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Updated estimates of the proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionising radiation

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Abstract

The aetiology of childhood leukaemia remains generally unknown, although exposure to moderate and high levels of ionising radiation, such as was experienced during the atomic bombings of Japan or from radiotherapy, is an established cause. Risk models based primarily upon studies of the Japanese A-bomb survivors imply that low-level exposure to ionising radiation, including to ubiquitous natural background radiation, also raises the risk of childhood leukaemia. In a recent paper (Wakeford *et al* 2009 *Leukaemia* **23** 770–6) we estimated the proportion of childhood leukaemia incidence in Great Britain attributable to natural background radiation to be about 20%. In this paper we employ the two sets of published leukaemia risk models used previously, but use recently published revised estimates of natural background radiation doses received by the red bone marrow of British children to update the previous results. Using the newer dosimetry we calculate that the best estimate of the proportion of cases of childhood leukaemia in Great Britain predicted to be attributable to this source of exposure is 15–20%, although the uncertainty associated with certain stages in the calculation (e.g. the nature of the transfer of risk between populations and the pertinent dose received from naturally occurring alpha-particle-emitting radionuclides) is significant. The slightly lower attributable proportions compared with those previously derived by Wakeford *et al* (*Leukaemia* 2009 **23** 770–6) are largely due to the lower doses (and in particular lower high LET doses) for the first year of life.

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1. Introduction

Studies of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki in 1945 and of other groups exposed to moderate or high levels of radiation have found that leukaemia is particularly sensitive to induction by ionising radiation, and that those exposed at young ages are especially at risk (NRC 2006, UNSCEAR 2008). Risk models for radiation-induced leukaemia that have been derived recently (NRC 2006, UNSCEAR 2008) using data generated from the experience of the Japanese atomic bomb survivors imply that children exposed to low doses and/or low dose-rates of radiation are at an increased risk of leukaemia and permit this increase to be quantified. There is also evidence that exposure of the foetus *in utero* to low-level radiation results in a proportional increase in leukaemia risk per unit dose received that is broadly comparable with that resulting from irradiation in early childhood (Wakeford and Little 2003, El Ghissassi *et al* 2009), although some controversy still surrounds this interpretation of the evidence (ICRP 2003a).

Exposure to low-level natural background ionising radiation is ubiquitous. All organs receive some dose including the red bone marrow (RBM), the tissue in which leukaemia is understood to originate (UNSCEAR 2000, ICRP 2007). In a recent paper (Wakeford *et al* 2009) the proportion of childhood leukaemia incidence in Great Britain resulting from this largely unavoidable exposure was calculated using two sets of recently derived risk models (NRC 2006, UNSCEAR 2008) and estimates of age-specific RBM doses that had been derived in the mid-1990s in the context of studies of childhood cancer in and around the village of Seascale in Cumbria, England (Simmonds *et al* 1995). These dose estimates have recently been revised for a typical child living in the UK using more recent dosimetric models (Kendall *et al* 2009).

In this paper we update our estimates of the proportion of childhood leukaemia caused by natural radiation using the latest dosimetry. The methodology is essentially the same as in the previous paper. It is summarised here for convenience; full details are to be found in Wakeford *et al* (2009) and in the associated supplementary material

2. Materials and methods

2.1. Risk models

Statistical models, based on the findings of epidemiological studies, have been developed to quantify the risk of radiation-induced leukaemia arising from the receipt of a given dose and how this excess risk is expressed following exposure. These empirical risk models take into account the radiation dose to the target tissue (the RBM), the shape of the dose–response relationship (linear-quadratic, curving upwards) and various risk-modifying factors (such as sex, age-at-exposure and time-since-exposure). These models reflect the large proportional increase in risk per unit dose in those exposed at a young age.

We employ two sets of recently derived risk models for radiation-induced leukaemia:

- that from the seventh report of the US Committee on the Biological Effects of Ionizing Radiations (BEIR VII) (NRC 2006), and
- that from the 2006 Report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2008).

Both sets of risk models are based upon data for leukaemia mortality over the period 1950–2000 among the Japanese atomic bomb survivors; leukaemia was almost invariably fatal in the early years of follow-up that is of relevance to childhood leukaemia. The models describe the expression over time of either the *excess relative risk* (ERR, the proportional increase in the

leukaemia risk when compared to the baseline risk in the absence of exposure) or the *excess absolute risk* (EAR, the additional leukaemia risk above the baseline risk); both sets of models adopt a minimum latent period of 2 years.

2.2. Transfer of risks between populations

Having derived leukaemia ERR and EAR estimates from the Japanese atomic bomb survivor data, the question then arises as to their applicability to other populations, in particular British children in whom the underlying leukaemia risk in recent years has been about 2 1/2 times that in Japanese children in the 1950s (Wakeford *et al* 2009). Transfer of the excess relative risk assumes that radiation interacts multiplicatively with background risk factors, whereas transfer of the excess absolute risk assumes that radiation acts additively with these factors.

