Original article

Meta-analysis of standardized incidence and mortality rates of childhood leukaemia in proximity to nuclear facilities

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The meta-analysis combined and statistically analysed studies of childhood leukaemia and nuclear facilities. Focus was on studies that calculated standardized rates for individual facilities. Due to variability between study designs, eight separate analyses were performed stratified by age and zone. One hundred and thirty-six sites were used in at least one analysis. Unadjusted, fixed effects and random effects models were used. Meta-rates greater than one were found in all models at all stratification levels often achieving statistical significance. Caution must be used when interpreting these results. The meta-analysis was able to show an increase in childhood leukaemia near nuclear facilities, but does not support a hypothesis to explain the excess. Each type of model utilized has limitations. Fixed effects models give greater weight to larger studies; however, population density may be a risk factor. Random effects models give greater weight to smaller studies that may be more likely to be affected by publication bias. A limitation of the overall study design is that standardized rates must be available for individual sites which led to exclusion of studies that only calculated rates for multiple sites and those that presented other statistical methods. Further, dose-response studies do not support excess rates found near nuclear facilities. However, it cannot be ignored that the majority of studies have found elevated rates, although not usually statistically significant.

Keywords: childhood leukaemia, nuclear, radiation, meta-analysis.

INTRODUCTION

In response to the cluster of childhood leukaemia reported near the Sellafield nuclear site in Great Britain in 1984 (Black 1984), there have been numerous studies assessing the possible risk of childhood leukaemia due to irradiation from nuclear sites. While many studies have found positive associations, few results have been significant. Although there is little doubt that exposure to radiation increases the risk of developing leukaemia (BEIR V 1990; Preston *et al*. 1994; United Nations Scientific Committee on the Effects of Atomic Radiation 1994; IARC 1999), there is disagreement as to whether the amount of exposure received by children living near nuclear sites is sufficient to increase risk.

Determining individual exposure in proximity to nuclear sites is problematic. Parameters that need to be considered include type of nuclear site, wind speed and direction, topography, plant emissions and distance from the site. For the child, parameters include age and lifestyle. Due to the difficulty in determining individual exposure levels, researchers have largely relied on identifying cases or deaths in a pre-defined area and calculating a standardized rate without a specific reference to exposure, instead, using geographical zones in the vicinity of a nuclear site as a surrogate for exposure.

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Within the multitude of studies, many type of inconsistencies in methodology have surfaced including:

- Age – The choice of age group to study has not only varied between studies in different countries, it has also varied between studies of a single nuclear site. This may reflect the uncertainties in determining at which age a child is no longer more susceptible in developing leukaemia than an adult.
- Area – Since the selection of area is often arbitrary (defined by an area with available census data), the choice naturally lends itself to selection bias. Too small an area may underestimate risk to children living outside the area and too large an area may miss a slight increase in risk if that risk is found near the nuclear site and much of the study area is not in the actual exposure zone.
- End point – Incidence data are generally preferable to mortality data as incidence data include the census area where the person lived at date of diagnosis. Residence at diagnosis is a better indicator of where the person may have resided at time of exposure. Conversely, mortality data are more easily affected by migration bias. Survival rates have also increased for childhood leukaemia making incidence a better indicator than mortality.

Another difficulty is that childhood leukaemia is a rare disease and nuclear sites are commonly found in rural areas leading to small sample sizes and, consequently, low power to detect slight increases in risk. An advantage of a meta-analysis is the ability to pool several cohorts that share common study characteristics to increase sample size and power.

MATERIALS AND METHODS

Study identification

Studies were identified by a comprehensive literature search, review of references, government publications and recommendations from researchers active in the field. Rates, observed cases and expected cases from candidate studies were validated by a second researcher to ensure that the appropriate data were identified and transcribed onto the spreadsheet correctly.

