risk Estimation for Multifactorial Disorders

In this paper, in estimating the risk of induction of multifactorial disorders, the consequences of assuming a mutation component of 5% (and a prevalence of 71% or 45%) or of 15% (and a prevalence of 45%) have been discussed. In this context, it is worth recalling that the BEIR V Committee (NAS, 1990) used a mutation component range of 5–35% for congenital abnormalities alone (and a prevalence of 2–3%). While it is obvious that there is a need to extend this analysis to all multifactorial disorders, it is instructive to note that the genetic basis of a number of multifactorial disorders is under study in a number of laboratories. The available results permit at least three tentative conclusions: (i) for at least some of these disorders, mutations in a small number of genes may play a greater role than those in others (see Bock and Collins, 1987; Scott, 1987 for recent discussions); (ii) the classical biometric models which invoke a very large number of loci each with small additive effects may need to be viewed with some caution, and (iii) since a majority of the multifactorial disorders have adult onset (i.e. after reproductive age), the mechanisms involved in the maintenance of these disorders in the population need to be better understood, especially whether they exist in the population due to mutation-selection balance.

EXPLANATORY NOTE 1

Risk Estimation for Multifactorial Disorders

1. *UNSCEAR (1977)*

Assumptions: Natural prevalence $90{,}000/10^6$; doubling dose, 1 Gy low dose rate low LET radiation; mutation component, 5%; expression in the first generation, 10% of that at equilibrium; expression in the second generation, 10% of the remainder; population exposed at a rate of 0.01 Gy of low LET radiation/generation.

Calculations: (a) Risk at equilibrium $= 90{,}000 \times 0.01 \times 0.05 = 45$ cases/10^6

(b) Risk coeff. for (a) $= 0.45 \times 10^{-2}$ Sv^{-1}

(c) Risk coeff. for population exposures at equilibrium [40% of (b)] $= 0.18 \times 10^{-2}$ Sv^{-1}

(d) Risk in generation 1 [10% of (a)] $= 4.5/10^6$

(e) Risk in generation 2 [10% of (a–d)] $= 4/10^6$

(f) Risk in generations 1 and 2 $= 8.5/10^6$

(g) Risk coeff. for (f) $= 0.085 \times 10^{-2}$ Sv^{-1}

(h) Risk coeff. for population exposures; 1st and 2nd generations [40% of (f)] $= 0.034 \times 10^{-2}$ Sv^{-1}

2. *The present paper (Section 9)*

Assumptions: Natural prevalence, $710{,}000/10^6$ (i.e. congenital abnormalities, 6% and other multifactorials, 65%); mutation component, 5%; expression in the first two generations, same as given under item (1) above and doubling dose 1 Gy of low dose rate low LET radiation; population exposed at a rate of 0.01 Gy/generation.

Calculations: (a) Risk at equilibrium $= 355/10^6/0.01$ Gy

(b) Risk coeff. for (a) without correction for severity of effects $= 3.55 \times 10^{-2}$ Sv^{-1}

(c) Risk coeff. for (a) with correction for severity of effects [1/3 of (b)] $= 1.2 \times 10^{-2}$ Sv^{-1}

(d) Risk coeff. for population exposures [40% of (c)] $= 0.5 \times 10^{-2}$ Sv^{-1}

(e) Risk to first generation $= 35.5/10^6/0.01$ Gy

(f) Risk to second generation = $33/10^6/0.01$ Gy
(g) Risk to generations 1 and 2 = $70/10^6/0.01$ Gy
(h) Risk coeff. for (g) without correction for severity = 0.7×10^{-2} Sv^{-1}
(i) Risk coeff. for population exposures, with correction for severity ($0.7 \times 0.4 \times 1/3 = 0.09 \times 10^{-2}$ Sv^{-1})

3. There are reasons to believe that some of the assumptions used in the above calculations may not be valid. For instance, the prevalence estimate of 6% in livebirths for congenital abnormalities may be inappropriate for use in the risk equation for at least two reasons: (i) the 6% Hungarian figure (Czeizel and Sankaranarayanan, 1984) includes an estimate for congenital dislocation of the hip (2.6%) which was believed to have an unusually high prevalence in Hungary; recent studies (Vizkelety, 1986; Czeizel and Vizkelety, 1988) lend credence to the belief that the current prevalence of this condition in Hungary (1.3%) is not more than in other Western European populations and that the earlier estimate was due to overdiagnosis, and (ii) as mentioned in Section 5, the "multifactorial sub-group" of congenital abnormalities category is probably no more than one-half of the total. It would therefore seem that for these conditions, a more appropriate figure for use in the risk equation is no more than about 3%.

4. Likewise, the estimate of 65% for the other multifactorial disorders is based on the number of conditions per 100 individuals in the population and does not refer to affected individuals per 100 livebirths. Furthermore, a given individual may have more than one disorder. In discussing these data, Czeizel *et al.* (1988) split the disorders into three groups (see Table 1): group I, clinically very severe (5 entities, together a total prevalence of 5.1%); group II, moderately severe and/or episodal or seasonal (15 entities, together 32.2%) and group III, less severe than those in the first two groups (5 entities, together 28.1%); for the third group the authors estimated that the cases needing medical attention is probably only about 12% of the last mentioned figure (i.e. 3.3%).

5. These disorders are aetiologically even more complex than congenital abnormalities and the numbers discussed thus far undoubtedly include an unknown proportion of those which follows Mendelian inheritance. Thus, the arguments developed in the preceding paragraphs lead to the suggestion that the prevalence figure that may be used for risk evaluation is probably about 40% (and not 65%). It bears mentioning here that, in arriving at the estimate of 65%, no account was taken of the possibility already mentioned, namely, that a given individual might have more than one disorder, since in the compilation of Czeizel *et al.* (1988), there was no simple or easy way to exclude counting the same individuals more than once. On the other hand, these authors have excluded certain conditions with an obvious genetic component (e.g. blindness, deafmutism, atherosclerosis, familial cancers, etc.). Thus, on balance, it would appear that a prevalence estimate for multifactorial disorders as a whole (i.e. including the above and congenital abnormalities) usable in the risk estimation context is of the order of about 45%.

6. We turn now to the mutational component. As was discussed earlier (Section 2), UNSCEAR (1977, 1982) used an average mutation component of 5% for multifactorial disorders as a whole. For congenital abnormalities alone, the BEIR (1990) Committee has used a 5–35% range. In what follows, the consequences of using two different values for mutational component, namely 5% and 15% (the latter is the approximate geometric mean of 5% and 50%, the range used in BEIR 1972 for multifactorial disorders as a whole) together with a prevalence estimate of 45% are examined to illustrate the point that the estimates of risk are very sensitive to these assumptions.

7. *Assumptions.* Prevalence: 45%
   Mutation component: 5%
   Doubling dose: 1 Gy of low dose rate low LET radiation
   Population exposed at a rate of: 0.01 Gy/generation.

   Calculations:
   (a) Risk at equilibrium = $225/10^6/0.01$ Gy
   (b) Risk coeff. for (a) without correction for severity = 2.25×10^{-2} Sv^{-1}
   (c) Risk coeff. for (a) with correction for severity, for total population exposures ($2.25 \times 1/3 \times 0.4 = 0.3$) = 0.3×10^{-2} Sv^{-1}
   (d) Risk coeff. for population exposures, with correction for severity, first two generations = 0.06×10^{-2} Sv^{-1}

8. *Assumptions.* Prevalence: 45%
   Mutation component: 15%
   Doubling dose: 1 Gy of low dose rate low LET radiation

   Calculations. Since the only difference (relative to the calculations in the preceding paragraph) is that the mutation component is now assumed to be 3-fold higher, it is clear that the estimates of risk coefficients will also be 3-fold higher.

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IONISING RADIATION AND THE DEVELOPING HUMAN BRAIN

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1. INTRODUCTION

Several years ago, in 1986, the International Commission on Radiological Protection examined the evidence supporting the occurrence of developmental effects of ionising radiation on the brain of the human embryo and fetus (ICRP, 1986). This report described the complex sequence of embryologic and fetal events that culminate in the mature human brain, and the bases for anticipating radiation-related effects. We do not propose to re-examine these bases here; however, it may be helpful to reiterate those differences identified by the Commission's Task Group that set the development of the

human brain and its adnexa apart from most other organs or organ systems. They noted that:

"(a) the brain is one of the most complex organs of the body, with an involved architecture in which different functions are localized in different structures. Differentiation of the latter takes place at different times and for different durations. This is particularly true of the development of the neocortex, which proceeds over a long time.

(b) Brain function critically depends on the disposition and interconnection of structures and cells and, normal structure and function hinge on an orderly sequence of events (cell division; programmed cell death, migration, including the positioning and selective aggregation of cells of the same kind; differentiation with the acquisition of new membrane properties; and synaptic interconnection), each of which must occur correctly, in time and space.

(c) The neurons of the central nervous system are not self-renewing. The capacity of neuronal precursors to divide is exhausted during histogenesis and culminates in differentiated neurons which do not undergo further division."

