APPENDIX: QUANTITATIVE RISK ASSESSMENT FOR CHILDHOOD LEUKAEMIA

Although a causal relationship between magnetic fields and childhood leukaemia has not been established, estimates of the possible public health impact which assume causality are presented below in order to provide a potentially useful input into policy analysis under different scenarios (Kheifets, Afifi & Shimkhada, 2006).

The public health impact of exposure to an agent can be based on calculations of attributable fractions. The attributable fraction, based on an established exposure-disease relation, is the proportion of the case load (of disease) that is attributable to the exposure assuming there is a causal relationship. The attributable fraction is based on the difference between the number of cases in a population that occur when the population is subject to a given exposure distribution, and the number that would occur in the same population if that distribution were changed (e.g. if exposure was reduced or eliminated by an intervention). In this calculation, it is assumed that all other population characteristics remain the same. Hence, the attributable fraction can be used to estimate the degree of incidence reduction that would be expected if exposure were reduced. Since the epidemiological literature has consistently found elevated risk of childhood leukaemia at ELF magnetic field exposure levels above 0.3 μT for the arithmetic mean and above 0.4 μT for the geometric mean, attributable-fraction estimates for these (relatively) high-level exposures allow the estimated impact on disease incidence of eliminating or reducing exposure above these levels, assuming the relation between exposure and leukaemia incidence is causal.

There are two basic pieces of information needed to make a crude estimate of the attributable fraction: (1) an estimate of the exposure effect on the disease and (2) the prevalence of exposure in the population.

A.1 Exposure distribution

In evaluating the risks from exposure to any biologically active agent, physical, biological, or chemical, it is important to understand the distribution and magnitudes of the exposures in the general population. In order to effectively quantify the risks of childhood leukaemia, if any, from exposure to ELF magnetic fields, we must first get some estimate of the degree of exposure in children. As noted in chapter 2, these exposures will different from country to country due to a number of factors, most notably the frequency and voltage used for power distribution.

There are two types of studies from which the exposure distribution is extracted: (1) exposure surveys to provide estimates of the exposure prevalence in children (P_0), and (2) case series from case-control studies to provide estimates of P_0 and P_1 where P_1 is the exposure prevalence in children with childhood leukaemia. Use of each of these sources provides some advantage. Case-control studies provide most relevant measurements of exposure, but may be biased, if for example, restrictions on the population (e.g. to live within a certain distance of power lines) make the case exposure

prevalence in the study different from the population prevalence P_1; this renders unusable the case and control prevalences from studies with exposure-related restrictions. Even if the cases are representative, the controls will not be if matching has been done and the matching factors are associated with exposure; in that case the P_0 estimate from the study will be biased upward, toward P_1; fortunately, the most common matching factors were child's age and sex, which appear to be almost independent of exposure in the studies (Greenland, 2001; 2005). Exposure surveys, on the other hand, included both children and adults, as well as personal measurements throughout the day, that are thus only tangentially related to the exposure in the child's bedroom. At the very least the use of both of these sources provides a range of relevant exposures and subsequently a range of attributable fractions and numbers for consideration.

In contrast, in the case-control studies, the exposure distributions of the cases were used. For those case-control studies included in each pooled analysis, the exposure distribution reported in the pooled analysis was used. For studies not included in either pooled analysis, the exposure distribution was extracted directly from the study. (See tables A.1 and A.2 for details of all the exposure distributions used.) It is assumed that there are no significant difference in the exposure distributions based on exposure surveys and on case-control studies. Furthermore, it is assumed that exposures obtained using personal measures are equivalent to those from household measurements, regardless of length of time of measurement.

Globally, there is disproportionately more information on exposure from industrialized countries; and among these countries, the majority of the studies have been in the USA and, to a lesser extent, in Europe. There are a number of regions of the world, such as Africa and Latin America, where no representative information on exposure is available. Furthermore, there can be substantial differences in the exposure distributions within a region; for example, exposures in Korea are probably very different from those in China and India. This poses a difficulty for a global estimation of attributable fractions and numbers since these are highly dependent on the exposure distribution, hence emphasizing the need for more data on exposure levels worldwide.