The criteria used for inclusion were:

1 The study must be a cohort study examining leukaemia in proximity to a nuclear site. A study must differentiate between leukaemia and lymphoma.
2 The study must include at least two of the following three variables: observed, expected, or end point [standardized incidence or mortality rate (SIR/SMR)] for individual nuclear sites, as opposed to a summarization that includes multiple sites.
3 If a site has zero observed cases or deaths, it is considered 0.01 for calculations.
4 The study must have at least one age category less than 26 (only ages less than 26 were used in the meta-analysis).
5 The study must indicate geographical zones in which cases or deaths occurred.

For multiple studies on the same cohort, the most complete study was used that met the study characteristics of interest for each analysis (defined below). The primary criterion used to identify the most complete study was the longest time interval, and the secondary criterion was the most recent publication.

Thirty-seven studies were identified for possible inclusion. Seventeen studies covering 136 nuclear sites in nine countries or former countries (East Germany) met the criteria for at least one analysis.

Statistical methods

Since one of the inclusion criteria is that an end point had to be reported for individual nuclear sites, each site was considered as an individual study in the statistical analysis. After the appropriate subset of sites had been identified for each analysis, three separate models were used to calculate a meta-SMR or meta-SIR: an overall unadjusted model, a fixed effects model and a random effects model.

The unadjusted model is the total observed cases or deaths divided by the total expected cases or deaths. An alternative model to adjust for sample size is a fixed effects model using the inverse variance-weighted method as described by Sutton (Sutton *et al*. 2000).

The meta-analysis combines nuclear sites that perform different functions and are located in a multitude of environmental settings (with respect to topography, wind, etc.); it is unlikely that all studies estimate the same underlying effect size, a fixed effects model assumption. One way to account for variation in effect size is to use a random effects model (DerSimonian & Laird 1986; Sutton *et al*. 2000).

Forest plots were used to show each site's SMR or SIR and corresponding 95% confidence intervals calculated by the method of exact Poisson confidence intervals (Liddell 1984). The forest plot contains several sites and visually represents the variability between estimates (Sutton *et al*. 2000).

Heterogeneity was analysed with Chi-Square Tests for Homogeneity (Cochran 1952) and radial plots, which plot

the z-statistic for each study against the reciprocal of its standard error (Galbraith 1988). Radial plots also include an unweighted regression line constrained through the origin and corresponding 95% confidence regions. Studies located outside the confidence regions contribute to heterogeneity (Sutton *et al*. 2000).

Publication bias was analysed with funnel plots, which plot the log of the treatment effect from individual studies and the inverse of their standard error (Sutton *et al*. 2000). If the funnel plot is skewed, publication bias may be present.

Analysis

If childhood leukaemia from radiation exposure is more likely to occur in young children (i.e. 0–9 age group), an analysis of the 0–25 age group may not allow the excess risk to be identified. Similarly, if the population living within 10 km of the nuclear site is at a much higher risk than the population residing 10–25 km from the site, a study including all children residing within a 25 km radius of the nuclear site may again miss a small excess risk to the 0–10 km population. Because the numerous studies examined several different age groups, geographical zones and end points, it was not possible to calculate an overall meta-SIR or meta-SMR. Therefore, we developed multiple subsets of interest as defined in Table 1.

RESULTS

Table 2 lists the studies that appeared in at least one analysis. Table 3 shows the number of sites included for each analysis. One hundred and thirty-six sites were used in at least one analysis (For Great Britain, Burghfield was included in Aldermaston data due to the close proximity of the sites). Seventeen studies reported 70 SIRs and 193 SMRs that met the analysis criteria for the various sites. Five sites in the USA were excluded due to zero observed deaths, and expected could not be calculated because only observed and SMR were reported. When all geographical zones were used, SMRs were reported at least twice as often as SIRs. However, when geographical zones were restricted to <16 km, SIRs were reported more often than SMRs. The great disparity between reporting SIRs and SMRs can be attributed to the sites in the USA. Jablon reported 116 SMRs for USA sites, as compared with eight SIRs, that met the criteria (Jablon *et al*. 1990). The US