The BEIR VII Committee (NRC 2006) adopted, for US children, a weighted average of the results obtained from applications of the ERR (70% weight) and EAR (30% weight) models, considering that the interaction of radiation with other risk factors was more multiplicative than additive; these would also seem to be appropriate weightings for British children when using the BEIR VII models. UNSCEAR (2008) did not make any specific recommendation on how the excess leukaemia risk should be transferred from the Japanese survivors to other populations. However, the International Commission on Radiological Protection (ICRP 2007) has judged that the leukaemia EAR alone should be transferred between populations so that only the EAR model should be used to determine the excess risk among British children. In contrast, the BEIR V Committee (NRC 1990) considered that the leukaemia ERR alone should be transferred between populations so that the pure ERR model should be applied to the population of British children. As noted by Wakeford *et al* (2009), little justification for these various schemes for transporting the leukaemia risk from the Japanese atomic bomb survivors to other populations has been given by these committees.

In our previous investigation (Wakeford *et al* 2009) we argued that, while evidence was scanty, a pure EAR transfer model appeared less plausible than either a pure ERR transfer model or the BEIR VII Committee's ERR/EAR mixing scheme that places more weight upon transfer of the ERR rather than the EAR. In this paper we place most emphasis upon the 70%ERR/30% EAR weighted models, but we also present results for both pure ERR and pure EAR models.

2.3. Childhood leukaemia incidence data

Annual numbers of registered incident cases of childhood (<15 years of age) leukaemia by sex and year of age, diagnosed during 1991–2000 while resident in Great Britain, and the derived rates of incidence during this ten year period were obtained from the National Registry of Childhood Tumours (NRCT). The NRCT is a nationwide, population-based registry of childhood cancers, maintained by the Childhood Cancer Research Group in Oxford (Stiller 2007). The figures demonstrate a rise to the expected peak in incidence at ages 2–4 years, followed by a general decrease with age (Wakeford *et al* 2009).

2.4. Age dependent doses to red bone marrow

Recently, doses to the RBM of a typical child in the UK have been estimated by Kendall *et al* (2009). The variation with age of the various components of RBM dose was considered including doses received *in utero* and in each year of age up to the fifteenth birthday. Doses received *in utero* include contributions resulting from the ingestion of radionuclides by the mother and placental transfer to the embryo/foetus. Postnatal doses include those from

radionuclides in breast milk and from radionuclides ingested in other foods. The components of dose from radionuclides were estimated using recently published ICRP models as follows.

(1) Doses *in utero* from placental transfers of radionuclides were calculated using the models of ICRP Publication 88 (ICRP 2001), and Publication 95 (ICRP 2004).
(2) Doses from radionuclides in breast milk were calculated using the models of ICRP Publication 95 (ICRP 2004).
(3) Doses from radionuclides in ingested solid food were calculated using the models of ICRP Publication 72 (ICRP 1996) and dose coefficients given in the ICRP CD (ICRP 1998).

Doses from ^{222}Rn ('radon') and ^{220}Rn ('thoron') were based on recent publications (Kendall and Smith 2005, Kendall and Phipps 2007). Kendall *et al* (2009) presented RBM doses for Type F radon decay products; if the less soluble Type M is regarded as more appropriate, the RBM doses would be somewhat lower. Kendall and Smith (2005) present data for the annual dose from radon gas and Type M decay products for a 1 year old, a 10 year old and an adult. An estimate for a 15 year old can be obtained by interpolating between the 10 year old and adult values (which are in any case very similar). For the 5 year old the contribution for radon gas published by Richardson *et al* (1991) and an interpolated value for Type M decay products after Kendall and Smith (2005) can be combined. The resulting rounded annual doses, when allowance is made for indoor occupancy are 1.5 μGy, 2 μGy, 2.5 μGy, 3 μGy and 3 μGy for a 1 year old, 5 year old, 10 year old, 15 year old and adult, respectively. These can be compared with the estimate of 4 μGy at all ages for Type F radon decay products.

The RBM absorbed doses are separated into the high linear energy transfer (LET) component, consisting predominantly of the absorbed dose received from internally deposited radionuclides emitting densely ionising alpha-particles, and the low LET component from sparsely ionising gamma rays and beta-particles. To combine these two components of the absorbed dose, a radiation weighting factor (w_R) of 20 is applied to the high LET absorbed dose to account for the greater biological damage produced by alpha-particles (the w_R for low LET radiations being 1), resulting in the RBM equivalent dose (in sievert, Sv). (As a consequence, a w_R of 20 has also been applied to the small cosmic ray neutron component of the absorbed dose from high LET radiation, which will result in a slight overestimation of the RBM equivalent dose; we ignore this small overestimate for the purposes of this paper.) The equivalent dose is a radiological protection quantity designed to take account of the relative biological effectiveness of high LET radiations at inducing the full range of stochastic health effects rather than a specific effect such as childhood leukaemia (ICRP 2003b, 2007).

Kendall *et al* (2009) found that RBM doses are somewhat higher in the first year of life and that there is a general slow decline from the second year of life onwards. The low LET component of absorbed dose to the RBM is much larger than the high LET component. However, because of the higher radiation weighting factor for the latter, alpha-particles contribute about 40% of the equivalent dose incurred up to age 15 years.

The estimates of Kendall *et al* (2009) can be compared to those published by Simmonds *et al* (1995), as used by Wakeford *et al* (2009). Simmonds *et al* estimated, by single year of age, the RBM doses received from natural background radiation by a child living in the village of Seascale on the coast of North-West England. These dose estimates would not differ substantially from those for a typical child resident in Great Britain, though gamma ray doses in Cumbria are somewhat lower than those in the UK as a whole (Simmonds *et al* 1995).