At the time the report alluded to was written, the reassessment of the doses of the survivors of the atomic bomb explosions at Hiroshima and Nagasaki had not been completed. Estimates of risk were couched, therefore, in terms of the T65DR doses. Since the new doses are now available, and much of the reanalysis of the basic data has been completed, attention here is restricted to estimates of risk as they are revealed by the new DS86 doses (Roesch, 1987).

2. EFFECTS OF RADIATION EXPOSURE

There is abundant information on the biological effects caused by prenatal exposure of mammals to ionising radiation. These data, largely experimental, afford little quantitative insight, however, into central nervous system effects that may arise in human beings, although they do serve to identify possible ones. Much of this evidence was summarised in the 1986 Report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1986; see also UNSCEAR, 1977; Yamazaki, 1966; Mole, 1982). Therefore, in the paragraphs that follow, no effort is made to review these experimental findings exhaustively. Our remarks will only address selected observations. It is important to note, as the earlier report stated, that the limitations of the human data make inevitable the use of other animal species for both descriptive and experimental studies. Although extrapolations must be made with care, the use of experimental animals is vital to progress in understanding the neurologic and behavioural effects of exposure to potentially injurious substances, such as ionising radiation. However, direct evidence from human studies, especially that of a quantitative nature, will eventually be the most convincing.

2.1. Hiroshima and Nagasaki: The Prenatally Exposed

Few population-based studies of the effects of prenatal exposure on the developing human embryo and fetus exist. Among these, however, the size, length of study, variability in dose, and post-fertilisation age at exposure make the experiences in Hiroshima and Nagasaki the most important. These populations were exposed at a variety of developmental phases and, therefore, presumably a variety of sensitivities.

2.1.1. *Dose estimates*

Recently published analyses of the effects of prenatal irradiation on the developing brain have used the estimated absorbed dose to the mother's uterus based on the DS86 dosimetry (Roesch, 1987). Absorbed doses to the embryo or fetus are not available, and may not be for some time. Justification for the use of uterine doses rests on phantom studies that have shown that the correspondence between the dose in the uterus and in fetal tissues is high in the second half of pregnancy. It warrants noting, however, that uterus dose may slightly overestimate the energy absorbed by the developing tissues in the first half when more fluid surrounds the embryo or fetus (Hashizume *et al.*, 1973; Kerr, 1979), and thus the risk in the earlier months of gestation may be underestimated.

2.1.2. *Developmental ages*

Developmental age is the most important single biological factor in determining the nature of the insult to the embryo or fetus resulting from exposure to ionising radiation. Accordingly, since different functions in the human brain are localised into different structures, and since the differentiation of these takes place at different stages of gestation and over different periods of time, gestational ages (here taken to be synonymous with developmental ages) have been grouped so as to reflect these known phases in normal development. Four categories, measured from the presumed moment of fertilisation, have been used: fertilisation through the seventh week (0–7), the eighth through the fifteenth week (8–15), the sixteenth through the twenty-fifth week (16–25), and 26 or more weeks (26 + weeks). In the first period, the precursors of the neurons and neuroglia, the two principal types of cells that give rise to the cerebrum, have emerged and are mitotically active. In the second, a rapid increase in the number of neurons occurs; they migrate to their ultimate developmental sites and lose their capacity to divide, becoming perennial cells. In the third, differentiation *in situ* accelerates, synaptogenesis that began about the eighth week increases, and the definitive cyto-architecture of the brain unfolds. The fourth period is one of continued architectural and cellular differentiation and synaptogenesis of the cerebrum; with at the same time, accelerated growth and development of the cerebellum.

2.1.3. *Findings related to severe mental retardation*

Thirty of the 1,544 individuals included in the sample of survivors prenatally exposed in Hiroshima and Nagasaki on whom DS86 doses can be computed (doses are not available for 55 survivors in RERF's so-called clinical sample) terminated in a child with severe mental retardation (Otake *et al.*, 1987). Eighteen of these individuals, or 60%, had disproportionately small heads, that is, a head with a circumference more than two standard deviations below the mean observed among the 1,599 births in the entire sample (Blot and Miller, 1972; Miller, 1956; Miller and Blot, 1972; Miller and Mulvihill, 1976; Tabuchi *et al.*, 1967; Wood *et al.*, 1965, 1966). Severe mental retardation in this context implies an individual "unable to perform simple calculations, to make simple conversation, to care for himself or herself, or if he or she was completely unmanageable or had been institutionalized" (Wood *et al.*, 1965).

When the prenatally exposed survivors are distributed over the four age groupings previously described, and the frequency of mentally retarded individuals is examined in the light of their doses and the age at which they were irradiated, the following emerges (see Table 1, and Figures 1 and 2):

Table 1. Severe mental retardation in children exposed *in utero* to the atomic bombing of Hiroshima and Nagasaki by city, dose category and grouped gestational ages in weeks. Numbers and percents in parentheses reveal the results after the exclusion of five severely retarded cases with probable non-radiation-related etiologies. (Adapted from RERF TR 16-87, Table 2b)

Dose category (Gy)	Mean dose (Gy)	All ages			0–7 weeks			8–15 weeks			16–25 weeks			26 or more		
		N	*R*	%	*N*	*R*	%	*N*	*R*	%	*N*	*R*	%	*N*	*R*	%
Hiroshima																
Control	0	825	5	0.6	145	0	0.0	209	0	0.0	243	2	0.8	228	3	1.3
0.01–0.09	0.05	180	3	1.7	35	0	0.0	41	2	4.9	47	1	2.1	57	0	0.0
0.10–0.49	0.22	168	2	1.2	24	0	0.0	51	2	3.9	46	0	0.0	47	0	0.0
0.50–0.99	0.64	37	4	10.8	5	0	0.0	14	4	28.6	14	0	0.0	4	0	0.0
1.00–1.99	1.23	17	7	41.2	0	0	0.0	8	5	62.5	7	2	28.6	2	0	0.0
2.00+	2.91	2	1	50.0	1	0	0.0	1	1	100.0	0	0	0.0	0	0	0.0
Total		1229	22	1.8	210	0	0.0	324	14	4.3	357	5	1.4	338	3	0.9
Nagasaki																
Control	0	243	4	1.6	60	1	1.7	46	2	4.3	65	0	0.0	72	1	1.4
0.01–0.09	0.05	21	0	0.0	6	0	0.0	3	0	0.0	8	0	0.0	4	0	0.0
0.10–0.49	0.26	39	0	0.0	7	0	0.0	7	0	0.0	11	0	0.0	14	0	0.0
0.50–0.99	0.62	5	0	0.0	0	0	0.0	2	0	0.0	2	0	0.0	1	0	0.0
1.00–1.99	1.28	7	4	57.1	1	0	0.0	3	3	100.0	1	1	100.0	2	0	0.0
2.00+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total		315	8	2.5	74	1	1.4	61	5	8.2	87	1	1.1	93	1	1.1
Both cities combined																
Control	0	1068	9	0.8	205	1	0.5	255	2	0.8	308	2	0.6	300	4	1.3
0.01–0.09	0.05	201	3	1.5	41	0	0.0	44	2	4.5	55	1	1.8	61	0	0.0
0.10–0.49	0.23	207	2	1.0	31	0	0.0	58	2	3.4	57	0	0.0	61	0	0.0
0.50–0.99	0.64	42	4	9.5	5	0	0.0	16	4	25.0	16	0	0.0	5	0	0.0
1.00–1.99	1.25	24	11	45.8	1	0	0.0	11	8	72.7	8	3	37.5	4	0	0.0
2.00+	2.91	2	1	50.0	1	0	0.0	1	1	100.0	0	0	0.0	0	0	0.0
Total		1544	30	1.9	284	1	0.4	385	19	4.9	444	6	1.4	431	4	0.9

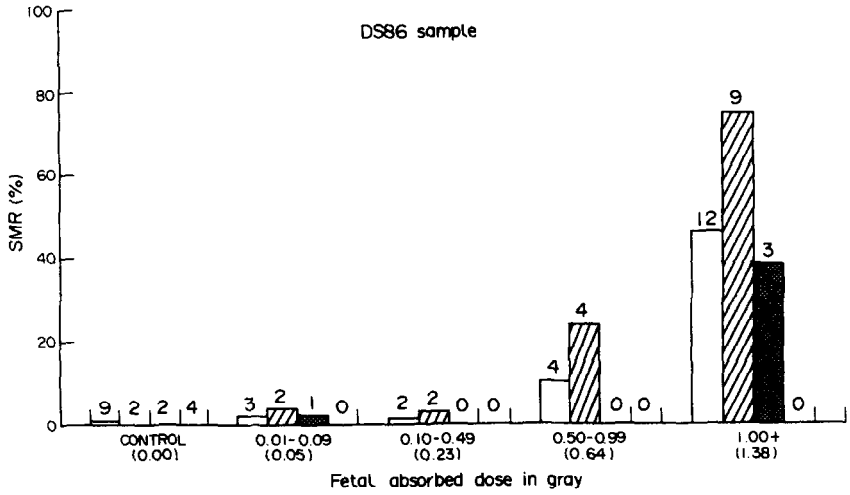

Fig. 1. The frequency of severe mental retardation among the prenatally exposed survivors of the atomic bombing of Hiroshima and Nagasaki and uterine absorbed dose. The number of cases upon which each frequency is based is indicated above the histogram. (Adapted from RERF TR 16-87, Figure 2.)