Table 1. Stratification of analysis by age group, geographic zone and end point

Analysis	Age group*	Geographic zone*	End point
1	0–9	All	SIR
2	0–9	All	SMR
3	0–9	<16 km†	SIR
4	0–9	<16 km†	SMR
5	0–25	All	SIR
6	0–25	All	SMR
7	0–25	<16 km†	SIR
8	0–25	<16 km†	SMR

*Contains all subsets within the defined range. If more than one study exists for a cohort, the study with the largest range within the defined range is used. For example, 0–9 age group may include a study that contains only 0–4 age group.
†Rounded to the nearest kilometer. For example, 10 miles converts to 16.09 km; therefore it is considered 16 km.
SIR, standardized incidence rate; SMR, standardized mortality rate.

Table 2. Studies of childhood leukaemia and nuclear facilities that met the criteria for the meta-analysis

Study	Country	End point	Age group*	Zone (km)*
COMARE III (1989)	Great Britain	SIR/SMR	0–9, 0–14, 0–24	<10, <16
Goldsmith (1992)	Great Britain	SIR/SMR	0–9	<16
Ewings *et al*. (1989)	Great Britain	SIR	0–24	District†, <12.5
Baron (1984)	Great Britain	SMR	0–14	<8
Clarke *et al*. (1989)	Canada	SIR/SMR	0–4	County†
Clarke *et al*. (1991)	Canada	SIR/SMR	0–14	County†
Viel *et al*. (1995)	France	SIR	0–4, 0–24	<10, <35
Viel & Richardson (1990)	France	SMR	0–4, 0–24	<35
Hattchouel *et al*. (1995)	France	SMR	0–25	<16
Jablon *et al*. (1990)	USA	SIR/SMR	0–9, 0–19	County†
Mohner & Stabenow (1993)	East Germany	SIR	0–14	<15
Heasman *et al*. (1987)	Scotland	SIR	0–24	<12.5
COMARE II (1988)	Scotland	SIR	0–24	<12.5, <25
Hole & Gillis (1986)	Scotland	SIR	0–14	Adjusted postcodes†
Kaletsch *et al*. (1997)	West Germany	SIR	0–14	<15
Iwasaki *et al*. (1995)	Japan	SMR	0–14	District†
Lopez-Abente *et al*. (1999)	Spain	SMR	0–24	<15, <30

*Categories used in at least one analysis.
†Considered greater than 16 km.
SIR, standardized incidence rate; SMR, standardized mortality rate.

study was conducted at the county level and the sites are assigned to 'All' geographical region, which also accounts for the disparity in number of sites between 'All' and '<16 km' geographical regions.

Mortality analyses

Although all unadjusted meta-SMRs were at least 1.00, none were statistically significant at alpha = 0.05. Table 4 shows the fixed effects and random effects meta-SMRs. All fixed effects and random effects models were greater than one and the 0–9 age group achieved statistical significance across geographical zones. Confidence intervals were similar between fixed effects and random effects models at a given strata suggesting the absence of significant heterogeneity. No significant heterogeneity was found using Cochran Chi-Square Test for Homogeneity at alpha = 0.10.

Radial plots indicated Rancho Seco and Zion might contribute considerably to heterogeneity for age group = 0–9 and geographical zone = 'All'. Removing the sites resulted in lower confidence bands of 1.00 for both models. Radial plots also indicated Dresden, Rancho Seco, Zion and Naraha might contribute considerably to heterogeneity for age group = 0–25 and geographical zone = 'All'. Removing the sites had a negligible effect on the meta-SMR and no change in significance. Last, radial plots indicated Aldermaston might contribute considerably to heterogeneity for age group = 0–25 and geographical zone = '<16 km'. Removing Aldermaston resulted in statistically significant SMRs for both models (Table 5).

The funnel plots for publication bias do not appear to be skewed leading us to reject that significant publication bias exists.

