Epidemiologic Studies of Leukemia among Persons under 25 Years of Age Living Near Nuclear Sites

Dominique Laurier and Denis Bard

INTRODUCTION

In November 1983, a local television station announced that a high number of cases of leukemia had occurred among children living in Seascale, Great Britain, a village located 3 km from the Sellafield nuclear fuel reprocessing plant. A committee investigation was then launched, and the following year this investigation confirmed the existence of an excess of cases of leukemia among the young people who had lived in Seascale (1). Since then, many epidemiologic studies have set out to analyze the risk of cancer near nuclear sites. They have primarily examined leukemia among the young, that is, those younger than 25 years of age, and most often have considered leukemia globally (codes 204 through 208 of the *International Classification of Diseases*, 9th revision (ICD-9)). Others have focused on specific types: acute lymphoblastic leukemia (ICD-9 code 204.0), acute myeloid leukemia (ICD-9 code 205.0), and chronic myeloid leukemia (ICD-9 code 205.1). Non-Hodgkin's lymphoma, characterized by malignancies similar to leukemia in the lymphoid tissues, has also been studied. Today, after 13 years of accumulated results, the existence of an increased risk of leukemia among young people living near nuclear sites remains highly controversial. The aim of the present literature review is to summarize the primary results obtained from around the world.

In this review we distinguish two types of epidemiologic studies that answer two different questions:

- "Is the frequency of leukemia near nuclear sites higher than it should be?" This question has been approached by descriptive "cluster" studies.

- "What factors are associated with these concentrations of leukemia cases?" This question has been the object of analytical studies, primarily case-control studies.

In view of the diversity of the work that has been published, our presentation gives priority to a factual description of the studies and then discusses generally studies of the same type.

DESCRIPTIVE STUDIES

The frequency of leukemia can be quantified by mortality studies or by incidence studies. Incidence studies are generally preferable for three reasons: 1) the remission rate for acute childhood leukemia is now almost 75 percent (2), 2) mortality rates are declining substantially over time (3), and 3) the type of leukemia can be hard to determine from death certificates (in France, for example, nearly one third of the leukemia death certificates do not specify the type (ICD-9 code 208)). Registries make possible the systematic recording of new leukemia cases on which incidence studies can be based. Some countries, including Great Britain (4) and Germany (5), have set up national childhood leukemia registries. In other countries, registries exist only in some regions (6).

Leukemia is a rare disease among the young. For those younger than 15 years, the incidence rates vary today between 1.5 and 5.0 per 100,000, according to country. Nearly 80 percent of these cases are acute lymphoblastic leukemia (7, 8).

Cluster studies search for an abnormally high concentration of cases at a given time or in a given place. They can concern a particular site ("local" studies) or may simultaneously analyze several sites ("multisite" studies).

Local studies

The first cluster studies examined the frequency of leukemia around particular sites. They were generally very small studies, concerning a single area and a few cases. The published studies are presented below, country by country. Table 1 summarizes the

local studies that showed an excess of leukemia cases.

Great Britain. The first cluster of leukemia cases was detected in England in 1984 near the Sellafield reprocessing plant (West Cumbria). Seven incident cases were recorded between 1955 and 1984 among those younger than 25 years of age living in Seascale, where less than one case was expected ($p < 0.001$) (1). Subsequently, numerous other studies have reanalyzed the situation around Sellafield (9–12). The cluster seems confined to the village of Seascale (12). The persistence of this excess over time has been confirmed by a recent study, with three new cases diagnosed during the 1984–1992 period, compared with the expected 0.16 case ($p = 0.001$) (13).

Two years later, a second cluster in the same age group was reported in Scotland, near the nuclear reprocessing plant of Dounreay (Caithness). It involved five incident cases observed over 6 years within a radius of 12.5 km ($p < 0.001$) (14, 15). It was suggested at the time that this cluster was related to the boundary lines, which cut the town of Thurso in half and included the eastern neighborhood where several of the case children lived. Follow-up of leukemia incidence here has continued, with the study radius extended to 25 km (16). The persistence of this cluster through 1993 was recently confirmed (nine cases observed over 26 years among those aged less than 15 years ($p = 0.03$)) (17).

In 1987, an excess of leukemia incidence was reported within a 10-km radius of the nuclear weapons plants in Aldermaston and Burghfield (West Berkshire). This excess was primarily in those aged 0–4 years (41 cases observed over 14 years among those younger than 15 years of age ($p < 0.02$), 29 of them among those younger than 5 years of age ($p < 0.001$)) (18, 19). In 1992, an excess was observed in the 16-km radius around the Aldermaston site (35 incident cases over 10 years among those aged 0–9 years ($p < 0.003$)) (9). In 1994, another incidence study over a longer period of time (1966–1987) and a wider radius (25 km) did not observe any significant excess near the Aldermaston plant. A slight excess of leukemia was, however, observed near the Burghfield plant (219 cases observed, 198.7 expected ($p = 0.03$)) (12). A year later, a mortality study studied seven districts of Oxfordshire and Berkshire near the sites of Harwell, Aldermaston, and Burghfield (0–14 years of age, from 1981 to 1995). Excess leukemia deaths were reported in the districts of Newbury (11 deaths observed, 5.7 expected ($p = 0.03$)) and South Oxfordshire (12 deaths observed, 4.9 expected ($p = 0.005$)) (20). Nonetheless, the ranking of the seven districts by incidence rates (0–14 years of age, 1969–1993) was not the same, and there was no longer

a significant excess in Newbury, South Oxfordshire, or in any of the other five districts (21).

A fourth cluster was reported in 1989 near the Hinkley Point (Somerset) nuclear power station. Nineteen incident cases were recorded among those aged 0–24 years over a 23-year period ($p < 0.01$) (22). This excess disappeared when the number of expected cases was estimated from regional rather than national rates. No subsequent findings confirmed the existence of this cluster (12).

In 1992, another cluster was reported among children under 10 years of age near the Amersham (Bucks County) plant that produces radioisotopes (60 incident cases recorded over 10 years ($p < 0.003$)) (9). Previous mortality studies had found no significant excess risk near this site, but a trend in the risk of death from leukemia with distance from the site had been suggested (23, 24). Nonetheless, in 1994, an incidence study over a longer period (1966–1987) found neither an excess risk nor any significant trend with distance (12).

United States. From 1965 onward, many studies have examined the health status of populations living near nuclear sites (25). Neither incidence nor mortality studies conducted in California (26) or around the sites at Rocky Flats (Colorado) (27), Hanford (Washington State), or Oak Ridge (Tennessee) (28) showed an excess of leukemia cases. Mangano (29) concluded that the cancer risk around the Oak Ridge site increased substantially between 1950–1952 and 1987–1989, but this study concerned mortality from all types of cancer and all age groups over a zone with a radius of 160 km (29).

An excess of incident leukemia, across all age groups, was noted for the 1982–1984 period around the Pilgrim plant in Massachusetts (30) but was counterbalanced by a deficit of cases for 1985–1986 (31, 32). In 1990, this site was examined as part of a large national study. No excess of leukemia mortality was observed among youth aged 0–19 years. The risk was similar before (1950–1972, 71 deaths observed, 76.3 expected) and after (1973–1984, 29 deaths observed, 30.4 expected) the plant began operation (33).

The Three Mile Island plant (Pennsylvania) has also been the object of study. Exposure following the 1978 accident and that associated with routine emissions have been reconstructed. Hatch et al. (34) noted that the incidence of leukemia among children (0–14 years, 1975–1985) tended to increase with dose in the regions most exposed by the accident, but this increase involved only four cases and was not statistically significant. The same trend was observed for exposure to routine emissions. Reexamining exactly the same data in 1997, Wing et al. (35) concluded that leukemia incidence for all ages tended to increase with the dose

TABLE 1.   Descriptive local studies of leukemia frequency among young people living near nuclear sites, in which an excess of leukemia was reported

Site and country	Study (reference no.) and year	Study period	Age (years)	Incidence (I)/ mortality (M)	Histologic type*	Zone (radius)	Cases Observed (O)	Cases Expected (E)	Cases O/E	95% confidence interval
Sellafield, Great Britain	Black (1), 1984	1955–1984	0–24	I	L	Village of Seascale	5	0.5	10.2	3.3, 23.8
	Goldsmith (9), 1992	1971–1980	0–9	I	L	(16 km)	8	4.2	1.9	0.8, 3.8
	Draper et al. (11), 1993	1963–1990	0–24	I	LL + NHL	Village of Seascale	6	<1	>10	
	Bithell et al. (12), 1994	1966–1987	0–14	I	L + NHL	(25 km)	24	18.5	1.3	0.8, 1.9
	COMARE† (13), 1996	1984–1992	0–24	I	LL + NHL	Village of Seascale	3	0.16	19.1	3.8, 55.8
Dounreay, Scotland	Heasmah et al. (14), 1986	1979–1984	0–24	I	L	(12.5 km)	5	0.5	9.8	3.1, 22.7
	COMARE (15), 1988	1968–1984	0–24	I	L	(25 km) (12.5 km)	6 5	3.0 1.5	2.0 3.3	0.7, 4.4 1.0, 7.6
	Black et al. (16), 1994	1968–1991 1985–1991	0–24	I	L + NHL	(25 km)	12 4	5.2 1.4	2.3 2.8	1.2, 4.0 0.7, 7.0
	Sharp et al. (17), 1996	1968–1993	0–14	I	L + NHL	(25 km)	9	4.5	2.0	0.9, 3.8
Aldermaston and Burghfield, Great Britain	Roman et al. (18), 1987	1972–1985	0–14 0–4	I	L	(10 km)	41 29	28.6 14.4	1.4 2.0	1.0, 1.9 1.3, 2.9
Aldermaston	Goldsmith (9), 1992	1971–1980	0–9	I	L	(16 km)	35	23.9	1.5	1.0, 2.0
Burghfield‡	Bithell et al. (12), 1994	1966–1987	0–14	I	L + NHL	(25 km)	219	198.7	1.1	1.0, 1.3
Aldermaston‡	Bithell et al. (12), 1994	1966–1987	0–14	I	L + NHL	(25 km)	160	145.8	1.1	0.9, 1.3
Aldermaston Burghfield-Harwell	Busby and Cato (20), 1997	1981–1995	0–14	M	L	Seven districts	47	33.0	1.4	1.0, 1.9
Aldermaston Burghfield-Harwell	Draper and Vincent (21), 1997	1969–1993	0–14	I	L	Seven districts	173	162.4	1.1	0.9, 1.2
Hinkley Point, Great Britain	Ewings et al. (22), 1989	1984–1986	0–24	I	L + NHL	(12.5 km)	19	10.4	1.8	1.1, 2.9
	Bithell et al. (12), 1994	1966–1987	0–14	I	L + NHL	(25 km)	57	57.2	1.0	0.8, 1.3
Amersham, Great Britain	Cook-Mozaffari et al. (24), 1989	1969–1978	0–24	M	L	(16 km)			1.2	
	Goldsmith (9), 1992	1971–1980	0–9	I	L	(16 km)	60	40.6	1.5	1.1, 1.9
	Bithell et al. (12), 1994	1966–1987	0–14	I	L + NHL	(25 km)	388	406.9	1.0	0.9, 1.1
La Hague, France	Dousset (41), 1989	1970–1982	0–24	M	L	(10 km)	0	0.4	0	0, 8.9
	Viel and Richardson (42), 1990	1968–1986	0–24	M	L	(35 km) (10 km)	21 1	23.6 1.1	0.9 0.9	0.6, 1.4 0.0, 4.9
	Hill and Laplanche (43), 1992	1968–1987	0–24	M	L	(21 km) (10 km)	12 1	14.9 0.8	0.8 1.2	0.4, 1.4 0.0, 7.0
	Viel et al. (44), 1993	1978–1990	0–24	I	L	(35 km) (10 km)	23 3	19.6 1.2	1.2 2.5	0.7, 1.8 0.5, 7.3
	Hattchouel et al. (55), 1955	1968–1989	0–24	M	L	(16 km)	2	5.4	0.4	0.1, 7.3
	Viel et al. (45), 1995	1978–1992	0–24	I	L	(35 km) (10 km)	25 4	22.8 1.4	1.1 2.8	0.7, 1.6 0.8, 7.3
	Guizard et al. (47), 1997	1993–1996	0–24	I	L	(30 km) (10 km)	8 0	7.1 0.7	1.1 0	0.5, 2.2 0.0, 5.5