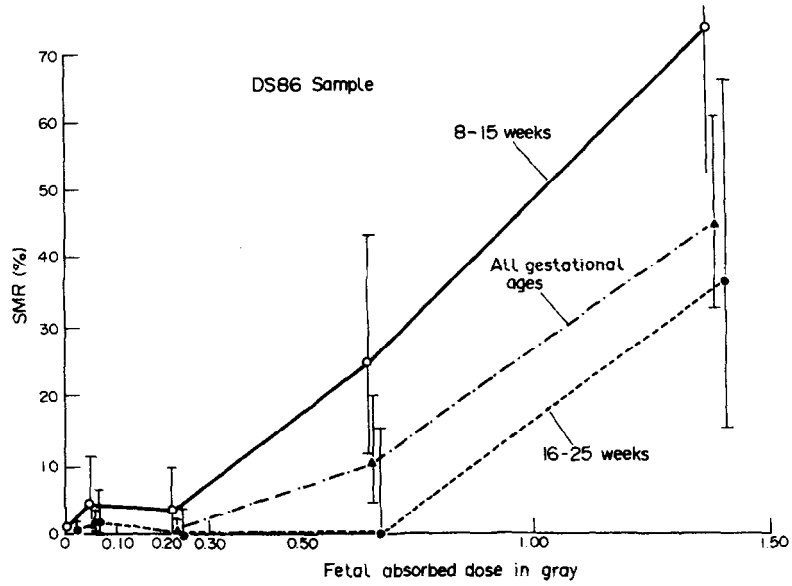

Fig. 2. The frequency of severe mental retardation among the prenatally exposed survivors in Hiroshima and Nagasaki by dose and gestational age in weeks, cities combined. (Adapted from RERF TR 16-87, Figure 3.)

First, the highest risk of severe mental retardation is seen when exposure occurred during the 8th through the 15th week after fertilisation (Otake *et al.*, 1987). As previously described, this exceptionally vulnerable period coincides with the most rapid production of neuronal elements and when all or nearly all, of the migration of the immature neurons to the cerebral cortex from the proliferating layers takes place. There is no demonstrable increased risk prior to the 8th week nor after the 25th. This should

not be construed, however, as evidence that brain damage does not occur during brain organogenesis (0–7 weeks), for it may, but be incompatible with continued survival to ages at which mental retardation can be recognised.

Second, within this critical period, damage expressed as the frequency of subsequent severe mental retardation can be suitably approximated by a linear dose–response model. Based on the atomic bomb survivor data, some forty-three percent or so of fetuses exposed to one gray in this period will be mentally retarded; this is a risk more than fifty times greater than that in the less than 0.01 Gy comparison group.

Third, a period of lesser vulnerability appears to exist in the 16th through the 25th week after fertilisation. However, here a threshold seems to exist; no increase in cases is seen at doses of less than 0.50 Gy.

Table 2 gives the intercepts and slopes obtained when a linear model, without threshold, is fitted to the data in Table 1 with and without the inclusion of the 0–0.01 Gy group (the "controls"), and when the "controls" are pooled over all prenatal ages. Within the most vulnerable age group (irradiated during the 8th through the 15th week following fertilisation), the rate of increase in incidence of severe mental retardation with dose is 0.427 Gy^{-1} with an estimated standard error of 0.087 Gy^{-1} when all "controls" are combined (see Table 2a).

Three of the severely mentally retarded children, all in Hiroshima (estimated uterine absorbed doses: 0, 0.29, and 0.56 Gy), are known to have, or have had (1 is dead), Down's Syndrome. A fourth, also in Hiroshima (estimated uterine absorbed dose 0.03 Gy), had Japanese B encephalitis in infancy, and a fifth, in Hiroshima had a retarded sibling (dose 0 Gy). It is conceivable that, in these instances, the mental retardation was merely a part of the former syndrome or secondary to the infection or inherited, but in any event not radiation-related. Virtually the same regression coefficients were obtained when these five children were excluded from the analysis; the increase at 1 Gy is now 0.396 and the standard error is 0.088 (see Table 2b, combined "controls"). Thus the main conclusions are not dependent upon the inclusion or exclusion of these individuals.

2.1.4. *Findings related to small head size*

As previously stated, the small head sizes were two or more standard deviations below the mean head size of all of the individuals in the study sample. About ten percent of the individuals with small head sizes were also mentally retarded, specifically 8 of some 71 (Wood *et al.*, 1965). Among the mentally retarded, as earlier noted, 18 out of 30 (60%) had small head sizes (Wood *et al.*, 1965). Head circumference was not standardised against body size, and since mental retardation is often seen in individuals whose head circumferences are disproportionately small for their body sizes, the value just cited may be spuriously low. The development of the bones forming the cranial vault is closely associated with the development of the brain and dura, and it is known that in fetal life these bones move with the growing brain. It is not clear, therefore, how independent the development of small head size may be of the severe mental retardation. However, glial cells retain their proliferative ability and could replace lost tissue mass as D'Amato and Hicks have observed experimentally (D'Amato and Hicks, 1965). It is known, too, that following chemical injury to the brain there is a dramatic increase in the production of glial fibrillary acidic protein, an astrocyte-localised protein, suggesting an injury related gliosis (Brock and O'Callaghan, 1987). Thus, conceptually brain volume could remain the same and head size develop normally, but cortical function would be diminished.

Table 2a. Linear dose–response relationship of severe mental retardation to grouped DS86 uterine absorbed doses including those persons with probable non-radiation-related mental retardation. (Adapted from RERF TR 16-87, Table 3a)

Gestational age	Cities combined						Hiroshima only					
	a	b	s_b	χ^2_{Reg}	χ^2_{RES}	P_{Res}	a	b	s_b	χ^2_{Reg}	χ^2_{RES}	P_{Res}
A. Relationship to uterine absorbed dose												
All ages	0.736	0.166	0.038	19.01[a]	13.74	<0.01	0.558	0.166	0.043	15.24[a]	7.38	0.06
8–15 weeks	0.747	0.429	0.088	24.17[a]	4.78	0.19	0.214	0.360	0.076	22.58[a]	4.47	0.21
16–25 weeks	0.608	0.095	0.054	3.12	6.90	0.08	0.794	0.073	0.053	1.92	4.48	0.21
B. Relationship to uterine absorbed dose when the "controls" are excluded												
8–15 weeks	0.239	0.441	0.097	20.50[a]	4.89	0.09	0.921	0.398	0.104	14.53[a]	2.87	0.24
16–25 weeks	0.375	0.100	0.060	2.83	6.86	0.03	0.670	0.076	0.057	1.74	4.51	0.10
C. Relationship to uterine absorbed dose when all "controls" are combined												
Pooled control (8–15 weeks)	0.832	0.427	0.087	24.02[a]	4.78	0.19	0.611	0.406	0.091	19.78[a]	2.98	0.39

χ^2_{Reg} has one degree of freedom; χ^2_{Res} has three (A and C) or two (B) degrees of freedom. P_{Res} is the probability (two-tailed) of exceeding the χ^2_{Res} by chance under the null hypothesis. a is the estimated number (intercept) of cases of mental retardation (per 100 individuals) in the 0 Gy group. b is the increase in the frequency of severe mental retardation with dose expressed in gray and s_b its standard error.

[a] Significant at the 1% level.

Table 2b. Linear dose–response relationship of severe mental retardation to grouped DS86 uterine absorbed doses after the exclusion of those five persons with probable non-radiation-related mental retardation. (Adapted from RERF TR 16-87, Table 3b)

Gestational age	Cities combined						Hiroshima only					
	a	b	s_b	χ^2_{Reg}	χ^2_{RES}	P_{Res}	a	b	s_b	χ^2_{Reg}	χ^2_{RES}	P_{Res}
A. Relationship to uterine absorbed dose												
All ages	0.550	0.149	0.036	17.13[a]	17.04	<0.01	0.321	0.146	0.040	13.45[a]	9.53	0.02
8–15 weeks	0.738	0.394	0.089	19.54[a]	6.95	0.07	0.180	0.258	0.066	15.38[a]	8.90	0.03
16–25 weeks	0.241	0.086	0.048	3.13	7.60	0.06	0.302	0.067	0.047	2.01	4.74	0.19
B. Relationship to uterine absorbed dose when the "controls" are excluded												
8–15 weeks	0.185	0.407	0.099	17.03[a]	7.10	0.03	0.794	0.359	0.105	11.73[a]	4.51	0.10
16–25 weeks	—	—	—	—	—	—	—	—	—	—	—	—
C. Relationship to uterine absorbed dose when all "controls" are combined												
Pooled control (8–15 weeks)	0.648	0.396	0.088	20.02[a]	6.95	0.07	0.370	0.371	0.092	16.08[a]	4.78	0.19

[a] Significant at the 1% level.