A.2 Exposure-response analysis using attributable fraction estimates for EMF and childhood leukaemia

If no adjustment for covariates is needed, the values of the estimates of (1) the exposure effect on the disease and (2) the prevalence of exposure in the population are simply entered into the unadjusted (crude) attributable fraction formula (Levin, 1953):

$$AF_p = P_0(RR - 1)/[P_0 (RR - 1) + 1]$$

where AF_p is the estimated attributable fraction and RR is the risk ratio estimate. If confounding is present, both RR and P_0 should be adjusted (Rothman & Greenland, 1998), but in practice only an adjusted estimate for RR is

usually available. To make this calculation for the ELF-childhood leukaemia relation, as leukaemia is a rare disease, the odds ratio is assumed to estimate the risk ratio. It is also assumed that the risk ratio estimates the effect in the target population, that there is no bias, and no change in the effect estimate moving from the study to the target population (Greenland, 2004). Performing analyses that incorporate uncertainty from biases and other sources of uncertainty beyond random error are highly informative and require sophisticated techniques.

The attributable number is defined as the excess number of cases attributable to exposure. For example, the attributable number associated with high exposures is interpreted as the number of cases that would be averted if these exposures were eliminated. The attributable number is obtained by multiplying the attributable fraction by the total number of cases:

$$AN = AF_p \times m_1$$

where AN is the attributable number and m_1 is the number of cases.

For case-control studies with adjusted odds ratios, a less biased formula than that given by Levin is:

$$AF_p = P_1(RR_a - 1) / RR_a$$

where RR_a is the adjusted rate ratio estimate (study odds ratio) and P_1 is the exposure prevalence among the cases in the target population (Rothman & Greenland, 1998). This formula has the advantage of requiring no adjustment of P_1 to be valid, and is unaffected by matching controls to cases. Furthermore, assuming that exposure is independent of the adjustment factors (which appears to be approximately true in studies that did not match at all or matched on age and sex only) allows one to estimate P_0 from P_1 and RR_a via the (rare-disease) formula:

$$P_0 / (1 - P_0) = P_1 / (1 - P_1) RR_a.$$

It is also possible to make the calculations using continuous exposure data as does Greenland et al. (2001) for 11 studies. It is not possible to do that here because such data were not available from all the sources used in this analysis, and the results in Greenland et al. (2001) indicate that results from continuous exposure would differ little from the categorical results.

Dose response functions from two pooled analyses were used for estimating the RRs. One of the differences between the two pooled analyses is in the exposure metric used: Ahlbom et al. (2000) looked at the association between the geometric mean magnetic field level and childhood leukaemia in nine epidemiologic studies, Greenland et al. (2000), however, used the arithmetic mean to examine this association in twelve studies; Greenland (2005) extended this analysis to include 14 studies using a dichotomy at

0.3 μT. The other difference in these two analyses relates to the categories used for classifying exposures. In Ahlbom et al. (2000), four categories were used relating to < 0.1 μT, 0.1–< 0.2 μT, 0.2–< 0.4 μT, and ≥ 0.4 μT. In contrast, Greenland et al. (2000) used ≤ 0.1 μT, > 0.1–≤ 0.2 μT, > 0.2 –≤ 0.3 μT, and > 0.3 μT. To address the sensitivity of attributable fraction estimates to the choice of data sets and exposure categorization, two sets of attributable fraction estimates are presented relating to these two methods for developing RRs.