Krümmel, Germany						
Grosche (37), 1992	1990–1991	0–14	—	L	Village of Elbmarsch (10 km)	5	0.1	41.7	13.4, 97.2
Lackland et al. (40), 1997	1990–1996	0–14	—	L		9	2.8	3.2	1.6, 6.0

* Histologic type: L, leukemia; LL, lymphoid leukemia; NHL, non-Hodgkin's lymphoma.
† COMARE, Committee on Medical Aspects of Radiation in the Environment.
‡ Not independent.

associated with the accident, but did not specifically analyze leukemia in children.

Israel. A study was performed near the Dimona nuclear generating station (Negev). Between 1960 and 1985, 192 new cases were counted among those under 25 years of age over the entire zone (maximum distance from the station, 45 km). The authors concluded that there was no excess incidence of leukemia near the power plant (36).

Germany. During 1990 and 1991, five children younger than 15 years of age living in the village of Elbmarsch, several kilometers from the nuclear power station at Krümmel (Schleswig-Holstein), were diagnosed with leukemia when only 0.12 cases were expected ($p < 0.001$) (37–39). Between 1994 and 1996, four new cases appeared in a 10-km radius around the plant (only one in Elbmarsch), thereby suggesting that this excess is persisting over time (nine cases observed over 7 years ($p < 0.002$)) (39, 40).

France. Between 1989 and 1992, three studies examined mortality from leukemia among those younger than 25 years of age, near the La Hague reprocessing plant (Nord Cotentin)—no excess mortality from leukemia was observed near the plant (41–43). In 1993, an incidence study of those aged 0–25 years found neither an excess risk near the plant nor a gradient of risk with distance (23 cases from 1978 through 1990) (44). Two years later, the same team resumed this study with a follow-up continued through 1992, and concluded an apparent existence of a cluster of childhood leukemia within a 10-km radius around the plant (four cases observed over 15 years, compared with 1.4 expected), at the borderline of statistical significance ($p = 0.06$) (45). A scientific committee was then set up to verify the existence of this excess risk (46). At the committee's request, the monitoring of leukemia incidence in the area was prolonged. No new cases were reported for the 1993–1996 period in the 10-km zone (47).

Multisite studies

In response to the local studies, multisite studies began in 1984; they are intended to test on a global basis the increase in the frequency of leukemia near all the nuclear sites of a region or a country. Because these studies involve large numbers, from several dozen to several thousand cases, they have better statistical power than is possible for local studies. The latters' results can thus be interpreted within a larger, more general framework. Table 2 summarizes the principal studies.

Great Britain. The first multisite study was carried out in Great Britain and analyzed cancer mortality data for all age groups combined around 14 nuclear sites.

TABLE 2. Descriptive "multi-site" studies of leukemia frequency among young people living near nuclear sites

Study (reference no.) and year	Country (locale)	No. of sites	Study period	Age (years)	Zone (radius)	Incidence (I)/ mortality (M)	Histologic type*	No. of cases	Conclusion
Baron (48), 1984	Great Britain	6	1963–1979	0–14	14 local authority areas	M	L	33	Global relative risk of 1.5; same risk at start-up and 5–10 years after
Forman et al. (23), 1987	Great Britain	14	1959–1980	0–24	(10 km)	M	LL	44	Global relative risk of 2
Cook-Mozaffari et al. (24), 1989	Great Britain	15 (+ 8 possible)	1969–1978	0–24	(16 km)	M	L	635	Excess mortality of 15% around sites; similar excess found around possible sites
Jablon et al. (52), 1991	United States	62	1950–1984	0–9	107 counties	M + I	L	1,390	No overall significant excess; no difference before and after start-up
Grosche (37), 1992	Germany (Bavaria)	5	1983–1989	0–14	(10 km)	I	L	16	No overall excess except in towns where sites are located
Goldsmith (9), 1992	Great Britain	14	1971–1980	0–9	(16 km)	I	L	200	No excess for power plants; excess at Sellafield, Aldermaston, and Amersham
Hill and Laplanche (43), 1992	France	6	1968–1987	0–24	(16 km)	M	L	58	No significant excess
McLaughlin et al. (54), 1993	Canada (Ontario)	5	1950–1987 1964–1986	0–14	(25 km)	M I	L	54 95	No overall excess
Michaelis et al. (58), 1992	Germany	20 (+ 6 possible)	1980–1990	0–14	(15 km)	I	AL	274	No excess, except for 0–4 years living <5 km from sites where operations began before 1970
Bithell et al. (12), 1994	Great Britain	23 (+ 6 possible)	1966–1987	0–14	(25 k m)	I	L + NHL	4,100	No overall excess, except around Sellafield and Burghfield
Iwasaki et al. (60), 1995	Japan	44	1973–1987	0–14	18 municipalities	M	L	33	No overall excess risk
Waller et al. (61), 1995	Sweden	4	1980–1990	0–14	Entire country	I	ALL	656	Risk of leukemia not higher at the four sites than elsewhere
Hattchouel et al. (55), 1995	France	13	1968–1992	0–24	(16 km)	M	L	69	No significant excess risk
Sharp et al. (17)	Scotland	6	1968–1993	0–14	(25 km)	I	L + NHL	399	No overall excess, except around Dounreay

* Histologic type: L, leukemia; LL, lymphoid leukemia; AL, acute leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma.

Supplementing this study of the overall population, a limited study examined leukemia mortality among children aged 0–14 years and living around six nuclear sites that began operations between 1962 and 1965. Considering periods 1963–1970 and 1972–1979 together, an excess of leukemia deaths was observed (a total of 33 deaths around these six sites, where 21.8 were expected ($p < 0.05$)), but there was no increase of leukemia mortality between the moment of start-up and 10 years later (48). This study of risk among the young was expanded to 14 sites in 1987 (23). Although the analysis concluded that mortality from all types of cancer did not increase among the 0- to 24-year-old age group near the 14 nuclear sites, it observed that mortality from lymphoid leukemia among the young was twice as high as in the control zones ($p < 0.005$). Two years later, this analysis was reopened still using mortality data, but with modified methods. It was concluded that there was an excess, on the order of 15 percent of leukemia mortality among those under 25 years of age living near these sites ($p < 0.01$) (24). Nonetheless, they noted that a similar excess had been recorded near "potential" sites under consideration for construction of nuclear plants (this aspect is discussed below) (49).

A study of leukemia incidence from 1971 through 1980 around the 14 nuclear sites did not observe an excess of cases around nuclear plants overall, but did conclude that an excess risk existed around a group of pre-1955 plants (in particular Sellafield, Aldermaston, and Amersham) (9).

In 1994, an incidence study was effectuated for all of England (29 sites). This study, probably the largest so far conducted in this domain, concerned nearly 4,000 leukemia incident cases and used improved statistical methodology, compared with prior studies. It was concluded that the frequency of leukemia had not increased around nuclear sites in England except at Sellafield ($p < 0.001$) and Burghfield ($p < 0.03$) (12).

In Scotland, Sharp et al (17) used the same methodology to analyze the incidence of leukemia around six nuclear sites among individuals younger than 15 years of age. These authors also concluded that leukemia incidence had not increased around the nuclear sites, except at Dounreay ($p = 0.03$) (17).

United States. Jablon et al. (33, 50, 51), in 1991, conducted a vast study which compared mortality from cancer in 107 counties with a nuclear installation and 292 control counties. In all, it considered 2.7 million cancer deaths that occurred between 1950 and 1984, including 1,390 leukemia deaths among children 0–9 years of age (50). The study did not find any increase in mortality from leukemia among children in the counties with nuclear sites (51). Moreover, mortality

from leukemia was similar before (relative risk (RR) among those 0–9 years of age = 1.08) and after (RR = 1.03) the plants began operations (33).

As part of this study, incidence data could also be analyzed for the counties in two states, Connecticut and Iowa. An excess of leukemia was detected near the Millstone plant (44 cases observed compared with 28.4 expected cases among those 0–9 years of age ($p < 0.01$)), but it began before the plant began operating. The authors concluded that their results did not indicate any excess risk of cancer near nuclear sites. Nonetheless, this study has an important limitation: the size of the geographic units considered. If an excess were to occur in the immediate vicinity of a given nuclear site, it is improbable that it would be visible for the entire county in which the site is located (52).