Table 3. Number of nuclear facilities used in each analysis

Age group	Geographic zone	End point	Number of sites
0–9	All	SIR	22
0–9	All	SMR	76
0–9	<16 km	SIR	13
0–9	<16 km	SMR	14
0–25	All	SIR	50
0–25	All	SMR	115
0–25	<16 km	SIR	41
0–25	<16 km	SMR	37

SIR, standardized incidence rate; SMR, standardized mortality rate.

Incidence analyses

All unadjusted meta-SIRs were at least 1.00 and statistically significant. Table 6 shows the fixed effects and random effects meta-SIRs. All fixed effects and random effects meta-SIRs were greater than 1.00 and statistically significant. As in the mortality results, confidence intervals were similar between fixed effects and random effects models at a given strata suggesting the absence of significant heterogeneity. Testing for heterogeneity using Cochran Chi-Square Test for Homogeneity, no analyses were significant at alpha = 0.10.

Radial plots for age group = 0–25 and geographical zone = 'All' indicated that Amersham (SMR = 1.48) might be contributing considerably to heterogeneity; and for age group = 0–25 and geographical zone = '<16 km', Amersham and Dounreay (SMR = 3.26) might be contributing

Table 4. Mortality meta-rates for childhood leukaemia in proximity to nuclear facilities by age group and geographic zone

		Fixed effects		Random effects	
Age group	Geographic zone	Rate	95% CI	Rate	95% CI
0–9	All	1.06	(1.01, 1.11)	1.06	(1.01, 1.12)
0–9	<16 km	1.23	(1.04, 1.46)	1.24	(1.03, 1.50)
0–25	All	1.02	(0.98, 1.06)	1.02	(0.98, 1.06)
0–25	<16 km	1.09	(0.97, 1.23)	1.09	(0.97, 1.23)

Table 5. Mortality meta-rates for childhood leukaemia in proximity to nuclear facilities by age group and geographic zone: excluding sites that may be contributing to heterogeneity

		Fixed effects		Random effects	
Age group	Geographic zone	Rate	95% CI	Rate	95% CI
0–9	All	1.05	(1.00, 1.11)	1.05	(1.00, 1.11)
0–9	<16 km	1.23*	(1.04, 1.46)	1.24*	(1.03, 1.50)
0–25	All	1.02	(0.98, 1.06)	1.02	(0.98, 1.06)
0–25	<16 km	1.18	(1.03, 1.34)	1.18	(1.03, 1.34)

*Models not reran.

Table 6. Incidence meta-rates for childhood leukaemia in proximity to nuclear facilities by age group and geographic zone

		Fixed effects		Random effects	
Age group	Geographic zone	Rate	95% CI	Rate	95% CI
0–9	All	1.25	(1.13, 1.38)	1.24	(1.12, 1.38)
0–9	<16 km	1.23	(1.07, 1.40)	1.22	(1.05, 1.41)
0–25	All	1.12	(1.06, 1.18)	1.12	(1.06, 1.18)
0–25	<16 km	1.11	(1.03, 1.18)	1.10	(1.03, 1.19)

Table 7. Incidence meta-rates for childhood leukaemia in proximity to nuclear facilities by age group and geographic zone: excluding sites that may be contributing to heterogeneity

		Fixed effects		Random effects	
Age group	Geographic zone	Rate	95% CI	Rate	95% CI
0–9	All	1.21	(1.09, 1.35)	1.21	(1.08, 1.35)
0–9	<16 km	1.14	(0.98, 1.33)	1.14	(0.98, 1.33)
0–25	All	1.10	(1.04, 1.17)	1.10	(1.04, 1.17)
0–25	<16 km	1.07	(1.00, 1.15)	1.07	(1.00, 1.15)

considerably to heterogeneity. All SIR analyses were rerun without Amersham (and Dounreay in age group = 0–25 and geographical zone = '<16 km'). Fixed effects and random effects rates were no longer significant for both age groups where geographical zone = '<16 km' (Table 7).