2.1.5. *Findings related to intelligence tests*

Intelligence has been variously described as the ability to manage oneself and one's affairs prudently; to combine the elements of experience; to reason, compare, comprehend, use numerical concepts and combine objects into meaningful wholes; to have the faculty to organize subject-matter experience into new patterns; or to have the aggregate capacity to act purposefully, think rationally and deal effectively with one's environment. Given such differences in definition, it is natural that the methods of measurement of intelligence should vary. Intelligence tests differ one from another in the importance given to verbal ability, psychomotor reactions, social comprehension, and so on. The score attained by an individual will, therefore, depend to some degree upon the type of test used; however, generally, individuals scoring high on one type of test tend to obtain high scores on other tests. Most intelligence tests are so structured that the distribution of test results follows an approximately normal curve, with some 95% of the population falling within two standard deviations of the mean. Individuals whose scores lie, consistently, two standard deviations or more below the mean are commonly described as retarded. In the Japanese experience, the highest IQ achieved by any of the severely mentally retarded children on the Koga test was 64.

Schull *et al.* (1988) describe an analysis of Koga intelligence test scores (Koga, 1937; Tanebashi, 1972) obtained in 1955 on survivors exposed prenatally. These results, with some additional data, are summarised in Tables 3 and 4. Table 3 relates to the whole data base, whereas Table 4 excludes those individuals who received doses of less than 0.01 Gy. Both tables illustrate the effects on the regression coefficients of test score on dose of excluding the clinically diagnosed cases of mental retardation. The data are also shown in Figure 3. The findings can be briefly summarised as follows: (1) there is no evidence of a radiation-related effect on intelligence among those individuals exposed within 0–7 weeks after fertilisation or in the 26th or subsequent weeks; (2) for individuals exposed during the 8th through the 15th week after fertilisation, and to a lesser extent those exposed in the 16th through the 25th week, the mean test scores, but not the variation in scores about the mean, are significantly heterogeneous among exposure categories (Figure 3); (3) the distribution of test scores suggests a progressive shift downwards in individual scores with increasing exposure; and (4) within the group most sensitive to the occurrence of clinically recognisable severe mental retardation, individuals exposed in the 8th through the 15th week after fertilisation, the diminution in intelligence score under the linear model is 21–29 points at 1 gray, based on the new dosimetry and the specific set of observations used (Table 4).

2.1.6. *Findings related to school performance*

As a part of the assessment of the effects on the developing embryonic and fetal brain of exposure to ionising radiation, the school performance of prenatally exposed survivors of the A-bombing of Hiroshima and a suitable comparison group have been studied (Otake *et al.*, 1988). At the time this information was collected these children were 10 to 11 years old, and most had recently completed the fourth grade. The records themselves include information on school attendance, performance in various subjects, the child's behaviour, and physical status.

In the first four years of elementary schooling the Japanese student is exposed to training in some seven different subjects ranging from language through science to physical education. Each student is scored on his or her performance in each subject

Table 3. Mean intelligence score (Koga) by age at exposure and grouped uterine absorbed doses. All individuals on whom data are available are tabulated, including the mentally retarded. (Adapted from RERF TR 3-88, Table 3a)

Gestational age	Dose categories (Gy)						P^a (df_1, df_2)
	< 0.01	0.01–0.09	0.10–0.49	0.50–0.99	1 +	All	
Clinical subsample based on DS86							
0–7 weeks							
N	142	21	13	1	2	179	0.19
Mean	106.2	109.1	97.9	115.0	95.0	105.9	
SD	14.76	16.62	12.68	—	42.43	15.25	
8–15 weeks							
N	171	39	34	7	5	256	< 0.01
Mean	107.3	110.5	102.4	90.6	69.2	105.9	
SD	14.57	17.01	14.27	22.58	9.86	16.24	
16–25 weeks							
N	253	48	34	13	4	352	< 0.01
Mean	111.0	108.3	107.9	104.1	73.3	109.7	
SD	15.21	18.49	15.02	15.83	24.60	16.28	
26 + weeks							
N	299	65	41	5	5	415	0.15
Mean	108.2	103.2	106.0	101.0	105.2	107.1	
SD	15.24	16.52	14.10	12.10	21.31	15.43	
All ages							
N	865	173	122	26	16	1202	< 0.01
Mean	108.5	107.0	104.7	100.3	84.7	107.4	
SD	15.10	17.23	14.44	17.57	25.64	15.89	
PE-86 sample based on DS86							
0–7 weeks							
N	196	52	18	1	2	269	0.76
Mean	106.6	105.1	103.7	115.0	95.0	106.1	
SD	14.33	16.53	15.79	—	42.43	15.03	
8–15 weeks							
N	218	79	40	7	6	350	< 0.01
Mean	108.4	111.6	104.7	90.6	71.5	107.7	
SD	15.81	17.82	15.39	22.58	10.46	17.22	
16–25 weeks							
N	327	99	35	15	4	480	< 0.01
Mean	110.7	107.4	107.4	100.7	73.3	109.2	
SD	15.42	16.67	15.11	17.17	24.60	17.11	
26 + weeks							
N	415	105	44	5	5	574	0.19
Mean	108.2	104.4	106.5	101.0	105.2	107.3	
SD	15.47	16.85	13.92	12.10	21.31	15.67	
All ages							
N	1156	335	137	28	17	1673	< 0.01
Mean	108.7	107.1	105.8	98.8	84.6	107.7	
SD	15.38	17.14	14.81	17.84	24.83	16.08	

[a] Indicates the significance of the difference among dose means within an age-group.

The two highest dose categories were combined when the cases were few in number.

The average uterine absorbed doses, corresponding to each dose category based on the DS86 doses, are 0, 0.04, 0.23, 0.64, and 1.29 Gy for the clinical sample, and 0, 0.04, 0.23, 0.65, and 1.33 Gy for the PE86 sample, respectively.

relative to his or her class peers. Their achievement or performance in these subjects can be summarised as follows: damage to the 8–15 week fetal brain appears to be linearly related to the absorbed dose, as judged by the relationship of average school performance score to dose (see Tables 5 and 6, and Figure 4). Damage to the fetus exposed

Table 4. The regression coefficients obtained when a linear model of intelligence test score on individual uterine absorbed dose is fitted to all of the data available. (Adapted from RERF TR 3-88, Table 4a)

Gestational ages (weeks) at exposure	Regression coefficients				Mean squares about regression
	a	S_a	b	S_b	
All cases included					
Clinical subsample based on DS86					
0–7	106.0	1.170	−0.0274	0.0527	233.4
8–15	108.2	0.990	−0.2900[a]	0.0422	223.2
16–25	111.0	0.892	−0.2036[a]	0.0441	250.6
26+	107.3	0.796	−0.0420	0.0503	238.3
All	108.4	0.472	−0.1579[a]	0.0237	243.5
Heterogeneity chi square = 22.30 $p < 0.01$					
PE86 sample based on DS86					
0–7	106.1	0.941	−0.0170	0.0510	226.6
8–15	109.5	0.916	−0.2530[a]	0.0395	266.0
16–25	110.3	0.758	−0.2138[a]	0.0417	249.5
26+	107.5	0.682	−0.0469	0.0503	245.7
All	108.5	0.404	−0.1572[a]	0.0224	251.4
Heterogeneity chi square = 20.08 $p < 0.01$					
After exclusion of clinically diagnosed cases of retardation					
Clinical subsample based on DS86					
0–7	106.0	1.170	−0.0274	0.0527	233.4
8–15	108.3	0.977	−0.2501[a]	0.0508	213.1
16–25	110.6	0.894	−0.0976[b]	0.0566	245.3
26+	107.4	0.789	−0.0444	0.0498	233.5
All	108.3	0.467	−0.1021[a]	0.0264	236.1
Heterogeneity chi square = 11.82 $p < 0.01$					
PE86 sample based on DS86					
0–7	106.1	0.941	−0.0170	0.0510	226.6
8–15	109.5	0.905	−0.2100[a]	0.0450	257.0
16–25	110.1	0.761	−0.1329[a]	0.0522	246.8
26+	107.6	0.678	−0.0487	0.0500	242.2
All	108.4	0.401	−0.1095[a]	0.0247	246.1
Heterogeneity chi square = 9.96 $p = 0.02$					

[a] $0.01 > p$.
[b] $0.05 < p < 0.10$.
[c] $0.05 > p$.

at 16–25 weeks after fertilisation is similar to that seen in the 8–15 week group. This trend appears slightly stronger, however, in the earliest years of schooling, suggesting the possibility of some amelioration of the effect with time. In the groups exposed within 0–7 weeks or 26 or more weeks after fertilisation, there is no evidence of a radiation-related effect on scholastic performance. As will be noted, these results parallel those previously found in prenatally exposed survivors with respect to achievement in standard intelligence tests in childhood.