The results of Kendall *et al* (2009) and of Simmonds *et al* (1995) are broadly similar except that Kendall *et al* found that the high LET component of dose in the first year of life was ~20% higher than the average for all years, while Simmonds *et al* reported that it was almost four times higher. Possible reasons for this are discussed by Kendall *et al* (2009).

Table 1. Doses to the red bone marrow (RBM) of a typical child living in the United Kingdom from natural background ionising radiation by single year of age. High and low LET contributions to RBM absorbed dose and the RBM equivalent dose are given. The results of Kendall *et al* (2009) are compared with those of Simmonds *et al* (1995).

	Kendall *et al* (2009)			Simmonds *et al* (1995)		
	RBM absorbed dose (μGy)			RBM absorbed dose (μGy)		
Age group (years)	High LET	Low LET	RBM equivalent dose (μSv)	High LET	Low LET	RBM equivalent dose (μSv)
In utero	10	528	728	12	587	827
0	35	935	1 635	119	806	3 186
1	29	856	1 436	30	804	1 404
2	32	843	1 483	25	803	1 303
3	32	842	1 482	23	828	1 288
4	30	842	1 442	25	829	1 329
5	29	841	1 421	24	828	1 308
6	28	841	1 401	24	828	1 308
7	28	810	1 370	23	828	1 288
8	27	810	1 350	22	828	1 268
9	26	809	1 329	22	828	1 268
10	25	809	1 309	23	828	1 288
11	25	808	1 308	23	828	1 288
12	25	726	1 226	22	828	1 268
13	25	726	1 226	22	828	1 268
14	24	725	1 205	21	828	1 248
Total to age 15	430	12 751	21 351	460	12 937	22 137

3. Results

Table 1 compares two sets of calculated doses to the RBM of a typical British child from natural background radiation: those of Kendall *et al* (2009) and those of Simmonds *et al* (1995). RBM doses are presented by single year of age. High and low LET contributions to RBM absorbed dose are shown separately and the RBM equivalent dose is also given.

Table 2 gives the percentages and numbers of cases of leukaemia in the population of children in Great Britain during 1991–2000 attributable to exposure to natural background ionising radiation by sex in each year of attained age. Calculations were carried out for the age-specific RBM doses of Kendall *et al* (2009) using the BEIR VII (NRC 2006) and UNSCEAR (2008) risk models. Risks were transferred to the population of British children using the BEIR VII (70% ERR:30% EAR) transfer model. The attributable proportion of 19.2% derived using the UNSCEAR (2008) models is similar to, but somewhat higher than, that of 14.6% estimated using the BEIR VII (NRC 2006) models. These proportions are also similar to, but rather smaller than, those previously derived byWakeford *et al* (2009) using the older RBM dosimetry (Simmonds *et al* 1995). Table 2 demonstrates the marked variation in the attributable proportion with attained age that is predicted by the BEIR VII models, increasing from about 5% in the first 2 years of life to about 20% from the age of 5 years onwards; this variation is not nearly as great using the UNSCEAR models.

Table 3 investigates the effects of excluding doses received *in utero* and in the first year after birth. The table presents the percentages and numbers of cases of leukaemia by sex in the population of children (0–14 years of age) in Great Britain during 1991–2000 attributable

Table 2. The percentages (and numbers) of cases of leukaemia in the population of children in Great Britain during 1991–2000 attributable to exposure to natural background ionising radiation by sex in each year of attained age, according to the BEIR VII (NRC 2006) and UNSCEAR (2008) risk models, assuming a 70% ERR:30% EAR model mixture and the age-specific RBM doses of Kendall *et al* (2009). Summary data for all ages 0–14 years as calculated by Wakeford *et al* (2009) using the RBM dose estimates of Simmonds *et al* (1995) are given for comparison.

	UNSCEAR		BEIR VII	
Attained age (years)	Males	Females	Males	Females
0	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
1	18.6 (39)	18.5 (33)	5.2 (11)	4.6 (8)
2	24.3 (88)	24.2 (73)	6.9 (25)	6.6 (20)
3	23.0 (85)	22.9 (65)	8.9 (33)	9.1 (26)
4	21.7 (65)	21.6 (49)	13.1 (39)	12.7 (29)
5	20.9 (39)	20.5 (32)	20.2 (38)	17.6 (28)
6	20.0 (32)	19.7 (22)	22.2 (36)	21.4 (24)
7	19.0 (31)	19.2 (16)	21.0 (35)	24.9 (21)
8	19.1 (21)	18.3 (16)	26.1 (28)	24.0 (21)
9	18.6 (19)	18.1 (12)	26.4 (27)	27.0 (19)
10	18.0 (18)	17.2 (13)	25.2 (26)	24.1 (19)
11	17.3 (19)	16.7 (12)	23.6 (26)	23.9 (18)
12	17.3 (16)	16.0 (13)	24.5 (23)	21.6 (17)
13	17.4 (14)	16.6 (10)	25.2 (21)	23.5 (14)
14	15.8 (18)	15.5 (11)	20.6 (23)	20.5 (14)
0–14	19.4 (503)	19.0 (378)	15.0 (389)	14.0 (277)
0–14 using the dose estimates of Simmonds *et al* (1995) (as in Wakeford *et al* (2009))	23.2 (602)	23.0 (456)	17.0 (440)	16.1 (319)

Table 3. The percentages (and numbers) of cases of leukaemia by sex in the population of children (0–14 years of age) in Great Britain during 1991–2000 attributable to exposure to natural background ionising radiation, according to the BEIR VII (NRC 2006) and UNSCEAR (2008) risk models, assuming a 70% ERR:30% EAR model mixture and the age-specific RBM doses of Kendall *et al* (2009), with and without the estimate of the dose received *in utero* included, and with the estimate of the dose received during the first year of life also included or excluded.