Forest and funnel plots

The log rate and 95% confidence intervals are shown in forest plots for SIR and SMR where age group = 0–9 and geographical zone = '<16 km', likely the most susceptible cohort (Figs 1 and 2). A solid vertical line is presented to indicate a rate equal to one and a dashed vertical line represents the random effects meta-rate. A smaller confidence interval represents a larger study, which will have a greater effect on the meta-rate. Although the majority of studies have rates greater than one, most of these studies have confidence intervals that contain one. Observing these plots, it is difficult to rule out heterogeneity.

The funnel plots (not displayed) do not indicate the presence of significant publication bias.

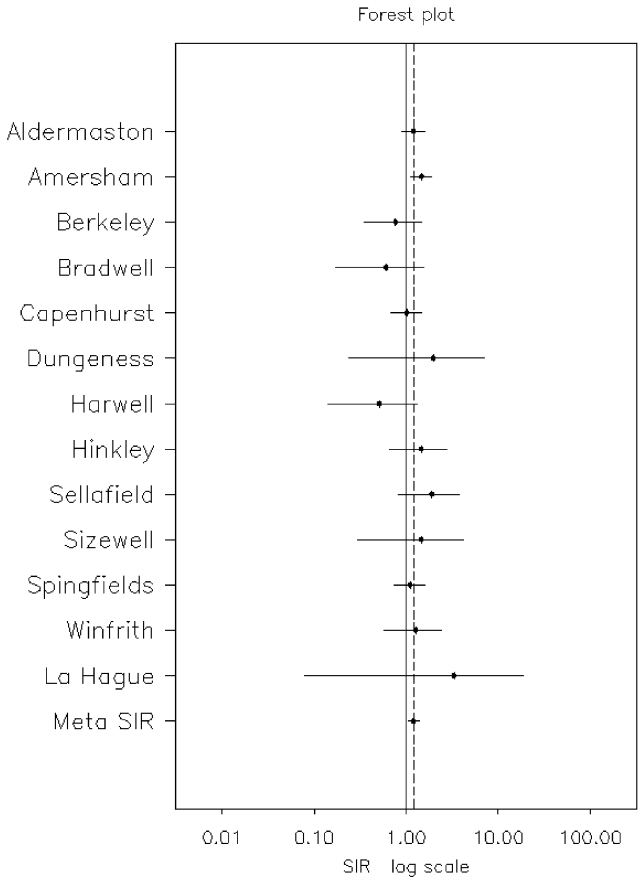

Figure 1. Forest plot of SIR for childhood leukaemia in proximity to nuclear facilities for: age group = 0–9, geographic zone = '<16 km'. Also includes the random effects meta-SIR. SIR, standardized incidence rate.

DISCUSSION

We attempted to compile the most complete list of professional journals and government publications, in English and other languages, from around the world that studied childhood leukaemia in the vicinity of nuclear facilities. Observed and expected numbers were available for 136 nuclear sites in nine countries or former countries. The number of sites allowed for multiple analyses based on area and age. We were able to develop unadjusted mod-