2.1.7. *Convulsions*

Seizures are a frequent sequela of impaired brain development, and therefore, could be expected to affect more children with radiation-related brain damage than children without. Dunn and her colleagues (1988) have described the incidence, and type, of

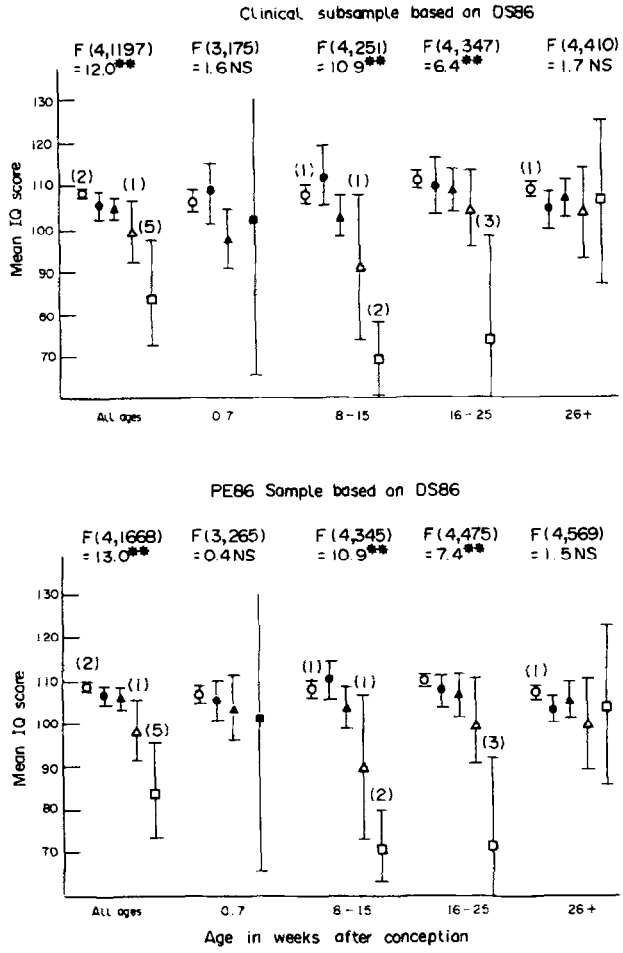

Fig. 3. Mean IQ score and 95% confidence limits by gestational age in weeks and uterine absorbed dose. The numbers in parentheses refer to the number of cases severely mentally retarded. (Adapted from RERF TR 3-88, Figure 3.)

seizures among survivors prenatally exposed to the atomic bombing of Hiroshima and Nagasaki, and their association with specific gestational ages at the time of irradiation. Histories of seizures were obtained at biennial routine clinical examinations starting at the age of two years. These clinical records were used to classify seizures as febrile or unprovoked (without an identifiable precipitating cause).

Seizures were not recorded among individuals exposed prior to the 8th week after fertilisation at doses higher than 0.10 Gy. After irradiation during the 8th through the 15th week, the incidence of seizures was highest among individuals with doses exceeding 0.10 Gy and was linearly related to the level of uterine exposure. This obtained for all seizures without regard to the presence of fever or precipitating causes, and for unprovoked seizures. When the 22 cases of severe mental retardation were excluded, the increase in seizures was only suggestively significant ($0.10 > p > 0.05$) and then only for unprovoked seizures. After exposure at earlier or later stages of development, there was no increase in recorded seizures.

Table 5. The regression coefficients obtained when a linear model of the average of the school performance score on individual uterine absorbed dose is fitted to all of the data without exclusion of the cases of mental retardation. (Adapted from RERF TR 2-88, Table 6b)

Gestational ages (weeks) at exposure	Number of cases	Regression coefficients				Mean squares about regression
		a	S_a	b	S_b	
		First grade				
0–7	106	3.09	0.082	0.0023	0.0032	0.67
8–15	225	2.86	0.057	−0.0115[a]	0.0022	0.63
16–25	267	3.03	0.051	−0.0097[a]	0.0024	0.60
26+	323	3.11	0.048	0.0023	0.0036	0.66
All	921	3.03	0.028	−0.0070[a]	0.0014	0.67
		Heterogeneity chi square = 20.48 $p < 0.01$				
		Second grade				
0–7	107	3.09	0.087	0.0036	0.0034	0.77
8–15	224	2.86	0.056	−0.0127[a]	0.0022	0.60
16–25	268	3.05	0.051	−0.0096[a]	0.0024	0.62
26+	324	3.16	0.048	0.0001	0.0036	0.68
All	923	3.05	0.029	−0.0076[a]	0.0014	0.69
		Heterogeneity chi square = 21.34 $p < 0.01$				
		Third grade				
0–7	107	3.11	0.097	0.0012	0.0038	0.95
8–15	221	2.86	0.060	−0.0117[a]	0.0025	0.69
16–25	265	3.02	0.055	−0.0101[a]	0.0025	0.69
26+	319	3.10	0.049	−0.0006	0.0037	0.70
All	912	3.02	0.030	−0.0074[a]	0.0015	0.75
		Heterogeneity chi square = 12.62 $p < 0.01$				
		Fourth grade				
0–7	56	2.78	0.108	−0.0172[b]	0.0084	0.57
8–15	204	2.88	0.064	−0.0095[b]	0.0042	0.71
16–25	260	3.03	0.054	−0.0109[a]	0.0026	0.65
26+	321	3.13	0.048	−0.0035	0.0032	0.66
All	841	3.02	0.030	−0.0089[a]	0.0018	0.68
		Heterogeneity chi square = 4.42 $p = 0.22$				

[a] $0.01 > p$.
[b] $0.05 > p$.
[c] $0.05 < p < 0.10$.

The risk ratios for unprovoked seizures, following exposure within the 8th through the 15th week after fertilisation, are 4.4 (90% confidence interval: 0.5–40.9) after 0.10–0.49 Gy and 24.9 (4.1–191.6) after 0.50 or more Gy when the mentally retarded are included; and 4.4 (0.5–40.9) and 14.5 (0.4–199.6), respectively, when they are excluded.

It is not clear which of these analyses, that based on the inclusion or the exclusion of the mentally retarded, should be given the greater weight. The choice hinges ultimately on the mechanisms underlying the occurrence of seizures and mental retardation following prenatal exposure to ionising radiation. If seizures can arise by two independent mechanisms, both possibly dose related, one of which causes seizures and the other mental retardation in some individuals who are then predisposed to develop seizures, the mentally retarded must necessarily be excluded to explore the dose–response relationship associated with the first mechanism. If, however, mental retardation and seizures arise from a common brain defect, which manifests itself in some

Table 6. The regression coefficients obtained when a linear model of the average of the school performance score on individual uterine absorbed dose is fitted to the data after the exclusion of the cases of mental retardation. (Adapted from RERF TR 2-88, Table 7b)

Gestational ages (weeks) at exposure	Number of cases	Regression coefficients				Mean squares about regression
		a	S_a	b	S_b	
		First grade				
0–7	106	3.09	0.082	0.0023	0.0032	0.67
8–15	216	2.86	0.058	−0.0066[a]	0.0036	0.62
16–25	263	3.04	0.051	−0.0081[b]	0.0026	0.59
26+	322	3.12	0.047	0.0022	0.0036	0.65
All	907	3.03	0.028	−0.0032[c]	0.0016	0.65
		Heterogeneity chi square = 9.65 $p = 0.02$				
		Second grade				
0–7	107	3.09	0.087	0.0036	0.0034	0.77
8–15	216	2.86	0.057	−0.0084[c]	0.0036	0.60
16–25	265	3.05	0.051	−0.0089[b]	0.0027	0.61
26+	323	3.16	0.048	−0.0002	0.0036	0.67
All	911	3.05	0.029	−0.0040[c]	0.0016	0.67
		Heterogeneity chi square = 10.89 $p = 0.01$				
		Third grade				
0–7	107	3.11	0.097	0.0012	0.0038	0.95
8–15	215	2.86	0.061	−0.0069[a]	0.0038	0.68
16–25	262	3.02	0.054	−0.0086[b]	0.0028	0.68
26+	318	3.11	0.049	−0.0007	0.0037	0.69
All	902	3.02	0.030	−0.0043[b]	0.0017	0.73
		Heterogeneity chi square = 5.85 $p = 0.12$				
		Fourth grade				
0–7	56	2.78	0.108	−0.0172[c]	0.0084	0.57
8–15	204	2.88	0.064	−0.0095[c]	0.0042	0.71
16–25	258	3.04	0.053	−0.0105[b]	0.0027	0.64
26+	320	3.13	0.047	−0.0037	0.0032	0.65
All	838	3.02	0.030	−0.0086[b]	0.0018	0.67
		Heterogeneity chi square = 3.93 $p = 0.27$				

[a] $0.05 < p < 0.10$.
[b] $0.01 > p$.
[c] $0.05 > p$.

instances as mental retardation and in others as seizures, the mentally retarded should not be excluded. At present the only evidence arguing for a common developmental defect is the occurrence of ectopic gray areas in some instances of both disorders (Layton, 1962; Schull *et al*, 1989). But, this evidence is difficult to put into perspective, for while it is known that ectopic gray areas occur among some of the radiation-related instances of mental retardation, the observation of ectopia in individuals with seizures is based on other studies. There has been no investigation of the frequency of occurrence of ectopic gray matter among the prenatally exposed survivors with seizures but no mental retardation.