	UNSCEAR		BEIR VII	
Assumptions	Males	Females	Males	Females
As per table 2 (including in utero and age 0 year dose)	19.4 (503)	19.0 (378)	15.0 (389)	14.0 (277)
No in utero dose	15.8 (409)	15.2 (301)	13.2 (341)	12.1 (240)
No in utero or age 0 year dose	10.1 (261)	9.4 (186)	10.5 (272)	9.3 (184)

to exposure to natural background ionising radiation. Omitting the dose received *in utero* materially reduces the attributable fraction—from 19.2% to 15.5% using the UNSCEAR (2008) models and with a slightly smaller decrease when using the BEIR VII (NRC 2006) models, from 14.6% to 12.7%. Additionally omitting the dose received in the first year of (postnatal) life further reduces the attributable proportion by a similar magnitude—from 15.5% to 9.8% using the UNSCEAR (2008) models and again a slightly smaller decrease for the BEIR VII (NRC 2006) models, from 12.7% to 10.0%.

Table 4. The percentages (and numbers) of cases of leukaemia by sex in the population of children (0–14 years of age) in Great Britain during 1991–2000 attributable to exposure to natural background ionising radiation, using UNSCEAR (2008) risk models, with variant assumptions on the mode of risk transfer: 70% ERR:30% EAR, pure EAR and pure ERR.

Risk transfer model	Males	Females
As per table 2 (70% ERR: 30% EAR)	19.4 (503)	19.0 (378)
Pure EAR	5.4 (140)	4.0 (79)
Pure ERR	23.8 (616)	23.7 (471)

Table 5. The percentages (and numbers) of cases of leukaemia by sex in the population of children (0–14 years of age) in Great Britain during 1991–2000 attributable to exposure to natural background ionising radiation, using the UNSCEAR (2008) risk models and a 70% ERR:30% EAR model mixture, with variant assumptions on the magnitude of the alpha-particle relative biological effectiveness (RBE) at inducing childhood leukaemia.

Alpha-particle relative biological effectiveness (RBE)	Males	Females
As per table 2 (radiation weighting factor = 20)	19.4 (503)	19.0 (378)
10	16.2 (421)	16.0 (317)
5	14.6 (378)	14.3 (284)
2	13.5 (351)	13.3 (264)
1	13.2 (342)	13.0 (257)

Table 4 illustrates the differences between alternative models for transferring risks from the Japanese atomic bomb survivors to the British population for the predicted percentages and numbers of cases of leukaemia induced by natural radiation. Calculations are for the population of children in Great Britain during 1991–2000 and use UNSCEAR (2008) risk models for each sex with variant assumptions on the mode of transfer (70% ERR:30% EAR mixture, pure EAR and pure ERR). As can be seen, a pure EAR model yields much lower risks for both sexes than either a 70% ERR:30% EAR mixture model or a pure ERR model—the attributable proportion is 4.9% for a pure EAR model, 19.2% for a 70% ERR:30% EAR model mixture and 23.8% for a pure ERR model.

Table 5 explores the effect of different assumptions on the magnitude of the alpha-particle relative biological effectiveness (RBE) on the percentages and numbers of cases of leukaemia calculated to be attributable to exposure to natural background radiation. The calculations are for the population of children in Great Britain for the period 1991–2000. Results are given for each sex using the UNSCEAR (2008) risk models and a 70% ERR:30% EAR model mixture for transfer to the British population. As can be seen, reducing the RBE from 20 progressively reduces the attributable proportion, from 19.2% when an RBE of 20 is used to 13.1% when an RBE of 1 is employed.

4. Discussion

4.1. Effects of revised dosimetry

The percentage of cases of childhood leukaemia incident in Great Britain during 1991–2000 that is predicted to be attributable to natural background radiation is somewhat lower if the recent RBM dose estimates of Kendall *et al* (2009) are employed rather than those of Simmonds

et al (1995) (table 2): using the BEIR VII risk models the attributable percentage is reduced from 16.6% to 14.6% and using the UNSCEAR (2008) models the reduction is from 23.1% to 19.2%. This is not primarily a consequence of a general reduction in the dose estimates—the estimates of total RBM equivalent dose incurred up to age 15 years differ by only ∼3% (table 1)—but because Simmonds *et al* calculated a substantially higher RBM dose in the first year of life, the higher estimate being due to the high LET component of dose (table 1).

Doses received *in utero* and in the first years of life have a proportionally greater effect upon the radiation-induced risk of childhood leukaemia because of the peak in the background incidence in the 2–4 year age range. The doses received *in utero* and during infancy are therefore of some importance to the results presented here. In table 3, which is based on the RBM doses estimated by Kendall *et al* (2009), the doses received *in utero* and during the first year of life are excluded from the calculations in a sensitivity analysis. Excluding the dose received *in utero* reduces the proportion of cases of childhood leukaemia predicted to be attributable to natural background radiation from 19.2% to 15.5% using the UNSCEAR (2008) risk models, and from 14.6% to 12.7% using the BEIR VII (NRC 2006) risk models; the additional exclusion of the dose received in the first year after birth further reduces the proportion of attributable cases from 15.5% to 9.8%, and from 12.7% to 10.0%, respectively. These results are presented purely to illustrate the importance of doses received *in utero* and in the first year after birth to the calculated proportions of radiation-induced childhood leukaemia; the exclusion of these doses is not meant to imply that treating these doses as zero is in any way realistic.