In the pooled analysis by Ahlbom et al. (2000), risk for childhood leukaemia with mean residential magnetic field exposure is: OR = 1.08, (95% CI = 0.891.31) for 0.1–0.2 μT, OR = 1.11 (0.89–1.47) for 0.2–0.4 μT, OR = 2.00 (1.27–3.13) for above 0.4 μT relative to exposure below 0.1 μT. In the pooled analysis by Greenland et al. (2000) OR = 1.01 (0.84–1.21) for 0.1–0.2 μT, OR = 1.06 (0.78–1.44) for 0.2–0.3 μT, and OR = 1.68 (1.24–2.31) for exposures greater than 0.3 μT, all compared to less than 0.1 μT (both the point estimate and confidence limits remain virtually unchanged by adding 2 studies). Incorporating, in addition to the random error, all sources of bias increases the last estimate to an OR = 2.7 (0.99–32.5) (Greenland, 2005) (Note: this estimate will be used later to incorporate additional uncertainty into the attributable fraction calculations.) .

A.3 Risk characterization

Attributable fraction (AF) estimates were made for all countries with an exposure distribution (see Figures A.1 and A.2). For the US and Germany, where there were multiple distributions, the largest of the case-control studies and the largest of the exposure surveys were used for the AF calculation used in Figure A.1. The AF estimates are divided into different exposure categories to enable a comparison of high exposures to overall exposure.

The attributable numbers (AN) of leukaemia cases were calculated for regions around the world and then added to obtain a global estimate. To compute these regional estimates, the lowest and highest exposure levels estimated in Tables A.1 and A.2 from the countries in that region were used to come up with a regional range. Where there was no information from any country in the region, the lowest and highest exposure prevalences from Tables A.1 and A.2 were used. The range of exposure prevalences for the arithmetic mean being > 0.3 μT used was 0.47% and 10.49% (Table A.1); that for the geometric mean being 0.4 μT was 0.37% and 4.78% (Table A.2). Yang's study (Yang, Ju & Myung, 2004), which is based on a larger sample and considered as more representative for non-Western regions, was used to calculate an upper range for regions with unknown levels (Latin America, Africa, Oceania). These low and high estimates were each added together to come up with a range for the entire world (Figures A.3 and A.4).

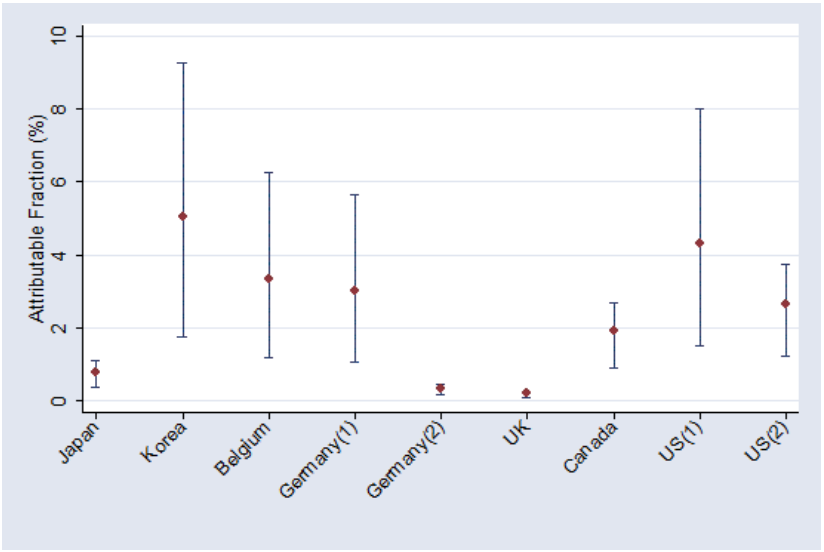

Figure A.1. Upper, lower and point estimates for attributable fractions, based on arithmetic mean exposure using exposure distributions for specific countries and estimate of effect from the pooled analysis by Greenland et al., 2000. (Japan: Kabuto et al., 2006; Korea: Yang, Ju & Myung, 2004; Belgium: Decat, Van den Heuvel & Mulpas, 2005; Germany(1): Brix et al., 2001; Germany(2): Schüz et al., 2001; UK: UKCCSI, 1999; Canada: McBride et al., 1999; US(1): Zaffanella & Kalton, 1998; US(2): Linet et al., 1997.)