2.1.8. *Findings related to neuromuscular performance*

Recently the studies of the prenatally exposed survivors in Hiroshima and Nagasaki have been extended to include two measures of neuromuscular performance—grip

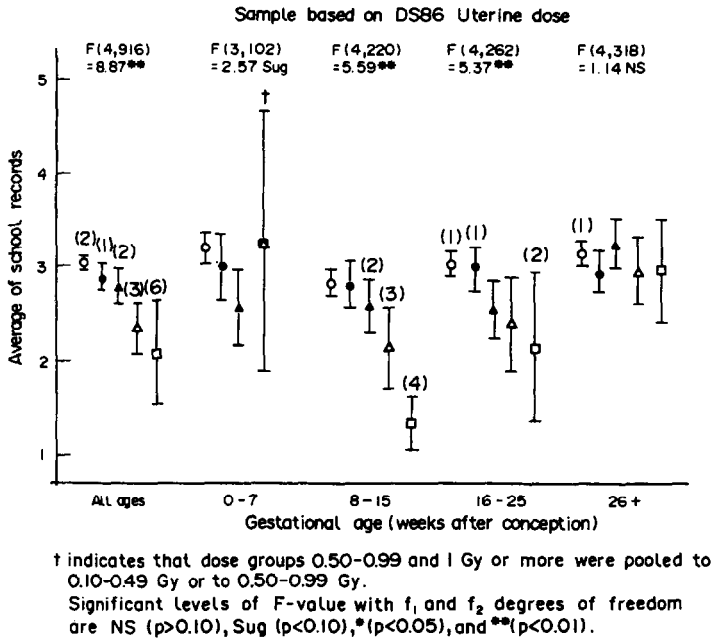

Fig. 4. Average school subject score in the first grade with the 95% confidence limits by gestational age in weeks and uterine absorbed dose. The numbers in parentheses refer to the number of cases severely mentally retarded. (Adapted from RERF TR 2-88, Figure 2.)

strength and fine motor coordination (Yoshimaru *et al.*, 1989). Grip strength involves the progressive contraction of a number of the larger muscles of the forearm and hand; whereas the repetitive action test involves the rapid contraction and relaxation of a large number of small muscles. Performances on both tests are influenced to some degree by the sex of the individual and his or her body size. Accordingly, these sources of variation have been taken into account either through the regression model used or through standardisation of all of the variables of interest except dose prior to analysis. The number of children with all of the requisite observations, i.e. who have data on the two neuromuscular tests, a DS86 dose, weight, stature, sitting height and chest circumference, is 888, including 15 cases of severe mental retardation.

The findings are as follows:

(a) When the cases of severe mental retardation are included in the analysis, an effect of prenatal exposure to ionising radiation on both of the tests is demonstrable only for individuals exposed in the 8th through the 15th week following fertilisation. The regression coefficients for absorbed uterine dose (Gy) are -0.691 (± 0.244) for the grip test score and -1.316 (± 0.234) for the repetitive action test score, when the scores are expressed in standardised units.

(b) When the results of a multiple regression analysis are considered, taking into account the body size measurements, no effect of exposure to radiation is seen in the grip test score save that explicable in terms of a reduction in individual body size. This is not true, however, for the repetitive action test score where the removal of body size differences does not alter the apparent effect of radiation.

(c) When the mentally retarded cases are excluded from the analysis, no significant

effect of absorbed dose on either neuromuscular test score is seen in any gestational age group although the regression coefficients are still negative in the interval from the 8th week through the 15th following fertilisation, and the probability level for the repetitive action test is 0.08 (one-tailed). Two observations seem warranted here. First, exclusion of the mentally retarded, who invariably do poorer on both tests than the average child (see Figure 1 in Yoshimaru *et al.*, 1989), considerably diminishes the power of the tests employed since such a high proportion of individuals exposed to 1 Gy or more are retarded. Second, it should be noted that, as Pierce *et al.* (1989) have pointed out, the presence of non-systematic errors in the individual dose estimates for the A-bomb survivors results in underestimation of radiation effects in dose–response analyses, and, in the specific case of the linear excess risk for cancer mortality, unbiased estimates are about 5%–15% greater than the estimates making no allowance for such errors. Presumably the same obtains with respect to the various estimates of radiation-related risk presented here.

The reasonableness of the findings we have described, indeed the justification for presuming that they might reflect cerebral or cerebellar damage, can only be seen in the nature and origin of the innervation of the muscles required in the respective tests. Eight muscles appear to be involved in the activities of the thumb (Moore, 1980). Innervation of these is largely through the recurrent branch of the median nerve. Grip involves a larger number of muscles, including those of the digits and forearm, and multiple nerves supply the innervation. In both instances, the pathways of stimulation are through the brachial plexus, the spinal cord, and ultimately the motor cortex. The latter is situated anteriorly to the sylvan fissure separating the frontal from the temporal and parietal lobes of the brain.

Why should there appear to be a stronger, indeed an almost two-fold greater radiation-related effect on one of these measures of neuromuscular performance than on the other, if the apparent difference in effect that is seen is real? A variety of explanations can be pursued, but possibly the most attractive involves the relative number of neurons in the motor cortex required to effect fine motor control, on the one hand, as opposed to activities requiring larger muscle masses, on the other. It is known, for example, that the innervation ratio, the ratio of the number of motor neurons, on average, supplying a muscle to the number of muscle fibers within the muscle, is much smaller in the case of massive axial muscles supporting the torso, than in the innervation of the extraocular muscles (about 1 neuron per 1000 muscle fibers in the former instance, and 1 to 3 in the latter). Thus, although the muscle mass involved in the grip test is larger than that in repetitive action of the thumb, it does not follow that the number of neurons involved in innervation is also greater. Indeed, it is known that a disproportionate number of the neurons in the motor cortex are allocated to the control of muscles involved in the most precise movements (Evarts, 1984). There is also evidence that rapid, but goal-oriented responses, such as the repetitive action test, in contradistinction to the grip, involve not only the motor cortex, but also the cerebellum, the premotor cortex and possibly other structures as well (Evarts, 1984). Thus the seemingly greater sensitivity to radiation damage in the one instance, the repetitive action test, than in the other, grip strength, may reflect a larger population of neurons at risk of radiation damage. This is admittedly speculative, but it is not unreasonable to presume that the risk of damage is proportional to the target involved.

Finally, it is still unclear whether the various effects of radiation that have been reported are manifestations of the same or different events. Given the modest correlation

that obtains between IQ score and school performance (0.54; see Otake *et al.*, 1988), or IQ score and performance on the neuromuscular tests (less than 0.10 for the grip test, and about 0.25 for the repetitive action), and the different regions of the cerebral cortex presumably involved in the control of the endpoints measured, it seems unlikely that all of the effects are attributable to damage to precisely the same neuronal cells. A fully satisfactory answer to this issue is doubtful, however, until more is known about the cellular and molecular events involved.

2.2. Uncertainties

Many uncertainties are associated with these estimates of risk. They include the limited nature of the data, especially on mental retardation and convulsions, the appropriateness of the comparison group, errors in the estimation of the tissue absorbed doses and the prenatal ages at exposure, and other confounding factors in the post-bomb period, including nutrition, disease and radiation-related hematopoietic damage to the mother and (or) her developing child, which could play a role. The possible importance of these factors has been discussed elsewhere (see ICRP, 1986; Mole, 1990a,b, for some of the limitations inherent in the endpoints measured). Suffice it here to state that no fully satisfactory assessment of their contributions, singly or collectively, to the observed frequency of brain damage can be made at this late date. Given the present uncertainties, since most of these extraneous sources of variation would have a greater impact at high than low doses, and produce a concave upwards dose–response function, the prudent course would be to assume that the dose–response relationship is not materially altered other than additively by these potential confounders. This would have the effect of overestimating the risk at low doses where greatest regulatory concern exists.

Three issues do warrant further discussion here; they are: the shape of the dose–response function, the existence of a threshold in the dose–response, and the effects of dose fractionation.

2.2.1. *The dose–response function*

Within the period of maximum vulnerability, virtually without exception, the data presented can be satisfactorily approximated by more than one dose–response function, generally a linear or a linear-quadratic model. Given that a variety of biologic events, e.g. neuronal death, mismanaged migration, and faulty synaptogenesis, could play a role in the occurrence of mental retardation or cortical dysfunction more generally, and that each could have its own different dose–response relationship, there is little or no prior basis for presuming that one or the other of these models better describes the biological events involved. The "true" model, therefore, remains a matter of conjecture, and it seems unlikely that epidemiological studies alone will ever be able to determine what the "true" model may be. Perforce the estimation of risk must rest on a series of considerations, not all of which are biological.