4.2. Further dosimetric uncertainties

The components of low LET radiation deliver doses that are reasonably constant across the body of a typical child (a variation of a few tens of per cent for gamma rays), and there is relatively little scope for estimates of low LET dose to the RBM to be greatly in error. Thus, the 12.8 mSv RBM dose accumulated before the 15th birthday from low LET radiation can be considered a reasonably stable estimate. On the other hand, the high LET dose (8.6 mSv RBM dose received up to the age of 15 years) is delivered largely by alpha-particles having short ranges of only a few tens of micrometres in soft tissue, and dosimetric calculations depend critically on assumptions about the relative locations of the radionuclides undergoing decay and the sensitive target cells in the RBM. For example, the RBM dose from alpha-particle-emitters is taken to be the average dose received throughout the RBM, whereas alpha-particles emitted by radionuclides deposited on bone surfaces will irradiate only the peripheral RBM, which may not contain the same concentration of target cells as the RBM as a whole (Harrison 2009). Further, the dose received by sensitive cells may be age dependent owing to the smaller dimensions of the bones in childhood and the different distribution of the RBM within the skeleton. As discussed by Kendall *et al* (2009) these assumptions introduce very considerable scope for uncertainty in the estimated risk of leukaemia arising from alpha-particle-emitters (see also ICRP 2007, Harrison and Day 2008, Harrison 2009).

One particular source of uncertainty over the leukaemogenic effect of irradiation by alpha-particles arises from the use of a radiation weighting factor of 20. The radiation weighting factor (w_R) is a radiological protection quantity that is universally applied to an absorbed dose to obtain an equivalent dose representing the consequent risk of stochastic health effects as a whole. The w_R of 20 for densely ionising alpha-particles scales the absorbed dose to obtain the degree of microscopic biological damage of relevance to induced stochastic effects that is equivalent to that produced by an absorbed dose of reference low LET radiation received at a low dose and/or low dose-rate, and the w_R for alpha-particles may thus be regarded as an

averaged overall measure of relative biological effectiveness (RBE) appropriate for radiological protection purposes. The RBE of alpha-particles emitted by naturally occurring radionuclides relevant specifically to inducing leukaemia in children when compared with irradiation of the sensitive cells by low dose/dose-rate reference low LET radiation may not be 20. There is no direct information on the RBE of alpha-particles for the induction of childhood leukaemia. However, there is evidence that the RBE of alpha-particles in the specific case of radiation-induced leukaemia in adults could be appreciably less than 20 (IARC 2001, ICRP 2003b, 2007, Harrison and Muirhead 2003, Little *et al* 2007, Harrison 2009). One possible reason for this is a comparatively high efficiency of alpha-particles in killing sensitive cells, which would lead to an overestimation of the risk of leukaemia from exposure to naturally occurring alpha-emitters. Table 5 illustrates the effect on the attributable proportion of a reduction in the alpha-particle radiation weighting factor, and shows that if the value of the RBE is taken to be 1 then the fraction of cases of childhood leukaemia attributable to natural radiation reduces from 19.2% to 13.1%.

Hence, there is substantial uncertainty associated with both the estimates of the absorbed doses of alpha-radiation received from naturally occurring radionuclides by the cells sensitive to radiation-induced childhood leukaemia and the RBE of these alpha-particles at inducing childhood leukaemia.

4.3. Location of the sensitive cells for leukaemia induction

The doses used in this paper are to the RBM. However, during the development of the haematopoietic system *in utero* the location of the cells sensitive to radiation-induced leukaemia is more complicated. In the embryo haematopoiesis occurs initially in the allantois, then the yolk sac, before the liver assumes blood production around the eighth week of pregnancy (Pearson 2002). Haematopoiesis in the liver reaches a maximum at about the fifth month of gestation at which time the foetal RBM takes on an increasing role so that it predominates in the third trimester (Pearson 2002). For low LET radiation the dose to the embryo/foetus is relatively uniform, so the dose to the exact site of the sensitive cells during development *in utero* is unlikely to vary greatly; but this may not be so for alpha-particle-emitting radionuclides. Consequently, these considerations introduce uncertainty about the relevant tissue dose received *in utero* from high LET radiation (Harrison 2009). Further, the variation of the risk of radiation-induced leukaemia with gestational age is assumed to be constant in the calculations made in this paper, but is unlikely to be, although suggestions that the risk is significantly greater for exposure in the first trimester are not convincing (Doll and Wakeford 1997). Finally, as discussed by Wakeford *et al* (2009), the BEIR VII (NRC 2006) and UNSCEAR (2008) leukaemia risk models have been applied to the dose received *in utero* whereas they are derived from data for exposure after birth. Although there is evidence that the childhood leukaemia ERR coefficient for doses received by the foetus is comparable with that for doses received by children (Wakeford and Little 2003), the application of the risk models to intrauterine doses is an additional source of uncertainty.