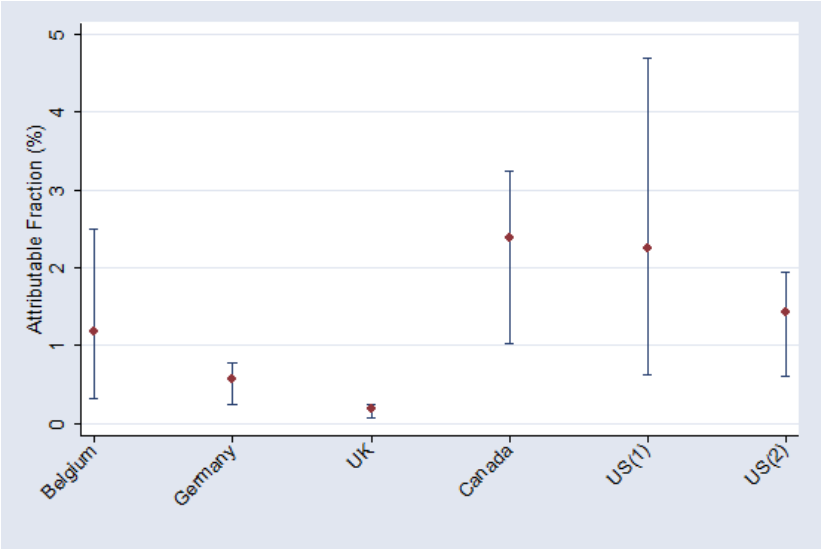

Figure A.2. Upper, lower and point estimates for attributable fractions, based on geometric mean exposure using exposure distributions for specific countries and estimate of effect from the pooled analysis by Ahlbom et al., 2000. (Belgium: Decat, Van den Heuvel & Mulpas, 2005; Germany: Michaelis et al., 1998; UK: UKCCSI, 1999; Canada: McBride et al., 1999; US(1): Zaffanella & Kalton, 1998; US(2): Linet et al., 1997.)

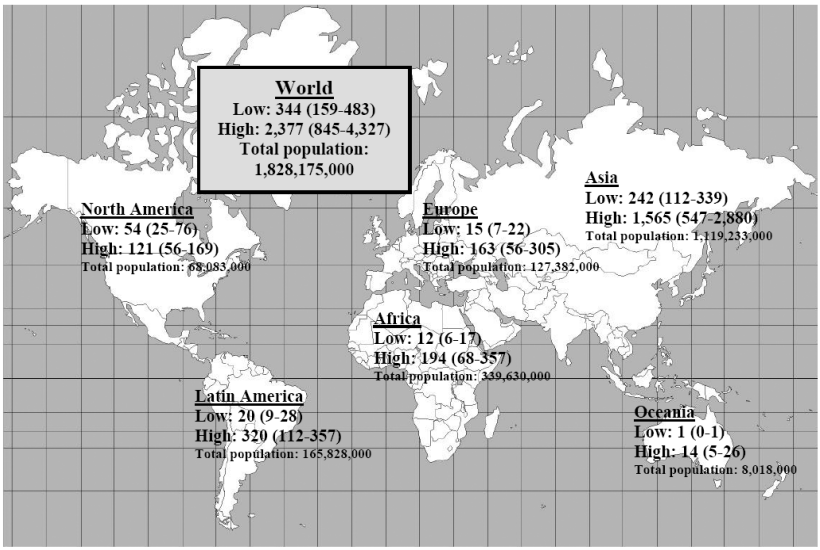

Figure A.3. Estimated number and range of world-wide and regional cases of childhood leukaemia among children under 14 years of age that are possibly attributable to EMF arithmetic mean exposure > 0.3 μT (and the corresponding derived confidence interval). Regional range is based on the lowest level and highest exposure levels from the countries in a given region. Where there was no information from any countries in the region, the lowest and highest exposure levels overall were used.