Canada. An Ontario study (53, 54), based on data from the cancer registry, did not show any overall increase in the risk of leukemia near five nuclear sites among those younger than 15 years, either for the incidence of leukemia (95 cases observed, 88.8 expected) or its mortality (54 deaths observed, 46.1 expected). This remained true whether the cases were identified according to place of birth or of diagnosis. Finally, the risks observed before and after start-up were similar (study limited to the Pickering plant).

France. Two multisite analyses of cancer mortality have been published (43, 55). Both studies concluded that the number of leukemia deaths recorded near French nuclear sites among those younger than 25 years was similar to the number expected. The same conclusion was reached for other types of cancer and for leukemia recorded for all age groups from 0 to 65 years (56, 57).

Germany. A study by Grosche (37) analyzed the risk of leukemia near five Bavarian nuclear sites. An excess of incident cases was observed in the communities where the sites were located, but this result was based on a total of only five cases and could not be reproduced using another set of data. The author concluded that there was an absence of excess overall. An incidence study (58) carried out in 1992 involved 20 nuclear sites and was based on data from the national children's cancer registry (West Germany). It found no excess in the number of leukemia cases among those under 15 years of age living less than 15 km from a nuclear site. The authors did observe an increased risk among those younger than 5 years living less than 5 km from sites that began operations before 1970 ($p < 0.02$). They attributed this to a particularly low incidence in the control zones selected. This analysis was recently extended to cover 16 years (1980–1995) and some installations in the former East Germany (59). It found an excess of leukemia near the Krümmel plant.

Nonetheless, the risk of leukemia within a 15-km radius around the sites considered was identical to that in the control zones, although the relative risk among the children under 5 years of age living less than 5 km from the sites remained on the borderline of significance (RR = 1.49; 95 percent confidence interval (CI): 0.98, 2.20).

Japan. In a mortality study among those aged less than 15 years in 18 municipalities containing 44 nuclear reactors, the risk of death from leukemia did not differ from that in the control municipalities (60).

Sweden. The existence of leukemia clusters among those less than 15 years of age living near four nuclear sites was analyzed as part of a study of the geographic distribution of leukemia incidence in Sweden. Three independent methods were used to test an increase in the probability of a cluster according to its proximity to a given site. A cluster (based on only two cases) was detected near the Forsmark nuclear plant, but was not confirmed by the other two methods. The authors concluded that the probability of leukemia clusters was not higher near the four nuclear sites than elsewhere (61).

Other relevant studies

Studies around potential sites. Three of the multisite studies (12, 49, 58) also considered the frequency of leukemia among young people near sites where the construction of a nuclear installation was envisaged.

In Great Britain, a mortality study considered eight potential sites (six sites under serious consideration for nuclear plants and two sites where plants began operations after the study period). The relative risk of childhood leukemia around these sites was nearly identical to that observed around existing nuclear sites (RR = 1.14 compared with 1.16) (49).

Also in Great Britain, an incidence study analyzed the incident cases of leukemia around six sites for which the suitability of constructing nuclear installations had been investigated. No excess was observed around any of these sites (12).

The incidence study performed in Germany, in 1992, included six sites where the construction of nuclear installations had been considered. The relative risk was slightly higher than that recorded around existing sites (58).

Clusters far from any nuclear site. Excess leukemia has also been observed in areas where there is no nuclear site.

In Scotland, an acute lymphoblastic leukemia cluster was reported among those aged 0–14 years in the Largo Bay region (district of Kirkcaldy); 11 incident cases were observed, compared with 3.6 expected, from 1970 through 1984 ($p < 0.001$) (62). A second

cluster of leukemia was uncovered in the region of Cambuslang, near Glasgow. Nine cases of leukemia were recorded between 1975 and 1988 among those under 25 years of age, compared with 3.6 expected ($p < 0.02$). This excess of leukemia was also apparent among adults (63–65).

In Germany, five cases of childhood leukemia were recorded from 1987 through 1989 in the village of Sittensen (more than 40 km from the nearest nuclear reactor), where only 0.4 cases were expected ($p < 0.001$) (37).

In Italy, a cluster was detected in the city of Carbonia, with seven cases recorded between 1983 and 1985 compared with 0.82 expected ($p < 0.001$) (66). A case-control study has been launched to seek the causes of this cluster (67).

Studies of the geographic distribution of leukemia. Whether leukemia tends to cluster, independent of the location of nuclear sites, is not a new question. In 1964, Ederer et al. published an article entitled "A statistical problem in space and time: do leukemia cases come in clusters?" (68). Since then, numerous studies have looked at the distribution of leukemia cases over time and in space. These studies generally take into account large areas and thus consider very large numbers. Several types of methods have been used: Knox's test (based on the distance between pairs of cases, in time and space) (69–72), systematic sampling throughout regions by circles of different radii (73, 74), or tests of extra-Poisson variability (75–79).

Several studies conducted in the Netherlands (80), in Germany (75), in England and Wales (81), and in Sweden (61, 74) have concluded that leukemia does not come in clusters. Nonetheless, most studies have concluded that leukemia cases have a "natural" tendency to cluster. Most have considered England (70, 71, 73, 76, 82–84), but Greece (72, 78) and Hong Kong (79) have also been considered. Very recently, an international study of more than 13,000 cases, concluded that there is a tendency, small but significant, towards spatial clustering of childhood leukemia cases (85).

Discussion of the descriptive studies

The "ecologic" character of cluster studies means that they are subject to some recognized biases: No individual information is available, monitoring of the migration of subjects is not possible, and the results depend upon the limits and numbers of zones chosen as well as upon, among other things, the period, the age group considered, the definition of the disease, and the source of the reference rates (86, 87). With only a few exceptions (the studies around Three Mile Island (34, 35)), these studies do not take into account any

information about the exposure levels in the various zones. The distance to the site is, therefore, the only reflection, even indirect, of the level of any possible exposure.

These studies generally concern small numbers observed in small zones. Very high standardized incidence ratios or standardized mortality ratios are obtained in relation to a number of expected cases that is often close to or less than one (see above the examples of the clusters at Seascale, Dounreay, La Hague, and Krümmel). These results are very sensitive to random fluctuations in the spatial and temporal distribution of observed cases, fluctuations that can be quite substantial for rare diseases such as leukemia (88). Most current statistical methods are based on the hypothesis that leukemia cases occur according to a Poisson distribution. If, as recent geographic studies indicate, leukemia cases have a natural tendency toward clustering (so that a simple Poisson law cannot adequately represent their distribution), then this hypothesis may well be inappropriate for testing an excess of cases around a given point.

Some uncertainty can also exist concerning the estimation of the number of expected cases. The size of the resident population is generally obtained by interpolation between censuses. This method does not allow consideration of population migrations that might have take place between two successive censuses. Reference rates are sometimes obtained from small registries and are thus based upon limited numbers of cases. These reference rates are then likely to present some variability in time and space. This uncertainly about the expected numbers is almost never considered in the calculation of standardized incidence ratios.

Two phenomena may lead to overestimating the number of clusters. First, some studies have been performed specifically in response to an announcement of an excess (the Seascale cluster, for example). They, therefore, have as their goal the verification of the existence of this excess, and not the evaluation of the probability of rejecting the null hypothesis (no excess of cases near the sites studied). As cluster research mostly takes place near nuclear sites, this could exaggerate the proportion of excess leukemia cases in these areas. Secondly, the probability that a cluster study will be published is probably higher if it concludes that an excess exists than if it concludes that the level of risk is normal (publication bias).

Cluster studies raise problems concerning both analytical methodology (89, 90) and the interpretation of results (91, 92). In response to the question concerning the value of this type of study (93), some authors and organizations have drafted recommendations and pro-

cedural guidelines for performing or interpreting cluster studies (94, 95). To limit the risk of mistaken conclusions, the first suggestion is that monitoring the area around a site should be continued after any cluster is observed in order to verify the persistence of the excess. The second suggestion is to adjust for factors that might influence the frequency of leukemia, such as, for example, socioeconomic status (96, 97). A third solution is to develop new methods to reduce some of the defects of these studies. Methodological research on this theme can almost be said to have boomed (89, 98–103). In particular, new methods can free researchers from the limitations inherent in the choice of geographic zone borders. Such techniques include Stone's test (17, 45, 104, 105), as well as the possibility of not counting by zone at all but, rather, assessing the distance of each case from the site in question, by using, for example, point process and smoothing methods (45, 106, 107). Other approaches using Bayesian methods take into account the strong instability of the rates calculated in very small geographic units (108, 109). New computer tools that facilitate extensive geocoding of spatial phenomena (in particular the use of geographic information systems) should help extend and generalize the use of these methods for spatial analysis (74, 90, 110, 111).

We note that the issue of leukemia around nuclear sites is not the only problem using this type of investigation, and many other studies have also considered the spatial distribution of diseases (leukemia or other) near non-nuclear sites, such as industrial facilities (111–113) and radio transmitters (114, 115). The increased use of this type of analysis has even led to the creation in Great Britain of a unit specialized in the analysis of spatial phenomena—the Small Area Health Statistics Unit (116).

Communicating these results is also sensitive, especially because the announcement that a local excess of cancer cases has been observed often receives substantial media coverage. Efforts to improve the interpretation and communication of the results of this type of study to the general public are also needed (117).

Conclusion about descriptive studies

The descriptive studies of the frequency of leukemia near nuclear sites are limited by their methodology. The current development of new methods should help reduce some of these defects.

These studies show that an excess of leukemia exists near some nuclear sites (at least, for the reprocessing plants at Sellafield and Dounreay). Nonetheless, the results of the multisite studies do not support the hypothesis that the frequency of leukemia generally increases among young people living near nuclear

sites. Furthermore, excesses of leukemia have also been shown far from any nuclear site and around potential sites, and studies of the geographic distribution of leukemia show that incident cases tend toward spatial clustering.

ANALYTICAL STUDIES

Beginning in the 1990s, analytical studies have searched for factors that might explain these localized excesses of leukemia (118). Thus, the descriptive studies that found case clusters around a nuclear site have often been followed by one or more analytical studies. Reviewing the history of different leukemia clusters (Sellafield, Dounreay, Aldermaston-Burghfield, Krümmel, La Hague), we see a fairly similar time sequence: 1) a local excess of leukemia cases is reported; 2) its existence is evaluated by a committee of experts; 3) an analytical study is set up to research its causes.