2.2.2. *Is there a threshold?*

Although a linear or a linear-quadratic dose–response relationship describes the observed frequency of severe mental retardation in the 8th through the 15th week adequately, inspection of Figures 1 and 2 indicates that there could be a threshold with the DS86 dosimetry. As Otake *et al.* (1987) have shown, the estimation of the value of this presumed threshold depends upon whether the cases of mental retardation

presumably attributable to causes other than ionising radiation are or are not included in the analysis. When all of the cases of mental retardation are included, the lower bound of the estimated threshold includes zero, that is to say, a threshold cannot be shown to exist by statistical means. If, however, the two cases of Down's syndrome in the 8–15 week period are excluded, the 95% lower bound of the threshold appears to range from 0.12, when the dose data are grouped, to 0.23 Gy, when individual doses are used. It should be noted that the imposition on the data of a linear model with a threshold gives rise to a rate of increase with dose that predicts virtually every fetus exposed to one gray or more will be retarded. This is at variance with the actual observations, but this would not necessarily be true if a curvilinear model with a threshold were fitted. When exposure occurs in the 16th through the 25th week, the DS86 dosimetry suggests a threshold of 0.64 (doses grouped) to 0.70 Gy (individual doses) with a lower 95% bound of 0.21 Gy in both instances.

The presence of a threshold at 16–25 weeks, but its uncertainty in the 8–15 week period is not necessarily contradictory. These differences are consistent with the supposition that the biological events involved in the induction of mental retardation are different in the earlier period of development than the later. In the first instance the neuronal cells are largely immature, undifferentiated; whereas in the second, when neuronal production lags and migration has been largely completed, the cortical cells at risk are differentiating or already differentiated. And it is known that differentiated cells are less vulnerable to ionising radiation than immature ones.

These estimates of a threshold are not inconsistent with experimental findings, but the latter too are somewhat confusing. For example, Kameyama *et al.* (1978) suggested that the threshold for mitotic delay in the developing telencephalon of the day 13 mouse embryo, corresponding roughly to 9 weeks after fertilisation in the human, was slightly lower than 0.1 Gy. However, recently, Hoshino and Kameyama (1988) have examined the developmental stage-dependent radiosensitivity of neural cells in the ventricular zone of the telencephalon of mouse and rat fetuses, and have demonstrated that the dose–response relationship for the appearance of pycnotic cells is linear in the dose range lower than 0.24 Gy. It is difficult to put these two observations into a common perspective, since mitotic delay is not necessarily related to cell death nor is the appearance of pycnotic cells an unequivocal testimony to real brain damage. Konermann (1987) has postulated a threshold of 0.125 Gy in the mouse based on the decrease in post-natal diameter of brain structures such as the corpus callosum. Patently, the issue of the presence or absence of a threshold, particularly in the 8–15 week period, cannot as yet be resolved with either the epidemiological or experimental information at hand. Under these circumstances, the prudent course, particularly from the regulatory perspective, would be to assume there is no threshold, since at lower doses, where the evidence of an effect is weakest, risk is apt to be overestimated.

2.2.3. *Dose fractionation*

Little is known about the effects on the developing human embryo and fetus of chronic or fractionated exposures to ionising radiation. Given the complexity of brain development and the differing durations of specific developmental phenomena, it is reasonable, however, to assume that dose fractionation will have some effect. The hippocampus, for example, and the cerebellum continue to have limited neuronal multiplication, and migration does occur in both organs. Changes continue in the hippocampus and cerebellum into the first and second years of life. Continuing events such as these may

show dose-rate effects differing from those associated with the multiplication of cells of the ventricular and subventricular areas of the cerebrum, or the migration of neurons to the cerebral cortex.

Most of the information available on the effects of dose rate involves the experimental exposure of rodents, and must be interpreted with due regard to the differences between species in developmental timing and rates relative to birth. Brizzee and Brannon (1972; see also Jacobs and Brizzee, 1966) have examined cell recovery in the fetal brain of rats. The incidence and severity of tissue alterations generally varied directly with dose, and were clearly greater in single dose than in split dose groups with the same total exposure. Presumably, the same would obtain with regard to the developing human brain, and that the risk of damage to the brain from protracted doses would be less than that seen with the acute exposures in Hiroshima and Nagasaki. However, neither of the studies cited nor others provide a clear basis for the estimation of a dose rate effectiveness factor.

2.3. Exposure *In Utero*: Other Human Data

Numerous studies aimed at an understanding of the possible role of ionising radiation in the origin of central nervous system abnormalities have been published (Goldstein and Murphy, 1929; Murphy, 1947; see also Rose, 1989), but few, aside from the Japanese experience, provide a reliable basis for risk estimation. Generally, there is little information on the exposures, or on the ages after fertilisation at the time of exposure. However, Granroth (1979), in Finland, has examined the association of diagnostic x-ray examinations with the occurrence of defects of the central nervous system. The data, drawn from the Finnish Registry of Congenital Malformations, reveal a significant increase in central nervous system abnormalities, primarily anencephaly, hydrocephaly, and microcephaly, among newborn infants exposed *in utero*, when contrasted with time-area-matched control subjects. No estimate is given of the fetal absorbed dose. Moreover, as the author notes, the majority of these infants were exposed because of the clinical suspicion of either maternal pelvic or fetal anomaly and, therefore, the exposures were unlikely to have occurred at a time when abnormalities, such as anencephaly, could be induced (Muller and O'Rahilly, 1984). Accordingly, it seems unlikely that the results reflect a teratogenic effect of radiation.

Neumeister (1978) has described the findings on 19 children exposed *in utero* to doses between 0.015 and 0.1 Gy. No instances of severe mental retardation are recorded, but developmental age at the time of exposure was not taken into consideration. Meyer and colleagues (Meyer *et al.*, 1976) failed to find evidence of an increased frequency of severe mental retardation among 1455 women who were exposed to small doses of radiation *in utero* as a result of diagnostic pelvic examinations of their mothers. It seems uncertain, however, whether their case-finding mechanism would have identified women who were severely mentally retarded, and, of course, the increased probability of premature death among such individuals would lead to under representation of the retarded later in life. In addition, exposure must commonly have occurred late in pregnancy, after the most vulnerable period. Other studies, such as those of Oppenheim *et al.* (1976) and Nokkentved (1968), have similar limitations for the estimation of radiation effects.

More recently, Sever and his colleagues (Sever *et al.*, 1988a,b) have examined the prevalence of congenital malformations in communities near the Hanford site presumably exposed to low levels of ionising radiation. Although they report an increased frequency of neural tube defects, which they are inclined to ascribe to non-radiation

related factors, they do not describe an increased frequency of mental retardation. It should be noted, however, that the focus of this study was upon birth records, and mental retardation would not normally be diagnosed sufficiently early to be reported on such records nor during the usual postpartum hospital stay, save in exceptional circumstances.

3. THE BIOLOGICAL NATURE OF THE DAMAGE TO THE BRAIN

Could this apparent association of mental retardation and the other measures of cortical dysfunction with exposure be fortuitous? What basis is there for presuming the effects to be real? What, in fact, do we know about the biological bases of the effects on the developing brain that we see? And can we distinguish between several alternative explanations for their occurrence? It has been suggested, for example, that the distribution of cases of severe mental retardation among the prenatally exposed survivors in Hiroshima and Nagasaki could be explained either on the basis of a large radiation-related effect on a relatively small number of survivors (presumably more inherently susceptible to radiation damage), or a small effect on virtually every survivor, an effect that merely shifts downward the normal distribution of functional potentials. Although these are not mutually exclusive alternatives, they suggest different susceptibilities to and possibly different mechanisms for brain damage following exposure to ionising radiation.

As yet we know far too little about the cellular and molecular events involved in corticogenesis to do more than speculate on the origin of the effects that are seen. Thus far the most informative insights have come either from autopsy examinations or from the use of magnetic resonance imaging, a recently introduced non-invasive means of visualising the living brain. Briefly, these studies reveal the following:

Four prenatally exposed survivors who have died have come to autopsy. Two were mentally retarded and two were not. All were exposed but only one received a dose in excess of 10 mGy. In the two with normal intelligence, the brains were of normal weight and the architecture appeared normal on visual inspection and microscopically. Both of the mentally retarded, however, had brain weights substantially below normal. One had a brain weighing 840 g and the other 1000 g; whereas the normal weight is about 1450 g. Multiple transections of the larger brain, that of a female exposed in the 31st week after fertilisation, revealed the usual pattern of gray and white matter and no evidence of swelling through the accumulation of fluid in the spaces between the brain cells. She had died at age 20 of heart failure. The other mentally retarded individual, a male with the smaller brain, died at age 16 of acute meningitis of probable viral origin. He had been exposed at 12 weeks after fertilisation. The estimated dose to his mother's uterus was approximately 1.2 Gy. Both of his eyes were abnormally small, and within each the retina was conspicuously underdeveloped, particularly near the macula. Posterior subcapsular opacities were present in both eyes. Sections across the cerebrum revealed massive amounts of gray matter around the lateral ventricles where typically there would be little. Microscopic examination of these misplaced gray areas disclosed an abortive laminar arrangement of nerve cells, imitating the usual arrangement of the cortical neurons. The cerebellum and the hippocampi were normal visually and upon microscopic study. Misplaced gray matter was not observed in any of the other three autopsied cases, including the second mentally retarded individual.