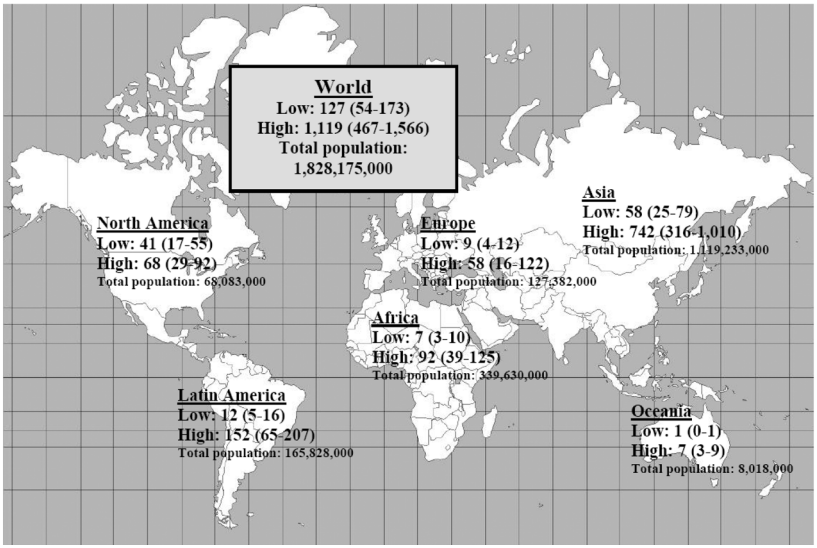

Figure A.4. Estimated number and range of world-wide and regional cases of childhood leukaemia among children under 14 years of age that are possibly attributable to EMF geometric mean exposure ≥ 0.4 μT (and the corresponding derived confidence interval). Regional range is based on the lowest level and highest exposure levels from the countries in a given region. Where there was no information from any countries in the region, the lowest and highest exposure levels overall were used.

Table A.1. Exposure distribution of the arithmetic mean based on exposure of cases in a case-control study or all respondents in an exposure survey

Country	Study	Study type	Measurement	Magnetic field category (μT)				N
				0.1	> 0.1–≤ 0.2	> 0.2–≤ 0.3	> 0.3	
Belgium	Decat, Van den Heuvel & Mulpas, 2005	Exposure survey	24-hr personal	81.9%	11.5%	1.6%	5.1%	251
Canada	McBride et al., 1999 [a]	Case-control	48-hr personal	58.59%	25.93%	10.77%	4.71%	297
Germany	Michaelis et al., 1998 [a]	Case-control	24-hr bedroom	85.23%	9.66%	1.70%	3.41%	176
	Brix et al., 2001	Exposure survey	24-hr personal	73.6%	17.8%	4.1%	4.5%	1952
	Schüz et al., 2001 [b]	Case-control	24-hr bedroom	91.83%	6.42%	0.97%	0.78%	514
Japan	Kabuto et al., 2006 [b]	Case-control	7-day home	88.46%	5.77%	3.85%	1.92%	312
Korea	Yang, Ju & Myung, 2004	Exposure survey	24-hr personal	64.0%	24.2%	4.0%	7.8%	409
UK	UKCCSI, 1999 [b]	Case-control	48-hr home	92.73%	5.31%	1.49%	0.47%	1073
USA	London et al., 1991 [a]	Case-control	24-hr bedroom	67.90%	18.52%	3.09%	10.49%	162
	Linet et al., 1997 [a]	Case-control	24-hr bedroom	63.17%	23.82%	6.43%	6.58%	638
	Zaffanella & Kalton, 1998	Exposure survey	24-hr personal	64.2%	21.1%	7.8%	6.6%	995
	Zaffanella, 1993	Exposure survey	24-hr home	72.3%	17.5%	5.6%	4.6%	987

[a] Based on the distribution for pooled analysis reported by Greenland et al., 2000 .

[b] Exposure categories: < 0.1, 0.1–< 0.2, 0.2–≤ 0.4, ≥ 0.4 μT.