It has been suggested that, since childhood leukaemia is primarily due to acute lymphoblastic leukaemia, especially in early childhood, the dose to the lymphatic system may be of relevance. In particular, the dose from inhaled radionuclides to the thoracic lymph nodes has been proposed as possibly being of importance in the risk of radiation-induced childhood leukaemia (COMARE 1996). We discuss doses to the lymphatic system in the appendix. Doses from terrestrial gamma and cosmic rays are reasonably constant across the body, but doses from intakes of radionuclides (both ingested and inhaled) are more variable. The nuclides of greatest radiological importance deliver the highest doses to cells on bone surfaces. RBM

receives a dose that is comparable to those received by other of the more highly exposed organs, and higher than those to many organs with a significant content of lymphatic tissue. While definitive conclusions are not possible, and different parts of the lymphatic system may differ in their radiosensitivity so far as leukaemogenesis is concerned, it seems reasonable to concentrate attention on the RBM, the tissue most strongly linked to the induction of leukaemia. Consequently, we do not consider that doses to the lymphatic system will have a major impact upon the estimate of the proportion of cases of childhood leukaemia caused by natural radiation, although such doses from internally deposited radionuclides increase the uncertainty associated with this estimate.

4.4. Uncertainties in risk models and transfer models

Wakeford *et al* (2009) discuss in detail the uncertainties arising from the derivation of risk models from the Japanese atomic bomb survivor data—illustrated by the fact that the BEIR VII Committee (NRC 2006) and UNSCEAR (2008) derived two sets of different risk models from the same leukaemia mortality data—and in the transfer of the radiation-induced excess risk from the Japanese survivors to the population of British children. The transfer model adopted is particularly important for the UNSCEAR risk models, as illustrated by table 4: a pure ERR transfer model produces an attributable fraction of 23.8% whereas a pure EAR transfer model produces an attributable fraction of 4.9%. As Wakeford *et al* (2009) note, the difference (at least when employing the UNSCEAR risk models) in the results obtained from using the ERR and EAR models derived from the experience of the Japanese atomic bomb survivors in the 1950s to estimate effects in British children in the 1990s is the consequence of the materially lower (by a factor of about 2 1/2) background risk of leukaemia among the Japanese children at this earlier time (Wakeford and Little 2003, Stiller 2007). We have argued (Wakeford *et al* 2009) that the existing evidence points to the transfer of risk being more of an ERR transfer than an EAR transfer (as in the case of the 70% ERR:30% EAR mixture used by the BEIR VII Committee). This is based on a variety of data. Wakeford and Little (2003) showed that the childhood leukaemia ERR coefficients derived from British children exposed to diagnostic radiography *in utero* in the mid-1950s and from the Japanese survivors irradiated in the first few years of postnatal life were more compatible than the EAR coefficients. Little (2008) surveyed risks in the Japanese atomic bomb survivors exposed in childhood (Preston *et al* 1994) and in three radiotherapy studies relating to childhood exposure (Ron *et al* 1988, Lundell and Holm 1996, Ronckers *et al* 2001) and documented, for leukaemia at all ages, statistically significant heterogeneity between the EARs in these four groups, but no significant heterogeneity of ERRs (Little 2008). Nonetheless, the ICRP (2007) has chosen a pure EAR transfer for leukaemia, in contrast to the BEIR VII Committee (NRC 2006) 70% ERR:30% EAR mixture model. Although we favour the use of an ERR transfer or the BEIR VII 70% ERR:30% EAR mixture rather than a pure EAR transfer, the uncertainties in the choice of risk transfer model are still considerable, and the selection of the transfer model plays a major role in the uncertainty in the prediction of the proportion of childhood leukaemia attributable to natural radiation.

One noticeable feature of the results is the substantially lower attributable proportions obtained from the BEIR VII (NRC 2006) models when compared with the UNSCEAR (2008) models for attained ages up to about 4 years. The EAR component of the attributable fraction is fairly low for both UNSCEAR and BEIR VII models at these young attained ages (Wakeford *et al* 2009), although even for this component there are differences, the reasons for which are discussed at greater length by Wakeford *et al* (2009). Therefore, the difference essentially results from the materially lower estimate derived from the BEIR VII ERR model compared with the analogous UNSCEAR model. This difference is mainly due to the fundamentally

composite nature of the BEIR VII ERR model, which, as noted in the supplementary material B of Wakeford *et al* (2009), has a lot of the flavour of an EAR model. This is particularly marked when exposures are within 5 years of the age-at-risk, when the ERR coefficient is effectively multiplied by the ratio, $h_0(e+5)/h_0(a)$, of the baseline leukaemia rate at the age-at-exposure plus 5 years, $e+5$, to that at the current attained age, a; since childhood leukaemia incidence decreases after the age of 4 years this accounts for the rather lower BEIR VII ERR in this age range following exposure in infancy.

Owing to the statistical compatibility of the childhood leukaemia ERR coefficient obtained from the Oxford Survey of Childhood Cancers (OSCC) for antenatal exposure to diagnostic radiography with the estimate derived from the Japanese atomic bomb survivors exposed in childhood (Wakeford and Little 2003), we would not anticipate any substantial difference being made by use of ERRs derived from the OSCC rather than those used here to estimate attributable proportions following exposure *in utero*. However, as Wakeford and Little (2003) document, given the difference in the baseline rates of childhood leukaemia for British and Japanese children in the mid-20th century, the EAR coefficient obtained from the OSCC will be materially higher than that using the Japanese data, so that for this risk model it is anticipated that attributable proportions would substantially increase were one to use OSCC EAR values.