The latter are most often case-control studies. Table 3 summarizes the characteristics and the results of seven case-control studies specifically concerned with the risk of leukemia around nuclear sites. Other types of studies have also been carried out: prospective (16, 119, 120), radioecologic (121, 122), and geographic (123, 124).

Risk factors for leukemia

Research on the risk factors for leukemia extends far beyond the limits of studies of clusters around nuclear sites (125, 126). Today, some of these risk factors are known or suspected (127). Nonetheless, they concern only a small proportion of cases, and most cases of leukemia are without any known cause.

The recognized risk factors are exposure to ionizing radiation (during childhood or in utero) (128, 129), consumption of some medications (e.g., chloramphenicol), and some congenital malformations (e.g., trisomy 21) (130). A high socioeconomic status seems to be associated with an increased incidence of childhood leukemia (131). Other suggested risk factors include maternal smoking (132), viral infections during pregnancy (133–135), and exposure to pesticides during childhood (136).

Hypotheses proposed to explain leukemia clusters

In addition to the various risk factors described above, three principal hypotheses have been explored regarding leukemia clusters near nuclear sites: paternal preconceptional exposure, environmental exposure to ionizing radiation, and an infectious cause.

Paternal preconceptional exposure. The hypothesis of a genetically transmitted disease was advanced

in 1990 by Gardner et al. to attempt to explain the Sellafield cluster (137, 138). In this case-control study, the authors observed that, according to their dosimetric records, fathers of children with leukemia had higher preconceptional exposure than did fathers of children without leukemia. In particular, four (of 46) fathers of children with leukemia had received a cumulative dose greater than 100 mSv before conception, compared with three (of 276) among the controls. The relative risk was thus estimated at 8.3 (95 percent CI: 1.4, 50.5; $p < 0.05$). This relation also existed when only the dose received during the 6 months preceding conception was considered. The authors then hypothesized that fathers' exposure to radiation before conception provoked germ cell mutations that resulted in an increased frequency of leukemia in their offspring. According to Gardner et al. (138), this relation was strong enough to explain the Seascale cluster.

Several studies then tried to verify the existence of this relation. In 1991, the case-control study around Dounreay did not find any such relation, and the authors concluded that occupational exposure of fathers could not explain the Dounreay cluster (139). Thereafter, two case-control studies observed a significant association of leukemia with fathers' preconceptional dose. One was a 1991 study around Sellafield, but of the six cases on which the association was based, three had already been included in Gardner's 1990 study (140). The other was a 1993 report about the area near the Aldermaston and Burghfield nuclear weapons plants in which the relation was based on three cases and two controls (141). Most studies that have analyzed this relation, however, have not found any significant association (119, 125, 142–144). Recently, Gardner's hypothesis was examined in an immense study based on record-linkage between the National Registry of Childhood Tumours and the National Registry for Radiation Workers (13,621 cases of childhood leukemia and non-Hodgkin's lymphoma diagnosed in Great Britain between 1952 and 1986, and 15,995 controls). The frequency of leukemia was four times (but not significantly) higher among the children of parents occupationally exposed to ionizing radiation, but there was no trend of risk according to the fathers' preconceptional dose. The authors concluded that their results did not support Gardner's hypothesis (145).

In addition, this hypothesis is inconsistent with the absence of an increased risk among the offspring of Hiroshima and Nagasaki (Japan) survivors (146), as well as with the absence of any increase in the frequency of leukemia in the villages around Seascale, where many Sellafield workers also live. The overall results require that this hypothesis now be abandoned (147, 148).

TABLE 3. Case-control studies of risk factors for leukemia clusters near nuclear sites

Study (reference no.) and year	Country	Zone	Sites included in the zone	Study period	Age (years)	Histologic type*	Cases/ controls	Conclusions
Gardner et al. (138), 1990	Great Britain	District of West Cumbria	Sellafield	1950–1985	0–24	L	52/357	Paternal preconceptual exposure to radiation
Urquhart et al. (139), 1991	Scotland	Caithness	Dounreay	1970–1986	0–14	L + NHL	14/55	Use of local beaches
McKinney et al. (140), 1991	Great Britain	Seven districts	Cumbria, Humberside, Gateshead	1974–1988	0–14	L + NHL	109–206	Paternal preconceptual exposure to radiation, wood dust, and/or benzene
McLaughlin et al. (142), 1992	Canada	Ontario	Five sites	1950–1988	0–14	L	112/890	No relation to paternal preconceptual exposure to radiation
Roman et al. (141), 1993	Great Britain	West Berkshire, Basingstoke, North Hampshire	Burghfield, Aldermaston	1972–1989	0–4	L + NHL	54/324	Paternal preconception exposure to radiation, no dose-effect relation
Kaatsch et al. (187), 1996	Germany	Lower Saxony	Elbmarsch, Sittensen	1988–1993	0–14	AL	219/863	No vaccination or immunization during infancy, prematurity, frequency of miscarriages
Pobel and Viel (144), 1997	France	Nord-Cotentin	La Hague	1978–1993	0–24	L	27/192	Use of local beaches; consumption of local fish and shellfish; living in a granite house

* Histologic type: L, leukemia; AL, acute leukemia; NHL, non-Hodgkin's lymphoma.

Environmental exposure to ionizing radiation. Exposure to ionizing radiation is a recognized risk factor for cancer in humans. It has been shown in several studies, in particular the follow-up of Hiroshima and Nagasaki survivors (149), but also the follow-up of populations treated by radiation therapy (128) or exposed in utero (129). Leukemia is recognized as one of the types of cancer that can be induced by ionizing radiation among young people (0–24 years), with a fairly short latency period after exposure (several years) (128).

Two types of studies have been set up to study this hypothesis: case-control studies and radioecologic studies.

Case-control studies have examined some types of behavior that might lead to increased radiation exposure or contamination. This is the case for recreational use of beaches and consumption of seafood, both of which could reflect increased exposure to possible marine contamination.

In the study near Seascale (138), no increased risk was observed with use of local beaches (odds ratio (OR) = 0.6 for use more than once a month; 95 percent CI: 0.2, 1.6). The Dounreay study, on the other hand, reported that risk increased significantly for children who went to local beaches more than once a month ($p < 0.04$). This relation, however, was based on only five cases, and the authors thought that this result might be an artefact (139). In the case-control study of the area around the La Hague reprocessing plant, a significant association was observed with recreational beach-going—by children (OR = 2.9 for use greater than once a month; 95 percent CI: 1.0, 8.7) and by mothers during pregnancy (OR = 4.5 for use greater than once a month; 95 percent CI: 1.5, 15.2) (144).

No significant association with the consumption of seafood was observed in either the Sellafield (138) or Dounreay (139) case-control studies. In the La Hague study, a relation on the borderline of significance was noted with the frequency of consumption of "local" fish and shellfish (OR = 3.7; 95 percent CI: 0.9, 9.5 for consumption more often than once monthly) (144), but no information was available about the exact provenance of the seafood.

It is clear that while this approach has the advantage of being based on individual data, the factors studied can only be considered remote indicators of environmental exposure (to radioisotopes or to other toxic substances). A conclusion on the basis of such data that any link exists between the risk of leukemia and environmental contamination requires much caution as well as an estimate of the dose that might be attributed to these activities.

The objective of radioecology studies around nuclear sites is to reconstruct the doses of ionizing radiations received by the neighboring population and, if possible, to estimate the associated cancer risk. These evaluations must be thorough, realistic, and based on discharge data or environmental radioactivity measurements and on a characterization as representative as possible of the local population (numbers, behavior).

The National Radiological Protection Board in Great Britain has effectuated several radioecology studies near nuclear sites after the detection of excess cases of childhood leukemia (121, 122, 150, 151). An analogous investigation is underway in France around the La Hague site (152).

The first radioecology analysis at Seascale began in 1984 (150). A second thorough dose reconstruction for the area around Sellafield was published in 1995 (13, 122); it took into account the various routes of contamination (external exposure, internal contamination) as well as all the possible sources of exposure (medical exposure, terrestrial and cosmic radioactivity, fallout from atomic testing and from Chernobyl (Ukraine), and routine waste from other sites). Birth registries helped reconstitute the population of young people between 0 and 24 years of age who had lived in Seascale between 1945 and 1992. Within that population, 80 percent of the estimated collective dose to the bone marrow was attributable to natural radioactivity and roughly 9 percent to routine discharges from the Sellafield plant. The number of expected cases attributable to radiation exposure can be calculated at 0.46 and 0.05, respectively, for all sources of exposure and for routine discharge from Sellafield (compared with the 12 cases actually recorded in Seascale between 1955 and 1992). The authors concluded that the excess of leukemia observed in the village of Seascale cannot be explained by environmental exposure to radiation (13).

Around Dounreay, the study conducted in 1986 concluded that the number of leukemia cases attributable to radiation exposure in the town of Thurso (where several cases in the initial cluster resided, roughly 10 km from the Dounreay reprocessing plant) was 0.34 (dose reconstruction for the population of youth aged 0–24 years born between 1950 and 1984), 80 percent of which was attributable to natural radioactivity (121).

In 1987, the radioecology study conducted around the factories at Aldermaston and Burghfield (18) concluded that the marrow dose attributable to waste discharged from these plants within a 5-km radius was at least 1,000 times lower than the dose due to natural exposure (151).

Overall, the dose estimations carried out around nuclear sites have shown that the doses attributable to

plant waste discharge constitute, at most, several percent (reaching 10 percent for Sellafield) of the total dose. In view of current knowledge about the relation between exposure to radiation and the risk of leukemia, these dose levels are incompatible with the excess risks observed around some nuclear sites. Moreover, leukemia clusters have been shown in areas far from any nuclear site. The studies conducted in the zones where nuclear sites were envisaged have concluded that the frequency of leukemia is as high near these potential sites (that is, where no radioactive waste has been discharged) as it is near active nuclear sites (12, 49, 58). Other studies have observed a similar frequency of mortality from leukemia before and after operations began at the sites under study (33).

The overall information currently available indicates that the hypothesis of a causal role of environmental exposure to radioactivity is not sufficient to explain leukemia clusters among young people near nuclear installations (13, 153).