Table A.2. Exposure distribution of the geometric mean based on exposure of cases in a case-control study or all respondents in an exposure survey

Country	Study	Study type	Measurement	Magnetic field category (μT)				N
				< 0.1	0.1–< 0.2	0.2–< 0.4	≥ 0.4	
Belgium	Decat, Van den Heuvel & Mulpas, 2005	Exposure survey	24-hr personal	91.9%	4.1%	2.8%	1.2%	251
Canada	McBride et al., 1999 [a]	Case-control	48-hr personal	63.97%	20.59%	10.66%	4.78%	272
Germany	Michaelis et al., 1998 [a]	Case-control	24-hr bedroom	89.14%	6.86%	2.86%	1.14%	175
UK	UKCCSI, 1999 [a]	Case-control	48-hr home	94.87%	3.54%	1.21%	0.37%	1073
USA	Zaffanella & Kalton, 1998	Exposure survey	24-hr personal	72.6%	17.6%	7.5%	2.3%	995
	Linet et al., 1997 [a]	Case-control	24-hr bedroom	70.25%	18.66%	8.24%	2.86%	595

[a] Based on the distribution for pooled analysis reported by Ahlbom et al., (2000).

Table A.3. Point, low and high estimates of the proportion (AF) and number (AN) of cases in the USA for the hypothetical scenario of 50% reduction in exposure

	Exposures above:		
Arithmetic mean	**0.1 μT**	**0.2 μT**	**0.3 μT**
Proportion of all cases attributable to exposure (AF):			
Current exposure distribution[a]	5.41% (-3.78%, 16.48%)	5.18% (-0.05%, 11.96%)	4.73% (1.65%, 8.73%)
Hypothetical distribution[b]: all exposures decreased by 50%	1.27% (-2.02%, 5.29%)	1.16% (-0.21%, 3.02%)	1.01% (0.34%, 1.93%)
Number of cases attributable to exposure (AN):			
Current exposure distribution	138 (-97, 421)	133 (-1, 306)	121 (42, 223)
Hypothetical distribution: all exposures reduced by 50%	32 (-52, 135)	30 (-5, 77)	26 (9, 49)
Number of cases averted due to exposure reduction	105 (-45, 286)	103 (4, 228)	95 (33, 174)
Geometric mean	**0.1 μT**	**0.2 μT**	**0.4 μT**
Proportion of all cases attributable to exposure (AF):			
Current exposure distribution[a]	3.95% (-2.83%, 12.30%)	2.46% (-0.71%, 6.77%)	1.67% (0.46%, 3.49%)
Hypothetical distribution[b]: all exposures decreased by 50%	0.94% (-0.99%, 3.32%)	0.37% (-0.20%, 1.17%)	0.20% (0.05%, 0.42%)
Number of cases attributable to exposure (AN):			
Current exposure distribution	101 (-72, 315)	63 (-18, 173)	43 (12, 89)
Hypothetical distribution: all exposures decreased by 50%	24 (-25, 85)	10 (-5, 30)	5 (1, 6)
Number of cases averted due to exposure reduction	77 (-47, 230)	53 (-13, 143)	38 (10, 83)

[a] Calculated log-normal distribution based on Zaffanella & Kalton, 1998.

[b] Calculated log-normal distribution based on Zaffanella & Kalton, 1998, with all exposures reduced by 50%

To estimate the impact of a hypothetical scenario where the population's exposure distribution is reduced by 50%, a new exposure distribution was calculated to reflect this change. Calculating the exposure distribution shift requires knowing the mean and standard deviation of the distribution; this information was available for only one of the distributions, the USA EMF Rapid Survey, 1998 (Zaffanella & Kalton, 1998). Hence, AF and AN estimates for exposures greater than 0.1 μT, 0.2 μT, 0.3 μT or 0.4 μT were calculated for the arithmetic mean and geometric mean exposure distributions, before and after making the 50% exposure reduction in the USA (see Table A.3). The difference in the AN reflects the number of cases that would be averted due to the exposure reduction of 50%.