Magnetic resonance imaging suggests several different probable causes of the mental retardation in the prenatally exposed. Although the number of individuals that have been studied is small, several different anomalies of development have been seen, and these correlate well with what is known of the embryological events transpiring at the time of

the exposures of the individuals. Among two survivors exposed at eight weeks following fertilisation, there is evidence of a failure of the neurons to migrate from the proliferative zone to their proper functional sites, and one of these individuals at least exhibits an underdeveloped area in the left temporal region. While ectopic gray matter has been seen in other instances of mental retardation not related to exposure to ionising radiation, the nature of the migratory error appears different. In the cases we describe, the failure is bilateral; whereas in non-radiation-related mental retardation it often involves only one side of the brain.

Two individuals exposed in the 12th to 13th week, that is, after completion of the initial wave of neuronal migration and late in the second, have been studied. Neither exhibits conspicuous ectopic areas, but the brain architecture is abnormal. In both instances, a mild macrogyria occurs, and there was a distinct abnormality in the cisterna magna. One of the cases exhibited a corpus callosum markedly smaller than normal, and a poorly developed cingulate gyrus suggesting an aberration in the development of the band of association fibers that passes over the corpus callosum. In the other case, the cingulate gyrus appears normal, but whether the corpus callosum is or is not normal is uncertain since sagittal sections of the brain were not obtained. Still later in development, at the 15th week, neither migrational errors nor conspicuous changes in brain architecture are seen. We presume, therefore, that the functional impairment that exists must be related to the connectedness that occurs between neurons. There is experimental evidence to show that exposure at this time in the development of the brain in other primates leads to a diminished number of connections between neuronal cells. If we presume that all of the connections have functional significance, then the diminution must compromise performance in some manner. Clinical neurological assessment of these individuals was not informative; no remarkable changes were seen but this undoubtedly reflects the coarseness of the usual clinical examination which is designed largely to reveal gross changes in coordination.

These observations, although biologically intriguing, still do not provide enough information to develop a coherent radiobiological model. Nor do they tell us the magnitude of the neuronal damage that is necessary to produce a measurable effect. However, Rakic (1988a,b) has argued that the cortex is a collection of developmental columns each arising from a specific proliferative unit. Substantial data can be mustered to support this contention. For example, Mountcastle (1979) has shown that the neurons within a single column in that portion of the cortex involved in the processing of sensory perceptions that arise elsewhere (the somatosensory cortex) are responsive to a specific modality and receptive field of stimulation. Other sensory and association areas in the cortex are now known to behave similarly. It is thought that those columns innervated by a single thalamic nucleus (subnucleus or cell cluster) serve as a basic processing module. To the extent that this perception of cortical organisation and function is correct, the loss of a few cells, conceivably even a single cell, could result in the loss or compromise of specific somatosensory or association abilities if that loss occurs in the formative periods for these processing modules. Clearly much more must be learned before it will be possible to base dose–response models on a sound understanding of the developmental processes at risk.

4. RISK ESTIMATES IN HUMANS

Quantitative risk estimates for radiation damage to the brain after prenatal exposure of

human beings are of importance for their practical implications to radiobiological protection. However, the human data on which to base such estimates are still limited and imperfect, and the bulk of the evidence stems from a single study, that of the prenatally exposed survivors of the bombing of Hiroshima and Nagasaki. Five types of observations are available on these survivors, namely, (1) the frequency of severe mental retardation recognised clinically, (2) the diminution of intelligence as measured by conventional intelligence tests, (3) scholastic achievement in school, (4) the occurrence of unprovoked seizures, and finally, (5) tests of neuromuscular performance. As a metric for radiation damage, each has its own short-comings. Although cognisant of these and other difficulties inherent in the interpretation of the available information, these observations are essentially the only ones on which risk estimates can be based. Anecdotal clinical evidence is of little assistance and experimental data, though important qualitatively, provide an uncertain basis for quantitative estimates of prenatal risks in the human.

Recent re-evaluations of these Japanese data have provided a new perspective on the periods of sensitivity of the developing brain to radiation-related damage, and the possible nature of the dose–response relationship. These findings have been described in some detail in previous sections; briefly, and as they specifically concern risk estimation, the salient observations are as follows.

The period of maximum vulnerability to radiation appears to be the time from approximately the beginning of the 8th through the 15th week after fertilisation, that is, within the interval when the greatest production of neurons and their migration to the cerebral cortex occur. A period of lesser vulnerability occurs in the succeeding eight weeks, i.e. from the 16th through the 25th week after fertilisation. The latter period accounts for about a fourth of the apparently radiation-related cases of severe mental retardation. The least vulnerable periods are those prior to the 8th week after fertilisation or subsequent to the 25th. In neither of these periods does there appear to be an increase in radiation-related cases of severe mental retardation. Within the period of maximum vulnerability, the simplest statistical model consistent with the data is a linear one without threshold. The slope of this relationship, based on the supposition that the occurrence of mental retardation is binomially distributed, corresponds to an increase in frequency of severe mental retardation of 0.43 per Gy (95% CI: 0.26–0.62). Thus, the frequency of severe mental retardation rises from about one case per hundred individuals exposed to less than 0.01 Gy to approximately 44 per hundred at an exposure of 1 Gy. Exclusion of those cases of mental retardation with probable non-radiation-related etiologies has little effect on this risk estimate (Otake *et al.*, 1987).

The data on intelligence tests, school performance, unprovoked seizures, and neuromuscular tests suggest the same two gestational periods of vulnerability to radiation, the first period showing the greatest sensitivity. More importantly, these data suggest a continuum of effects on the developing brain of exposure to ionising radiation; indeed, the downwards shift seen in the distribution of IQ scores with increasing exposure predicts reasonably well the actual increase in severe mental retardation that has been observed. This suggests, in turn, that the impact of exposure to ionising radiation will be related to where in the normal continuum of cortical function an individual would have resided if unexposed. Simply put, the loss, say, of 5 IQ points in an individual destined to have an IQ of 140 would hardly be handicapping, but a similar loss at an IQ of 75 could result in mental retardation.

At present, there is no evidence of radiation-related cerebellar damage without

concomitant damage to the cerebrum in the survivors of the bombing of Hiroshima and Nagasaki exposed prenatally. It may be difficult to identify such damage for reasons adduced elsewhere (see ICRP, 1986). Estimates of the risk of damage to the cerebellum following prenatal exposure, based on fixed or progressive neurologic deficit, are presently not possible.

Overt damage to the mid-brain and brain stem following prenatal exposure to ionising radiation has not been reported.

It should be noted that dose–response models other than a linear one, e.g. a linear-quadratic, cannot be categorically excluded with the present information, nor is it possible to assert unequivocally whether a threshold in the dose–response function does or does not exist. It must also be borne in mind that the risks cited above are conditional upon the embryo or fetus surviving the fact of exposure. Although human data are sparse, ionising radiation is known to increase the probability of the loss of a pregnancy in experimental animals, and therefore the overall risk (death or brain damage) to the embryo or fetus is actually greater than the risk of brain damage alone. The U.S. Nuclear Regulatory Commission (1989) in its projection of risk to a representative fetus exposed in the course of a nuclear power plant accident has attempted to account for these two different risks.

5. PROBLEMS IN RADIATION PROTECTION

It is fortunate, perhaps, that the evidence now at hand suggests that the greatest risk to the developing embryo or fetus surviving exposure to ionising radiation occurs in those months when the fact of pregnancy is clearly recognisable, and an adequate margin of safety can be more readily established, although denial of pregnancy even at eight weeks does occur. Nonetheless, recommendations for the protection of the pregnant woman and her developing child pose a series of difficult decisions. For example, given the uncertainties regarding the true dose–response relationship, it is a matter of judgment whether these recommendations should be based on the assumption that a threshold exists or that it does not exist. Neither the epidemiological or the experimental data nor theoretical radiobiological considerations provide a compelling argument for either assumption. Under these circumstances, prudence would seem to argue for regulatory recommendations based on the assumption of no threshold; however, the consequences of adopting such an approach are far-reaching, if too stringently applied. These range from the possible creation in the workplace of regulations that could be unintentionally discriminatory to the inadvertent establishment of a basis for litigation where, in fact, no biological risk exists. Moreover, it would imply a need for special measures to be taken for pregnant women in the event of a nuclear power facility accident involving the general population, such as prompt evacuation, and these may not be easily implemented.

In 1983, the ICRP, cognisant of the limitations of the data and the difficulties in setting a "practical" threshold, recommended that the methods of protecting pregnant women at work should provide a standard of protection for the fetus broadly comparable with that provided by protection of members of the general public. If substantial irregularities in the dose rate did not occur, under the now obsolete Working Condition B (where it is unlikely that annual exposures would exceed 3/10 of the dose-equivalent limits), this would imply that the dose received by the fetus over the critical 2 months (from 8–15 weeks) would not be expected to exceed 1 mSv. However, the Commission further recommended that specific operational arrangements should be made to avoid irregu-

larities in the rate at which the dose could be received and to keep the dose to the fetus as low as reasonably achievable. These recommendations still seem acceptable in the light of the revised dosimetry in Japan, and the further information that has accumulated on radiation-related damage to the developing brain.

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