Infectious agents. The hypothesis of an infectious etiology was proposed long ago for some types of leukemia. A virus transmits leukemia in cats (127). In humans, some viruses have been found to be associated with the development of some forms of lymphoma or leukemia. Examples include the Epstein Barr virus with Burkitt lymphoma and human T-cell lymphotrophic virus type 1 with adult T-cell leukemia (154, 155). During the 1970s and 1980s, many studies suggested that exposure to a viral agent during pregnancy (in particular, influenza) was associated with the occurrence of cancer (including leukemia) in children (133, 156, 157), but these results remain controversial (158). A recent German case-control study (121 cases, 197 controls) showed a higher rate of Epstein Barr virus infection during childhood in children with leukemia than in controls (159).

The hypothesis that childhood leukemia has a viral etiology was developed with a model in which the virus could be present in many individual carriers, but where very few subjects develop the disease (as for feline leukemia or infectious mononucleosis in humans) (160, 161). Nevertheless, such an unknown virus has not been detected in any child with leukemia. A second similar hypothesis supposes that the immune response to an infection, rather than a specific infectious agent, might be the origin of some types of leukemia (162). The combination of no immunization during early childhood and late exposure to infection might initiate an exaggerated immune response leading to cellular proliferation and the subsequent development of leukemia (163). Work showing a reduced risk of leukemia among children who attended day care at a very young age supports this hypothesis (164).

To explain the existence of concentrations of leukemia cases near some nuclear installations, Kinlen (161) has hypothesized viral transmission favored by high rates of population mixing that occur during the construction of these large industrial sites. The movement of migrant populations with a high infectious potential into rural zones would then facilitate contact between healthy virus carriers and susceptible subjects, and thereby cause a local increase in the frequency of leukemia. Such an increase was observed during the development of new towns in rural areas of England and Scotland (165), but has not been seen in France (166, 167). In another work, Kinlen et al. (123) suggest that the excess leukemia observed in the Dounreay region may be associated with the influx of population into the area following the development of the North Sea petroleum industry. Finally, a recent study observed that during the construction of industrial sites in rural regions of Great Britain, the risk of leukemia increased 37 percent among children younger than 15 years of age, a finding apparently compatible with considering such mixing to be a partial explanation of the Seascale cluster (13, 124, 168). Other recent work along similar lines adds support to this hypothesis (169).

Geographic studies showing that leukemia cases tend to cluster naturally in time and space also indirectly support this hypothesis (69–73, 79, 83, 170, 171). Other works showing an association with paternal occupation (172) or suggesting seasonality in the occurrence of leukemia (173, 174) also point in the same direction. In all, more than twenty independent studies now support the infectious or immune hypothesis (175, 176), although the biologic mechanisms have not been demonstrated.

Other hypotheses. Radon is a natural radioactive gas present especially in granite and volcanic subsoils. It is known to induce lung cancer (177). The largest part of the dose delivered by radon and its by-products (daughters) is deposited in airways, but a part of this irradiation may also be delivered to the hematopoietic bone marrow (178). Some ecologic studies have suggested that residential exposure to radon may be related to leukemia risk (179, 180). Nonetheless, no such relation was found in children in a recent very large study (76). Furthermore, cohort studies of uranium miners have not shown any increased risk of leukemia (181), and a recent and large case-control study concluded that cumulative residential radon exposure was not associated with the risk of acute lymphobalstic leukemia among children younger than 15 years of age (182). In the La Hague case-control study, a significant association was observed between duration of residence in a home built of granite or on gran-

ite soil and the risk of leukemia. The authors suggest that such an association could reflect a causal relation with residential radon exposure (144), but this characterization of the residence cannot be more than a very imprecise indicator of radon exposure.

Exposure to chemical pollutants has also been studied (183). Nonetheless, this hypothesis was dismissed in the context of the Seascale cluster study (13).

Discussion of the analytical studies

Limitations of case-control studies. The case-control studies present the usual risks of bias associated with this type of protocol (184). Nonetheless, in the studies of leukemia clusters around nuclear sites, some of these biases can be particularly important. Selection bias is more likely to occur when working with very few subjects (185). The main bias is recall bias, especially when parents are asked to remember how their children behaved during a childhood that may have been 20 or 30 years earlier. Such a bias is all the more likely to occur in a region where a major polemic about the risks of leukemia subsequently occurred in the region.

The case-control studies of leukemia clusters usually involve very few subjects—for the Sellafield reprocessing plant, 52 cases and 357 controls (138); for the Dounreay reprocessing plant, 14 cases and 55 controls (139); for the Aldermaston and Burghfield weapons factories, 54 cases and 324 controls (141); and for the La Hague reprocessing plant, 27 cases and 192 controls (144). All these studies have a limited power capable of observing only a strong association.

For the Krümmel plant cluster in Germany, a complete descriptive study, the only kind possible in view of the paucity of cases, did not uncover any factor that could link the five observed leukemias (37, 40, 186). The group of experts convoked for that occasion recommended that a large case-control study be set up from the overall data of the German Childhood Cancer Registry. An initial feasibility study was carried out in Lower Saxony (187). A case-control study is now underway for all of the former West Germany (59), with two objectives, the study of the risk factors associated with the occurrence of leukemia near nuclear sites (more than 600 cases and 600 controls) and the study of risk factors associated with clusters of leukemia cases independent of the presence of a nuclear site (more than 900 cases and 900 controls).

Limitations of radioecology studies. Estimating the radioactive dose received by the resident populations in the radioecology studies involves several steps: estimation of environmental exposure based on waste discharge or environmental measurements, modeling the behavior of radionuclides in the environment, and

modeling the metabolism of radioelements as a function of the different possible routes of absorption. Each step is based on many hypotheses and integrates many approximations and uncertainties (122, 188). Knowledge about the lifestyle and the behavior of the neighboring populations is often sparse (189). Therefore, many uncertainties persist in the dose estimations, and the final estimation must basically be considered as an order of magnitude of the dose received by the population.

The estimation of the risk of leukemia attributable to environmental exposure also involves several hypotheses. The risk models used are those recommended by international commissions (128, 190). They are derived principally from results from the follow-up of Hiroshima and Nagasaki survivors, with complementary input from studies of the effects of in utero exposure (13, 122). There are, again, uncertainties—about the adequacy of these coefficients and, in particular, their application to low doses received over long periods, about taking into account the variations of risk according to age, and about the relative importance of in utero exposure (122).

Approaches using physical dosimetry methods have been applied to evaluate the exposure of populations living near some nuclear sites. Measurements of the plutonium and strontium-90 concentrations in human teeth showed a gradient with the distance from Sellafield (191). As part of the study of the Dounreay cluster, in vivo radioactivity measurements were taken of 60 people living near the Dounreay plant (subjects with leukemia, their parents, other local residents) and a group of 42 controls living in areas far from any nuclear site. The measurements included ^{239}Pu and ^{90}Sr in urine, ^{241}Am in bones, gamma contamination by whole body counts, and chromosomal anomaly counts. No difference in the contamination levels of these two groups was observed (192). Such estimates of individual doses could prove to be useful in carrying out analytical studies testing the hypothesis of an association between doses received in the vicinity of nuclear installations and leukemia risk. Another approach to estimating individual dose might rely on biologic dosimetry, such as chromosomal aberration counts (193). However, the validity and precision of such an approach for very low doses remains hotly debated.

Limitations of the studies of the infectious hypothesis. Almost all studies assessing the hypothesis that the leukemia clusters have an infectious etiology are ecologic studies. They analyze the distribution of incidence rates in time and space, in relation to dates and places where important population mixing occurred. This is the case for the studies by Kinlen et al. (123, 124, 168), which seek to verify the consistency of this

hypothesis in explaining the clusters around Sellafield and Dounreay. These studies thus entail the limitations inherent in this type of approach (see the discussion about descriptive studies above) (161).

Conclusion about the analytical studies

Most of the studies carried out to search for the causes of leukemia clusters have important limitations (whether these involve the size of their populations, possible bias, or imprecision) that demand much prudence in the interpretation of their results. Nonetheless, the accumulation of results, although it does not uncover any definite risk factor, allows us to reject several hypotheses, in particular those related to paternal preconceptional exposure to radiation and to environmental exposure to ionizing radiation.

The information used to analyze the causes of the clusters is based on only a few cases (10 in Seascale, nine in Dounreay, and in Krümmel) that have been intensively studied (194). From these few cases we can hardly expect more results than they have already furnished. It is probable that future developments in our understanding of the causes of these clusters will not come from local studies but, rather, from systematic large-scale studies.

CONCLUSION

The descriptive studies effectuated since 1983 have shown the existence of high concentrations, or clusters, of leukemia cases among young people near some nuclear installations. This observation is not, however, a general rule, and case clusters have also been observed far from any nuclear site.

Although analytical studies set up to search for the causes of such excesses near nuclear sites have resulted in the rejection of some hypotheses, they have not yet provided a definitive explanation for the clusters observed. Many elements have led to the abandonment of the hypothesis of a relation with paternal preconceptional exposure to radiation and that of an association with environmental exposure to radiation. Other hypotheses have been proposed, in particular that of an infectious etiology, but its validity at an individual level has yet to be proven.

The existence of leukemia clusters around some nuclear installations constitutes an important public health question that extends beyond epidemiologic considerations: we must be aware that public perception of these risks generates fear and anxiety in those living in the vicinity of nuclear sites. Therefore, specific responses to this worry are needed. One possible action is to provide the public with information that is as honest, comprehensive, and clear as possible. It

should include facts about received doses and risk levels in the vicinity of nuclear installations. The former is, at least partly, compulsory in most developed countries (regulatory environmental radioactivity monitoring). Another step is the implementation of systematic and rigorous surveillance of leukemia incident cases around nuclear sites, through registries. Such an approach has recently been advocated in France (195). This kind of surveillance could also be used in other settings or at the national level, as it is, for example, in the United Kingdom and Germany (4, 5). Finally, the development of research on individual sensitivity, exposure, or effect biomarkers may. in the future, provide more sensitive tools that may also prove useful for epidemiologic purposes.