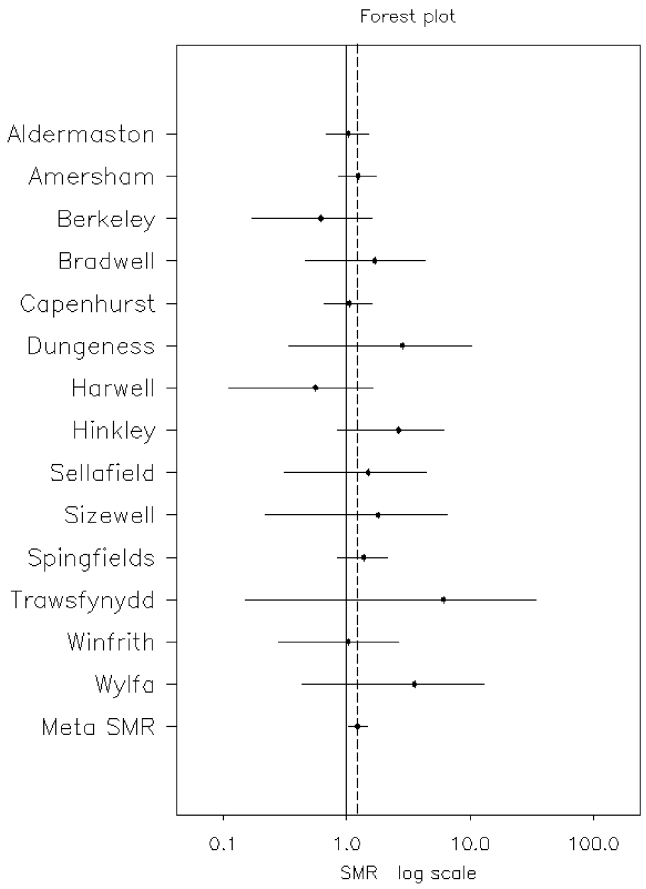

Figure 2. Forest plot of SMR for childhood leukaemia in proximity to nuclear facilities for: age group = 0–9, geographic zone = '<16 km'. Also includes the random effects meta-SMR. SMR, standardized mortality rate.

els (summing all observed and expected and calculating a meta-rate), fixed effects models and random effects models. Meta-SMRs and meta-SIRs were all greater than one. Within geographical zones and for meta-SMRs and meta-SIRs, the 0–9 age group experienced higher standardized rates than the 0–25 age group, suggesting that the 0–9 age group accounted for the majority of the excess cases and deaths. No pattern was found when comparing geographical zones within age groups.

It is highly unlikely that studies for different nuclear sites estimate the same underlying effect size. This is so because there are multiple types of nuclear generators operating at differing capacities, nuclear reprocessing sites, nuclear weapons sites and uranium mining sites. Therefore, even in the absence of evidence of heterogeneity between studies in a given strata, the use of a random effects model is more appropriate. In this meta-analysis, the meta-rates for the fixed effects and random effects models agree so closely that the choice of model is not critical.

Although many of the world's nuclear sites are represented in the meta-analysis, the inclusion rules did not allow certain sites to be used in calculated meta-rates. Four nuclear sites in Sweden were not included because only an overall *P*-value was published. Results in Sweden did not find a positive association between childhood leukaemia and nuclear sites (Waller *et al.* 1995). Israel's nuclear generator was not included because only incidence rates were reported. Similar to Sweden, no excess cases were found (Sofer *et al.* 1991). The inclusion of the Swedish and Israeli sites would have likely decreased the meta-rates, although it is difficult to determine whether that drop would have affected the statistical significance. It would also have been beneficial to include nuclear sites from the former Soviet Union, China and other countries with nuclear facilities. However, that was not possible and the consistently significant results that were found in the meta-analysis cannot be ignored.

Model limitations

The unadjusted model makes no attempt in adjusting for study size. Fixed effects models weight studies based on sample size. Thus, a larger study has more influence on the overall effect than smaller studies. This may be problematic when studying childhood leukaemia, since a possible risk factor is population density. The EUROCLUS study suggests that there might be an increase in cases in the areas of intermediate population density (Alexander *et al.* 1998). Therefore, weighting based on sample size has the unintended result of giving more influence to studies that cover areas of higher population density, a possible risk factor. Another disadvantage is the underlying assumption that each study is estimating the same treatment effect and the treatment effect differs solely as a result of random sample variability (Hedges & Olkin 1985; Friedenreich 1993). The assumption is highly unlikely for reasons explained throughout this paper. Formal tests for heterogeneity were carried out to test the underlying assumptions of fixed effects models. The results were not significant, but such tests suffer from low power (Sutton *et al.* 2000). Random effects models have their own limitations. An important limitation is the assumption that the studies included in the meta-analysis are from a hypothetical random distribution described by a common variance (Friedenreich 1993; Thompson & Sharp 1999). Another potential problem is that random effects models give greater weight to smaller studies than fixed effects models. Smaller studies may be more likely to reflect certain biases, including publication bias

(Thompson & Pocock 1991; Friedenreich 1993; Rothman & Greenland 1998).