It has been noted above that the doses received *in utero* and during the first year after birth are particularly influential in determining the attributable fraction, primarily because of the background peak of incidence of leukaemia in young children. Of note in this respect is that systematic follow-up of the Japanese atomic bomb survivors commenced only in October 1950, so the excess of leukaemia cases that is known to have occurred before this date (Folley *et al* 1952, Preston *et al* 1994) cannot be incorporated quantitatively in the leukaemia risk models, and the modelling of the expression of the excess risk during the period within 5 years of exposure (including the assumption of a minimum latent period of two years) must be obtained from information from other studies. This source of uncertainty is particularly important for the predicted effect of the doses received *in utero* and in infancy upon the consequent risk of leukaemia in early childhood.

4.5. Epidemiological studies

It is highly desirable to test the prediction of a 15–20% proportion of childhood leukaemia incidence attributable to natural background radiation through epidemiological investigation. Wakeford *et al* (2009) have reviewed the epidemiological evidence for an effect of natural radiation exposure on the risk of childhood leukaemia, which is not persuasive. However, statistical power is a major concern when assessing the epidemiological studies that have been conducted, and it may well be that the power of these studies has been insufficient to detect the predicted effect. In particular, if the variation in the UK of the RBM dose is not large then it will be difficult to discern the predicted influence of natural radiation. We are currently examining the variation of RBM dose and the impact upon statistical power.

5. Conclusions

The recent RBM dose estimates of Kendall *et al* (2009) are likely to be more realistic than the earlier estimates of Simmonds *et al* (1995). Using these dose estimates and the leukaemia risk models derived by the BEIR VII Committee (NRC 2006) and UNSCEAR (2008), together with the preferred 70% ERR:30% EAR transfer model, implies that 15–20% of cases of childhood leukaemia in Great Britain are predicted to be attributable to natural background radiation, slightly lower than previously estimated by Wakeford *et al* (2009). The inevitable uncertainties

associated with this prediction must be borne in mind, especially those associated with the transfer of risk from the Japanese atomic bomb survivors and with the leukaemogenic effect of exposure to naturally occurring alpha-particle-emitters, since these are large. It would be of value to test the leukaemia risk models for low dose and/or low dose-rate irradiation through suitable epidemiological studies of natural radiation exposures. It may be that the statistical power of such studies is insufficient to detect the predicted effect, at least in the UK where natural radiation levels are relatively low, but we are currently investigating this issue.

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Appendix. Doses to the lymphatic system

A.1. Structure of the lymphatic system

ICRP Publication 89 (ICRP 2002), discusses the lymphatic system. This is widely distributed in the body and consists of:

(a) The lymphocytes which are carried round the body in a network of lymphatic vessels and are found in most organs and tissues.
(b) Lymphatic tissue which is contained in the RBM and in the lymphatic organs: lymph nodes, spleen, thymus, mucous membranes, tonsils, adenoids, Peyer's patches, and the vermiform appendix.

ICRP gives age dependent estimates of the mass of lymphocytes in the body with estimates of the percentage in RBM, blood, and lymphatic organs. However, a large majority is described as 'outside haematopoetic tissue'. ICRP estimates the total mass of fixed lymphatic tissue in adults. However, there are many lymph nodes in various parts of the body and it is difficult to estimate either their total number or their mass.

In view of the diffuse and ill-defined nature of the lymphatic system it is unsurprising that there is no specific model for calculating the overall dose. Nevertheless models are available to calculate doses to some of the organs and tissues that contain lymphatic tissue, and we will use these to investigate whether there are indications that doses to other organs may rival in importance those to the RBM. The RBM and thymus are plausibly of particular relevance in the context of leukaemogenesis since these are where lymphocytes are produced and undergo early development. It has also been suggested that the thoracic lymph nodes may have a particular role in radiation-induced childhood leukaemia (COMARE 1996). Recently, Harley and Robbins (2009) have investigated the dose received by circulating lymphocytes in the tracheobronchial epithelium from inhaled radon and its decay products, and have suggested that this dose could be appreciable; but it should be noted that only a small fraction of lymphocytes will be exposed at any time. The average dose to lymphocytes as a whole may be a more reasonable basis upon which to estimate this component of the risk of childhood leukaemia.

A.2. General considerations on doses to the lymphatic system

The doses from cosmic and gamma rays vary relatively little between organs of the body. However, ingested or inhaled radionuclides deliver doses that differ much more substantially

across the body. Standard models are available for the calculation of doses from a variety of radionuclides to a spectrum of organs and tissues, some of which contain lymphatic tissue (ICRP 1990, 1996). In particular, the ICRP model of the human respiratory tract (ICRP 1994) leads to estimates of doses from inhaled material to:

- LN-ET, the lymphatics and lymph nodes that drain the extrathoracic region of the respiratory tract.
- LN-TH, the lymphatics and lymph nodes that drain the thoracic region of the respiratory tract.

The greatest variation in doses to organs is in doses delivered by radionuclides emitting alpha-particles of which the most important in the present context are ^{210}Pb, ^{210}Po, ^{226}Ra and ^{228}Ra. These have complex biokinetic models involving preferential retention in organs and tissues as follows (ICRP 1993):

lead: bone compartments, liver, kidneys;
polonium: liver, kidneys, spleen and RBM;
radium: bone compartments.