REFERENCES

1. Black D. Investigation of the possible increased incidences of cancer in West Cumbria. London, United Kingdom: Her Majesty's Stationary Office, 1984.
2. Liesner RJ, Goldstone AH. ABC of clinical haematology: the acute leukaemias. BMJ 1997;314:733–6.
3. Hill C, Benhamou E, Doyon F, et al. Evolution de la mortalité par cancer en France entre 1950 et 1985. (In French). Paris, France: Institut National de la Santé et de la Recherches Médicale (INSERM), 1989.
4. Stiller CA, Allen MB, Eatock EM. Childhood cancer in Britain: the National Registry of Childhood Tumours and incidence rates 1978–1987. Eur J Cancer 1995;31A:2028–34.
5. Kaatsch P, Haaf G, Michaelis J. Childhood malignancies in Germany—methods and results of a nationwide registry. Eur J Cancer 1995;31A:993–9.
6. Parkin DM, Muir CS, Whelan SL, et al. Cancer incidence in five continents. Vol VI. Lyon, France: International Agency for Research on Cancer, 1992. (IARC scientific publication no. 120).
7. Parkin DM, Stiller CA, Draper GJ, et al. The international incidence of childhood cancer. Int J Cancer 1988;42:511–20.
8. Stiller CA, Parkin DM. Geographic and ethnic variations in the incidence of childhood cancer. Br Med Bull 1996;52: 682–703.
9. Goldsmith JR. Nuclear installations and childhood cancer in the UK: mortality and incidence for 0–9-year-old children, 1971–1980. Sci Total Environ 1992;127:13–35.
10. Craft AW, Parker L, Openshaw S, et al. Cancer in young people in the north of England, 1968–85: analysis by census wards. J Epidemiol Community Health 1993;47:109–15.
11. Draper GJ, Stiller CA, Cartwright RA, et al. Cancer in Cumbria and in the vicinity of the Sellafield nuclear installation, 1963–90. BMJ 1993;306:89–94.
12. Bithell JF, Dutton SJ, Draper GJ, et al. Distribution of childhood leukaemias and non-Hodgkin's lymphomas near nuclear installations in England and Wales. BMJ 1994;309: 501–5.
13. Committee on Medical Aspects of Radiation in the Environment. The incidence of cancer and leukaemia in young people in the vicinity of the Sellafield site, West Cumbria: further studies and an update of the situation since the publication of the report of the Black Advisory Group in 1984. (COMARE IV). London, United Kingdom: Department of Health, 1996.
14. Heasman MA, Kemp IW, Urquhart JD, et al. Childhood

leukaemia in northern Scotland. (Letter). Lancet 1986;1:266.

15. Committee on Medical Aspects of Radiation in the Environment. Investigation of the possible increased incidence of childhood cancer in young persons near the Dounreay nuclear establishment, Caithness, Scotland. (COMARE II). London, United Kingdom: Her Majesty's Stationary Office, 1988.

16. Black RJ, Sharp L, Harkness EF, et al. Leukaemia and non-Hodgkin's lymphoma: incidence in children and young adults resident in the Dounreay area of Caithness, Scotland, in 1968–91. J Epidemiol Community Health 1994;48:232–6.

17. Sharp L, Black RJ, Harkness EF, et al. Incidence of childhood leukaemia and non-Hodgkin's lymphoma in the vicinity of nuclear sites in Scotland, 1968–93. Occup Environ Med 1996;53:823–31.

18. Roman E, Beral V, Carpenter L, et al. Childhood leukaemia in the West Berkshire and Basingstoke and North Hampshire District Health Authorities in relation to nuclear establishments in the vicinity. Br Med J (Clin Res Ed) 1987;294: 597–602.

19. Committee on Medical Aspects of Radiation in the Environment. Investigation of the possible increased incidence of childhood cancer in the West Berkshire and North Hampshire area, in which are situated the Atomic Weapons Research Establishment, Aldermaston, and the Royal Ordnance Factory, Burghfield. (COMARE III). London, United Kingdom: Her Majesty's Stationary Office, 1989.

20. Busby C, Cato MS. Death rates from leukaemia are higher than expected in areas around nuclear sites in Berkshire and Oxfordshire. (Letter). BMJ 1997;315:309.

21. Draper GJ, Vincent TJ. Death rates from childhood leukaemia near nuclear sites: findings were probably due to chance fluctuations in small numbers of deaths. (Letter). BMJ 1997;315:1233.

22. Ewings PD, Bowie C, Phillips MJ, et al. Incidence of leukaemia in young people in the vicinity of Hinkley Point nuclear power station, 1959–86. BMJ 1989;299:289–93.

23. Forman D, Cook-Mozaffari P, Darby S, et al. Cancer near nuclear installations. Nature 1987;329:499–505.

24. Cook-Mozaffari PJ, Darby SC, Doll R, et al. Geographical variation in mortality from leukaemia and other cancers in England and Wales in relation to proximity to nuclear installations, 1969–78. Br J Cancer 1989;59:476–85.

25. Patrick CH. Trends in public health in the population near nuclear facilities: a critical assessment. Nucl Saf 1977;18: 647–62.

26. Enstrom JE. Cancer near a California nuclear power plant. (Letter). Lancet 1985;2:1249.

27. Crump KS, Ng TH, Cuddihy RG. Cancer incidence patterns in the Denver metropolitan area in relation to the Rocky Flats plant. Am J Epidemiol 1987;126:127–35.

28. Goldsmith JR. Childhood leukaemia mortality before 1970 among populations near two US nuclear installations. (Letter). Lancet 1989;1:793.

29. Mangano JJ. Cancer mortality near Oak Ridge, Tennessee. Int J Health Serv 1994;24:521–33.

30. Clapp RW, Cobb S, Chan CK, et al. Leukaemia near Massachusetts nuclear power plant. (Letter). Lancet 1987; 2:1324–5.

31. Poole C, Rothman KJ, Dreyer NA. Leukaemia near Pilgrim nuclear power plant, Massachusetts. (Letter). Lancet 1988; 2:1308.

32. Wilson R. Leukemias in Plymouth County, Massachusetts. (Letter). Health Phys 1991;61:279.

33. Jablon S, Hrubec Z, Boice JD, Jr., et al. Cancer in populations living near nuclear facilities. Vol 2: Individual facilities: cancer before and after start-up. Washington, DC: US Department of Health and Human Services, Public Health Service, National Cancer Institute, 1990. (NIH publication no. 90-874-2).

34. Hatch MC, Beyea J, Nieves JW, et al. Cancer near the Three Mile Island nuclear plant: radiation emissions. Am J

Epidemiol 1990;132:397–412.

35. Wing S, Richardson D, Armstrong D, et al. A reevaluation of cancer incidence near the Three Mile Island nuclear plant: the collision of evidence and assumptions. Environ Health Perspect 1997;105:52–7.

36. Sofer T, Goldsmith JR, Nusselder I, et al. Geographical and temporal trends of childhood leukemia in relation to the nuclear plant in the Negev, Israel, 1960–1985. Public Health Rev 1991;19:191–8.

37. Grosche B. Leucémies infantiles dans le voisinage des centrales nucléaires en Allemagne. Symposium sur les agrégats de leucémie. (In French). Ottawa, Ontario, Canada: Atomic Energy Control Board, 1992:19–25.

38. Schmitz-Feuerhake I, Schroder H, Dannheim B, et al. Leukaemia near water nuclear reactor. (Letter). Lancet 1993; 342:1484.

39. Hoffmann W, Dieckmann H, Dieckmann H, et al. A cluster of childhood leukemia near a nuclear reactor in northern Germany. Arch Environ Health 1997;52:275–80.

40. Grosche B, Lackland D, Mohr L, et al. Leukemia in the vicinity of two tritium releasing nuclear facilities: a comparison of the Krümmel site, Germany, and the Savannah River site, South Carolina, USA. J Radiol Prot 1999;19:243-52.

41. Dousset M. Cancer mortality around La Hague nuclear facilities. Health Phys 1989;56:875–84.

42. Viel JF, Richardson ST. Childhood leukaemia around the La Hague nuclear waste reprocessing plant. BMJ 1990;300: 580–1.

43. Hill C, Laplanche A. Mortalité par cancer autour d'installations nucléaires françaises entre 0 et 24 ans. (In French). Paris, France: Institut National de la Santé et de la Recherches Médicale (INSERM)/Douin, 1992.

44. Viel JF, Richardson S, Danel P, et al. Childhood leukemia incidence in the vicinity of La Hague nuclear-waste reprocessing facility (France). Cancer Causes Control 1993;4: 341–3.

45. Viel JF, Pobel D, Carre A. Incidence of leukaemia in young people around the La Hague nuclear waste reprocessing plant: a sensitivity analysis. Stat Med 1995;14:2459–72.

46. Comité scientifique pour une nouvelle étude épidémiologique dans le Nord Cotentin. Rapport final: volets épidémiologique et radioécologique. (In French). Paris, France: Ministère de l'Environnement et de l'Aménagement du Territoire, 1997.

47. Guizard AV, Spira A, Troussard X, et al. Incidence of leukemias in people aged 0 to 24 in north Cotentin. (In French). Rev Epidemiol Sante Publique 1997;45:530–5.

48. Baron JA. Cancer mortality in small areas around nuclear facilities in England and Wales. Br J Cancer 1984;50: 815–24.

49. Cook-Mozaffari P, Darby S, Doll R. Cancer near potential sites of nuclear installations. Lancet 1989;2:1145–7.

50. Jablon S, Hrubec Z, Boice JD Jr, et al. Cancer in populations living near nuclear facilities. Vol 1: Report and summary. Washington, DC: US Department of Health and Human Services, Public Health Service, National Cancer Institute, 1990. (NIH publication no. 90-874-1).

51. Jablon S, Hrubec Z, Boice JD Jr, et al. Cancer in populations living near nuclear facilities. Vol 3: Individual facilities: cancer by 5-year time intervals. Washington, DC: US Department of Health and Human Services, Public Health Service, National Cancer Institute, 1990. (NIH publication no. 90-874-3).

52. Jablon S, Hrubec Z, Boice JD Jr. Cancer in populations living near nuclear facilities: a survey of mortality nationwide and incidence in two states. JAMA 1991;265:1403–8.

53. Clarke EA, McLaughlin J, Anderson TW. Childhood leukaemia around Canadian nuclear facilities—Phase I: Final report. Ottawa, Ontario, Canada: Atomic Energy Control Board, 1989. (Report INFO 300).

54. McLaughlin JR, Clarke EA, Nishri ED, et al. Childhood leukemia in the vicinity of Canadian nuclear facilities.

Cancer Causes Control 1993;4:51–8.