Explaining elevated rates near nuclear facilities

Although the meta-analysis found consistently elevated rates for all stratification levels, it is important to note that there are many questions still to be answered; and several hypotheses have been proposed to explain the excess of childhood leukaemia in the vicinity of nuclear facilities, including environmental exposure, paternal exposure and viral transmission [see Laurier and Bard for a thorough summary of these hypotheses (Laurier & Bard 1999)].

Environmental exposure to radiation is a known risk factor for leukaemia (BEIR V 1990; Preston *et al*. 1994; IARC 1999). However, there is a question as to whether the amount of exposure received by children living near nuclear sites is sufficient to increase risk. Authors that have used emissions data from nuclear facilities and conducted dose-response studies have consistently found that plant discharge was too low to account for the excess cases of childhood leukaemia (Committee on Medical Aspects of Radiation in the Environment 1986, 1988, 1989, 1996). It also appears highly unlikely that preconception paternal exposure to radiation increases the risk of leukaemia to the child, an original hypothesis from the Sellafield studies (Urquhart *et al*. 1991; McLaughlin *et al*. 1993a; Parker *et al*. 1993; Draper *et al*. 1997; Pobel & Viel 1997). Several problems arise when conducting dose-response studies in an epidemiologic setting. Determining an individual's dose relies not only on knowledge of plant emissions and geographical parameters but also on the lifestyles of the individuals in the population. Another difficulty is that the expected dose-response relationship is established in an external population, and exposure between the population of interest and the external population may differ. For example, many of the dose-response studies relied on the Life Span Study of Atomic Survivors (Shimizu *et al*. 1988) and the Oxford Survey of Childhood Cancers (Stewart *et al*. 1970). The Life Span Study was a single acute high-dose exposure and the Oxford Survey of Childhood Cancers was intermittent high doses; whereas, the potential exposure from a nearby nuclear facility is most likely a continuous low dose. It may also be that there are interactions between environmental exposures that we are yet to understand. Gibson and Wheldon believe that there may be a synergistic effect between radiation and chemicals that could increase the risk of developing childhood leukaemia (Gibson *et al*. 1968; Wheldon *et al*. 1989).

If the amount of exposure were too low to cause the excess risk, then one would expect that the rates remained consistent before and after the start-up of a nuclear facility. Several studies were able to calculate rates for regions before and after a nuclear facility began operation (Baron 1984; Clarke *et al*. 1989, 1991; Jablon *et al*. 1990; McLaughlin *et al*. 1993b; Mohner & Stabenow 1993). Rates generally remained unchanged before and after start-up, even in regions with elevated rates. For example, Jablon analysed 62 nuclear sites in the USA and found that SMRs for childhood leukaemia in the 0–9 age group were higher before start-up when compared with after start-up. For the four facilities that incidence data were available, three sites had higher SIRs after start-up; however, rates were above one for both time points (Jablon *et al*. 1990). Other authors compared regions that were considered for the installation of a nuclear facility and regions that had an existing nuclear facility. Both types of areas had excess mortality. It was suggested that there might be an unidentified risk factor shared by these regions, other than environmental radiation (Cook-Mozaffari *et al*. 1989).

A hypothesis that has been well received is the possibility of an infectious origin to childhood leukaemia caused by population mixing (Kinlen 1988). When a population is mixed with another population that has not previously been exposed to the virus, individuals in the previously unexposed population may develop the disease (Kinlen *et al*. 1990). Although the possibility of a viral agent is suggested by several studies (Greaves *et al*. 1985; Kinlen *et al*. 1990, 1993; Kinlen & Hudson 1991; Kinlen & John 1994; Smith *et al*. 1998), an infectious agent has yet to be identified.

CONCLUSION

Although there exists papers that summarize the many studies on childhood leukaemia in proximity to nuclear sites, as well as report other potential causes such as the possibility of an infectious origin associated with population mixing (Kinlen 1988; Laurier & Bard 1999), there has not been an attempt to combine and statistically analyse these many studies, which is the purpose of this meta-analysis.

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