The conventional calculations of AF do not reflect any source of uncertainty other than random error, and informal judgments regarding the effect of possible biases. To provide additional input to policy analysis also formal Bayesian analyses are provided of the impact of high residential magnetic-field exposure (as measured by AF), accounting for uncertainties about study biases as well as uncertainties about exposure distribution. These Bayesian analyses support the idea that the public-health impact of residential fields is likely to be limited, but both no impact and a large impact remain possibilities in light of the available data (Greenland & Kheifets, 2006). The difference between the two analyses varies in both directions, but on the whole the Bayesian results make the conventional results look overoptimistic and overconfident (Table A.4).

Table A.4. Conventional estimates (with 95% confidence limits) and Bayesian (posterior) percentiles for percentage of leukaemia case load attributable to exposure > 0.3 μT versus < 0.3 μT (AF%) in 15 case-control studies of magnetic fields and childhood leukaemia and in four populations with surveys of fields [a]

Reference	Country	Population AF% (95% limits)	
		Conventional	Posterior
Case-control:			
Coghill, Steward & Philips, 1996	England	0.5 (0.2, 0.7)	0.7 (-0.4, 18)
Dockerty et al., 1998	N.Z.	0.9 (0.5, 1.3)	0.9 (-0.5, 20)
Feychting & Ahlbom, 1993	Sweden	3.1 (1.4, 5.2)	8.6 (0.6, 44)
Kabuto et al., 2006	Japan	1.5 (0.7, 2.3)	3.2 (-1.0, 24)
Linet et al., 1997	U.S.	2.9 (1.4, 4.2)	3.5 (-1.1, 20)
London et al., 1991	U.S.	4.5 (2.2, 6.5)	4.9 (-1.2, 27)
McBride et al., 1999	Canada	2.1 (1.0, 3.1)	3.1 (-0.9, 23)
Michaelis et al., 1998	Germany	1.2 (0.6, 1.8)	1.0 (-0.5, 21)
Olsen, Nielsen & Schulgen, 1993	Denmark	0.1 (0.1, 0.2)	0.6 (0.0, 17)
Savitz et al., 1988	U.S.	2.1 (1.0, 3.5)	4.7 (-1.0, 34)
Schüz et al., 2001	Germany [b]	0.3 (0.1, 0.5)	0.7 (-0.4, 17)

Table A.4. Continued

Reference	Country	Population AF% (95% limits)	
		Conventional	Posterior
Case-control:			
Tomenius, 1986	Sweden	0.9 (0.4, 1.4)	0.7 (-0.5, 18)
Tynes & Haldorsen, 1997	Norway	1.0 (0.4, 1.6)	0.6 (0.0, 15)
UKCCSI, 1999	UK [b]	0.2 (0.1, 0.3)	0.6 (-0.4, 16)
Verkasalo et al., 1993	Finland	1.1 (0.5, 1.9)	0.8 (0.0, 20)
Surveys:			
Brix et al., 2001	Germany	3.1 (1.3, 5.5)	3.8 (0.0, 36) [c]
Decat, Van den Heuvel & Mulpas, 2005	Belgium	3.0 (1.1, 6.5)	3.8 (0.0, 36) [c]
Yang, Ju & Myung, 2004	Korea	5.2 (2.2, 9.6)	5.6 (-0.1, 44) [d]
Zaffanella, 1993	U.S.	3.2 (1.3, 5.9)	3.9 (0.0, 36) [c]
Zaffanella & Kalton, 1998	U.S.	4.4 (1.9, 8.0)	4.5 (-0.1, 38) [c]

[a] Adopted from Greenland & Kheifets, 2006.

[b] AF for > 4 μT vs. ≤ 2 μT, excluding 2-4 μT.

[c] Adjusted using the odds-ratio model for North America (direct measurement, high prevalence) and the summary field-leukaemia odds ratio of 2.9 (CI: 0.99–8.6).

[d] Adjusted using the odds-ratio model for Kabuto (direct measurement, high prevalence).