55. Hattchouel JM, Laplanche A, Hill C. Leukaemia mortality around French nuclear sites. Br J Cancer 1995;71:651–3.

56. Hattchouel JM, Laplanche A, Hill C. Mortalité par cancer autour d'installations nucléaires françaises entre 0 et 64 ans. (In French). Paris, France: Institut National de la Santé et de la Recherches Médicale (INSERM), 1995.

57. Hattchouel JM, Laplanche A, Hill C. Cancer mortality around French nuclear sites. Ann Epidemiol 1996;6:126–9.

58. Michaelis J, Keller B, Haaf G, et al. Incidence of childhood malignancies in the vicinity of West German nuclear power plants. Cancer Causes Control 1992;3:255–63.

59. Michaelis J. Recent epidemiological studies on ionizing radiation and childhood cancer in Germany. Int J Radiat Biol 1998;73:377–81.

60. Iwasaki T, Nishizawa K, Murata M. Leukaemia and lymphoma mortality in the vicinity of nuclear power stations in Japan, 1973–1987. J Radiol Prot 1995;15:271–88.

61. Waller LA, Turnbull BW, Gustafsson G, et al. Detection and assessment of clusters of disease: an application to nuclear power plant facilities and childhood leukaemia in Sweden. Stat Med 1995;14:3–16.

62. Gerrard M, Eden OB, Stiller CA. Variations in incidence of childhood leukaemia in south east Scotland (1970–1984). Leuk Res 1986;10:561–4.

63. Hole DJ, Lamont DW, Brogan RT, et al. Concurrent childhood and adult excesses of leukaemia in geographical areas. (Letter). Lancet 1994;343:1439–40.

64. Alexander FE, Cartwright RA, McKinney PA. Leukaemia in Cambuslang. (Letter). Lancet 1994;344:551–2.

65. Wilkie D. Leukaemia in Cambuslang. (Letter). Lancet 1994;344:551–2.

66. Cocco P, Bernardinelli L, Biddau P, et al. Childhood acute lymphoblastic leukemia: a cluster in southwestern Sardinia (Italy). Int J Occup Environ Health 1995;1:232–8.

67. Cocco P, Rapallo M, Targhetta R, et al. Analysis of risk factors in a cluster of childhood acute lymphoblastic leukemia. Arch Environ Health 1996;51:242–4.

68. Ederer F, Myers MH, Mantel N. A statistical problem in space and time: do leukemia cases come in clusters? Biometrics 1964;20:626–38.

69. Knox EG, Gilman E. Leukaemia clusters in Great Britain. 1. Space-time interactions. J Epidemiol Community Health 1992;46:566–72.

70. Knox EG, Gilman E. Leukaemia clusters in Great Britain. 2. Geographical concentrations. J Epidemiol Community Health 1992;46:573–6.

71. Gilman EA, Knox EG. Childhood cancers: space-time distribution in Britain. J Epidemiol Community Health 1995; 49:158–63.

72. Petridou E, Revinthi K, Alexander FE, et al. Space-time clustering of childhood leukaemia in Greece: evidence supporting a viral aetiology. Br J Cancer 1996;73:1278–83.

73. Openshaw S, Craft AW, Charlton M, et al. Investigation of leukaemia clusters by use of a geographical analysis machine. Lancet 1988;1:272–3.

74. Hjalmars U, Kulldorff M, Gustafsson G, et al. Childhood leukaemia in Sweden: using GIS and a spatial scan statistic for cluster detection. Stat Med 1996;15:707–15.

75. Westermeier T, Michaelis J. Applicability of the Poisson distribution to model the data of the German Children's Cancer Registry. Radiat Environ Biophys 1995;34:7–11.

76. Richardson S, Monfort C, Green M, et al. Spatial variation of natural radiation and childhood leukaemia incidence in Great Britain. Stat Med 1995;14:2487–501.

77. Muirhead CR, Butland BK. Methods for investigating localized clustering of disease: testing for over-dispersion using an adapted form of the Potthoff-Whittinghill method. IARC Sci Publ 1996;(135):40–52.

78. Petridou E, Alexander FE, Trichopoulos D, et al. Aggregation of childhood leukemia in geographic areas of Greece. Cancer Causes Control 1997;8:239–45.

79. Alexander FE, Chan LC, Lam TH, et al. Clustering of childhood leukaemia in Hong Kong: association with the childhood peak and common acute lymphoblastic leukaemia and with population mixing. Br J Cancer 1997;75:457–63.

80. van Steensel-Moll HA, Valkenburg HA, Vandenbroucke JP, et al. Time space distribution of childhood leukaemia in the Netherlands. J Epidemiol Community Health 1983;37:145–8.

81. Cartwright RA, Alexander FE, McKinney PA, et al. Leukaemia and lymphoma: an atlas of distribution within areas of England and Wales 1984–1988. London, United Kingdom: Leukaemia Research Fund, 1990.

82. Gibson BE, Eden OB, Barrett A, et al. Leukaemia in young children in Scotland. (Letter). Lancet 1988;2:630.

83. Draper GJ, ed. The geographical epidemiology of childhood leukaemia and non-Hodgkin lymphomas in Great Britain 1966–83. Studies on medical and population subjects no. 53. London, United Kingdom: Her Majesty's Stationary Office, 1991.

84. Stewart A, Kneale G. Childhood cancer and nuclear installations. (Letter). Lancet 1994;343:111.

85. Alexander FE, Boyle P, Carli PM, et al. Spatial clustering of childhood leukaemia: summary results from the EURO-CLUS project. Br J Cancer 1998;77:818–24.

86. Richardson S, Stucker I, Hemon D. Comparison of relative risks obtained in ecological and individual studies: some methodological considerations. Int J Epidemiol 1987;16: 111–20.

87. Diggle P, Elliott P. Disease risk near point sources: statistical issues for analyses using individual or spatially aggregated data. J Epidemiol Community Health 1995;49(Suppl 2): S20–7.

88. Valenty M, Laurier D. Geographic distribution of leukemia mortality in young people aged 0–24 years in France. (In French). Rev Epidemiol Sante Publique 1997;45:527–30.

89. Hills M, Alexander F. Statistical methods used in assessing the risk of disease near a source of possible environmental pollution: a review. J R Stat Soc A 1989;152:353–63.

90. Elliott P, Martuzzi M, Shaddick G. Spatial statistical methods in environmental epidemiology: a critique. Stat Methods Med Res 1995;4:137–59.

91. Cradduck TD. Leukaemia clusters: real or random? (Editorial). Nucl Med Commun 1992;13:859–60.

92. Urquhart JD. Studies of disease clustering: problems of interpretation. In: Elliott P, Cuzick J, English D, et al., eds. Geographical and environmental epidemiology: methods for small-area studies. Oxford, United Kingdom: Oxford University Press, 1996:278–85.

93. Wartenberg D. Should we boost or bust cluster investigations? (Editorial). Epidemiology 1995;6:575–6.

94. Guidelines for investigating clusters of health events. MMWR Morb Mortal Wkly Rep 1990;39(RR-11):1–23.

95. Wartenberg D, Greenberg M. Solving the cluster puzzle: clues to follow and pitfalls to avoid. Stat Med 1993;12:1763–70.

96. Elliott P. Investigation of disease risks in small areas. Occup Environ Med 1995;52:785–9.

97. Dolk H, Mertens B, Kleinschmidt I, et al. A standardisation approach to the control of socioeconomic confounding in small area studies of environment and health. J Epidemiol Community Health 1995;49(Suppl 2):S9–14.

98. Waller LA, Lawson AB. The power of focused tests to detect disease clustering. Stat Med 1995;14:2291–308.

99. Elliott P, Cuzick J, English D, et al., eds. Geographical and environmental epidemiology: methods for small-area studies. Oxford, United Kingdom: Oxford University Press, 1996.

100. Alexander FE, Cuzick J. Methods for the assessment of disease clusters. In: Elliott P, Cuzick J, English D, et al., eds. Geographical and environmental epidemiology: methods for small-area studies. Oxford, United Kingdom: Oxford University Press, 1996:238–50.

101. Richardson S. Current developments in biostatistics. (In French). Rev Epidemiol Sante Publique 1996;44:482–93.

102. Openshaw S. Methods for investigating localized clustering of disease: tests of clustering based on pattern-recognition procedures. IARC Sci Publ 1996;(135):203-6.

103. Black RJ, Sharp L, Urquhart JD. Methods for investigating localized clustering of disease: analysing the spatial distribution of disease using a method of constructing geographical areas of approximately equal population size. IARC Sci Publ 1996:28-39.

104. Stone RA. Investigations of excess environmental risks around putative sources: statistical problems and a proposed test. Stat Med 1988;7:649–60.

105. Shaddick G, Elliott P. Use of Stone's method in studies of disease risk around point sources of environmental pollution. Stat Med 1996;15:1927–34.

106. Lawson AB, Williams FL. Applications of extraction mapping in environmental epidemiology. Stat Med 1993;12:1249–58.

107. Lawson AB, Viel JF. Tests for directional space-time interaction in epidemiological data. Stat Med 1995;14:2383–91.

108. Mollie A, Richardson S. Empirical Bayes estimates of cancer mortality rates using spatial models. Stat Med 1991;10:95–112.

109. Lawson AB. MCMC methods for putative pollution source problems in environmental epidemiology. Stat Med 1995;14:2473–85.

110. Briggs DJ, Elliott P. The use of geographical information systems in studies on environment and health. World Health Stat Q 1995;48:85–94.

111. Knox EG, Gilman EA. Hazard proximities of childhood cancers in Great Britain from 1953–80. J Epidemiol Community Health 1997;51:151–9.

112. Elliott P, Shaddick G, Kleinschmidt I, et al. Cancer incidence near municipal solid waste incinerators in Great Britain. Br J Cancer 1996;73:702–10.

113. Wilkinson P, Thakrar B, Shaddick G, et al. Cancer incidence and mortality around the Pan Britannica Industries pesticide factory, Waltham Abbey. Occup Environ Med 1997;54:101–7.

114. Dolk H, Shaddick G, Walls P, et al. Cancer incidence near radio and television transmitters in Great Britain. I. Sutton Coldfield transmitter. Am J Epidemiol 1997;145:1–9.

115. Dolk H, Elliott P, Shaddick G, et al. Cancer incidence near radio and television transmitters in Great Britain. II. All high power transmitters. Am J Epidemiol 1997;145:10–17.