ICRP thus assigned specific uptake of these radionuclides to only a few of the organs with lymphatic tissue and only one as being preferentially taken up by an organ without its own weighting factor—polonium taken up by the spleen. Where there is activity on bone compartments this implies a dose to RBM. In addition, some material is assumed to be distributed to soft tissue generally and doses will also be delivered to gut and the urinary system as activity is excreted. Further components of dose may be delivered by radioactive decay products. Nevertheless, the organs and tissues listed above will receive the highest doses.

A.3. Calculated doses to some organs of the lymphatic system

Table A.1 lists the committed doses from intakes of radionuclides to those organs and tissues suggested by Simmonds *et al* (1995) as accounting for a substantial fraction of the total lymphatic system. Doses are calculated for a 10 year old child as a representative age. All of the organs listed contribute to the effective dose (ICRP 2007), some with their own weighting factors but most as part of the 'remainder'. Committed organ doses have been estimated as follows:

- For radionuclides in food, using the methodology of Kendall *et al* (2006).
- For radon and decay products, using the methodology of Kendall and Smith (2005).
- For thoron decay products, using the methodology of Kendall and Phipps (2007).

A.4. Discussion

The table A.1 shows that bone surfaces receive a dose more than twice as high as the next most exposed organ. Spleen and kidney receive the next largest doses, followed by liver and RBM. Over half the dose from radionuclides to bone surfaces comes from ^{226}Ra and ^{228}Ra. Epidemiological studies of those exposed to ^{226}Ra and ^{228}Ra show an excess risk of bone cancer and cancers of the airways (which were plausibly an effect of exhaled ^{222}Rn, formed on the decay of ^{226}Ra) (Wakeford 2009). However, there is little evidence for an excess of leukaemia.

The decay products of radon and of thoron are too short-lived for doses to LN-ET or LN-TH to be significantly higher than those to the generality of low exposed organs. It seems likely that radionuclides in food when generally dispersed into the body will give a dose to LN-ET

Table A.1. Committed organ equivalent doses (μSv) to the lymphatic system of a 10 year old from one year's intake of naturally occurring radionuclides at average UK concentrations (Notes to the table: for the total dose the doses for Type F radon decay products have been used. Tissue weighting factors are from ICRP (2007). 'Colon' is taken as a combination of upper large intestine and lower large intestine. 'R' indicates a remainder tissues. Remainder tissues include 'lymph nodes', taken as the mean of LT-TH and LN-ET. Organ masses are from ICRP Publications 89 (2002) and 54 (ICRP 1989); the masses of LN-ET and LN-TH are from ICRP publication 66 (ICRP 1994).)

			Committed equivalent dose (μSv)				
				Radon gas plus			
	Mass (g)	Tissue weighting factor	Nuclides in food	Type F decay products	Type M decay products	Thoron decay products	Total dose from intakes of radionuclides
Thoracic lymph nodes	7	R	180	27	10	5	212
Extrathoracic lymph nodes	7	R	180	39	20	7	226
Liver	830	0.04	620	67	15	27	714
Spleen	80	R	930	39	9	4	973
Kidneys	180	R	930	670	74	68	1668
Pancreas	60	R	180	27	8	5	212
Uterus	4	R	190	27	7	5	222
Thymus	40	R	180	27	8	5	212
Thyroid	8	0.04	180	27	7	4	211
Stomach	85	0.12	190	33	18	5	228
Small intestine	370	R	190	31	14	6	227
Upper large intestine	93	0.12	340	30	10	5	375
Lower large intestine	70	0.12	450	29	9	5	484
RBM	630	0.12	530	104	63	17	651
Bone surfaces	68	0.01	2600	400	44	230	3230

and LN-TH very much like that to muscle and this contribution is substantially larger than that from radon and thoron.

These results should not be over-interpreted in terms of the doses to lymphatic tissue. Many of the organs listed in the table are large and lymphatic tissue is not the major constituent. ICRP models calculate the mean dose to the organ as a whole and lymphatic tissue may not be distributed uniformly across the organ. As discussed in the main text, considerable uncertainties attach to the calculation of doses from alpha-emitters, particularly if the sensitive cells and the radionuclide in question are not homogeneously distributed within the organ. Equally importantly, no models are available to allow the calculation of doses for some organs containing lymphatic tissues (for example lymph nodes in the neck).

Simmonds *et al* (1995) suggested that the mass-weighted mean of the dose to the organs in the table was an estimate of the overall dose to lymphatic tissue. In view of the factors discussed above we are reluctant to give a single numerical estimate. However, the spectrum of doses in the table indicate the range of doses to organs some of which have preferential uptake of the important nuclides and some of which have average concentrations of the body.

We note that the thymus receives a dose which is at the lower end of the range of doses. Because alpha-emitting radionuclides are not preferentially deposited in the thymus the contribution from these nuclides will be smaller than for organs such as RBM. The four alpha-emitting radionuclides discussed above, ^{210}Pb, ^{210}Po, ^{226}Ra and ^{228}Ra, contribute about two thirds of the equivalent dose to RBM from all radionuclides, but only about 15% of the dose to thymus. This means that the potential inhomogeneity in doses across the thymus is lower. The same will apply to other soft tissues with no preferential uptake of alpha emitters.

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