116. Elliott P, Westlake AJ, Hills M, et al. The Small Area Health Statistics Unit: a national facility for investigating health around point sources of environmental pollution in the United Kingdom. J Epidemiol Community Health 1992;46:345–9.

117. Greenberg M, Wartenberg D. Understanding mass media coverage of disease clusters. Am J Epidemiol 1990;132:S192–5.

118. Shleien B, Ruttenber AJ, Sage M. Epidemiologic studies of cancer in populations near nuclear facilities. Health Phys 1991;61:699–713.

119. Parker L, Craft AW, Smith J, et al. Geographical distribution of preconceptional radiation doses to fathers employed at the Sellafield nuclear installation, West Cumbria. BMJ 1993; 307:966–71.

120. Gardner MJ. Childhood leukaemia around the Sellafield nuclear plant. In: Elliott P, Cuzick J, English D, et al., eds. Geographical and environmental epidemiology: methods for small-area studies. Oxford, United Kingdom: Oxford University Press, 1996:291–309.

121. Dionan J, Muirhead CR, Wan SL, et al. The risks of leukemia and other cancers in Thurso from radiation exposure. National Radiological Protection Board. London, United Kingdom: Her Majesty's Stationary Office, 1986. (NRPB-R196).

122. Simmonds JR, Robinson CA, Philipps AW. et al. Risks of leukemia and other cancers in Seascale from all sources of ionising radiation exposure. National Radiological

Protection Board. Chilton, United Kingdom: Her Majesty's Stationary Office, 1995. (NRPB-R276).

123. Kinlen LJ, O'Brien F, Clarke K, et al. Rural population mixing and childhood leukaemia: effects of the North Sea oil industry in Scotland, including the area near Dounreay nuclear site. BMJ 1993;306:743–8.

124. Kinlen LJ, Dickson M, Stiller CA. Childhood leukaemia and non-Hodgkin's lymphoma near large rural construction sites, with a comparison with Sellafield nuclear site. BMJ 1995; 310:763–8.

125. Sorahan T, Roberts PJ. Childhood cancer and paternal exposure to ionizing radiation: preliminary findings from the Oxford Survey of Childhood Cancers. Am J Ind Med 1993; 23:343–54.

126. Robison LL, Buckley JD, Bunin G. Assessment of environmental and genetic factors in the etiology of childhood cancers: the Childrens Cancer Group epidemiology program. Environ Health Perspect 1995;103(Suppl 6):111–16.

127. Ross A, Davies SM, Potter JD, et al. Epidemiology of childhood leukemia, with a focus on infants. Epidemiol Rev 1994; 16:243–72.

128. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionising radiation. UNSCEAR 1994 report to the General Assembly, with scientific annexes. New York, NY: United Nations, 1994.

129. Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. Br J Radiol 1997;70:130–9.

130. Robison LL. Down syndrome and leukemia. Leukemia 1992;6:5–7.

131. Alexander FE, Ricketts TJ, McKinney PA, et al. Community lifestyle characteristics and lymphoid malignancies in young people in the UK. Eur J Cancer 1991;27:1486–90.

132. Golding J, Paterson M, Kinlen LJ. Factors associated with childhood cancer in a national cohort study. Br J Cancer 1990;62:304–8.

133. Fedrick J, Alberman ED. Reported influenza in pregnancy and subsequent cancer in the child. BMJ 1972;2:485–8.

134. Bithell JF, Draper GJ, Gorbach PD. Association between malignant disease in children and maternal virus infections. Br Med J 1973;1:706–8.

135. Blot WJ, Draper G, Kinlen L, et al. Childhood cancer in relation to prenatal exposure to chickenpox. Br J Cancer 1980; 42:342–4.

136. Meinert R, Kaatsch P, Kaletsch U, et al. Childhood leukaemia and exposure to pesticides: results of a case-control study in northern Germany. Eur J Cancer 1996;32A: 1943–8.

137. Gardner MJ, Hall AJ, Snee MP, et al. Methods and basic data of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. BMJ 1990;300:429–34.

138. Gardner MJ, Snee MP, Hall AJ, et al. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. BMJ 1990;300: 423–9.

139. Urquhart JD, Black RJ, Muirhead MJ, et al. Case-control study of leukaemia and non-Hodgkin's lymphoma in children in Caithness near the Dounreay nuclear installation. BMJ 1991;302:687–92.

140. McKinney PA, Alexander FE, Cartwright RA, et al. Parental occupations of children with leukaemia in West Cumbria, north Humberside, and Gateshead. BMJ 1991;302:681–7.

141. Roman E, Watson A, Beral V, et al. Case-control study of leukaemia and non-Hodgkin's lymphoma among children aged 0–4 years living in west Berkshire and north Hampshire health districts. BMJ 1993;306:615–21.

142. McLaughlin JR, Anderson TW, Clarke EA, et al. Occupational exposure of fathers to ionising radiations and the risk of leukaemia in offspring—a case control study. Ottawa, Ontario, Canada: Atomic Energy Control Board, 1992.

143. Kinlen LJ. Can paternal preconceptional radiation account

for the increase of leukaemia and non-Hodgkin's lymphoma in Seascale? BMJ 1993;306:1718–21.

144. Pobel D, Viel JF. Case-control study of leukaemia among young people near La Hague nuclear reprocessing plant: the environmental hypothesis revisited. BMJ 1997;314:101–6.

145. Draper GJ, Little MP, Sorahan T, et al. Cancer in the offspring of radiation workers: a record linkage study. BMJ 1997;315:1181–8.

146. Yoshimoto Y, Neel JV, Schull WJ, et al. Malignant tumors during the first two decades of life in the offspring of atomic bomb survivors. Am J Hum Genet 1990;46:1041–52.

147. Doll R, Evans HJ, Darby SC. Paternal exposure not to blame. Nature 1994;367:678–80.

148. Little MP, Charles MW, Wakeford R. A review of the risks of leukemia in relation to parental pre-conception exposure to radiation. Health Phys 1995;68:299–310.

149. Preston DL, Kusumi S, Tomonaga M, et al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. Radiat Res 1994; 137(suppl):S68–97.

150. Stather JW, Wrixon AD, Simmonds JR. The risks of leukemia and other cancers in Seascale from radiation exposure. National Radiological Protection Board. London, United Kingdom: Her Majesty's Stationary Office, 1984. (NRPB-R177).

151. Dionan J, Wan SL, Wrixon AD. Radiation doses to members of the public around AWRE, Aldermaston, ROF, Burghfield and AERE, Harwell. National Radiological Protection Board. London, United Kingdom: Her Majesty's Stationary Office, 1987. (NRPB-R202).

152. Groupe Radioécologie Nord Cotentin. Rapport final. (In French). Fontenay-aux-Roses, France: Ministère de l'Environnement et de l'Aménagement du Territoire, 1999.

153. Doll R. Epidemiological evidence of effects of small doses of ionising radiation with a note on the causation of clusters of childhood leukaemia. J Radiol Prot 1993;13:233–41.

154. Mueller N. Overview: viral agents and cancer. Environ Health Perspect 1995;103(Suppl 8):259–61.

155. Cavrois M, Wain-Hobson S, Gessain A, et al. Adult T-cell leukemia/lymphoma on a background of clonally expanding human T-cell leukemia virus type-1-positive cells. Blood 1996;88:4646–50.

156. Austin DF, Karp S, Dworsky R, et al. Excess leukemia in cohorts of children born following influenza epidemics. Am J Epidemiol 1975;101:77–83.

157. Knox EG, Stewart AM, Kneale GW. Foetal infection, childhood leukaemia and cancer. Br J Cancer 1983;48:849–52.

158. Shore RE, Pasternack BS, Cumen MGM. Relating influenza epidemics to childhood leukemia in tumor registries without a defined population base: a critique with suggestions for improved methods. Am J Epidemiol 1976;103:527–35.

159. Schlehofer B, Blettner M, Geletneky K, et al. Seroepidemiological analysis of the risk of virus infections for childhood leukaemia. Int J Cancer 1996;65:584–90.

160. Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. Lancet 1988;2:1323–7.

161. Kinlen U. Epidemiological evidence for an infective basis in childhood leukaemia. Br J Cancer 1995;71:1–5.

162. Greaves MF. Speculations on the cause of childhood acute lymphoblastic leukemia. Leukemia 1988;2:120–5.

163. Greaves MF. Aetiology of acute leukaemia. Lancet 1997; 349:344–9.

164. Petridou E, Kassimos D, Kalmanti M, et al. Age of exposure to infections and risk of childhood leukaemia. BMJ 1993; 307:774.

165. Kinlen LJ, Clarke K, Hudson C. Evidence from population mixing in British New Towns 1946–85 of an infective basis for childhood leukaemia. Lancet 1990;336:577–82.

166. Laplanche A, de Vathaire F. Leukaemia mortality in French communes (administrative units) with a large and rapid population increase. Br J Cancer 1994;69:110–13. [See comments in Br J Cancer 1994;70:180–1.]

167. Kinlen U. Leukaemia mortality among young people in growing French communes. (Letter) Br J Cancer 1994;70: 180–1.

168. Kinlen LJ, Craft AW, Parker L. The excess of childhood leukaemia near Sellafield: a commentary on the fourth COMARE report. J Radiol Prot 1997;17:63–71.

169. Stiller CA, Boyle PJ. Effect of population mixing and socioeconomic status in England and Wales, 1979–85, on lymphoblastic leukaemia in children. BMJ 1996;313:1297–300.

170. Alexander FE. Space-time clustering of childhood acute lymphoblastic leukaemia: indirect evidence for a transmissible agent. Br J Cancer 1992;65:589–92.

171. Alexander FE, Boyle P, Carli PM, et al. Spatial temporal patterns in childhood leukaemia: further evidence for an infectious origin. EUROCLUS project. Br J Cancer 1998;77: 812–17.

172. Kinlen U. High-contact paternal occupations, infection and childhood leukaemia: five studies of unusual population-mixing of adults. Br J Cancer 1997;76:1539–45.

173. Badrinath P, Day NE, Stockton D. Seasonality in the diagnosis of acute lymphocytic leukaemia. Br J Cancer 1997; 75:1711–13.

174. Gilman EA, Sorahan T, Lancashire RJ, et al. Seasonality in the presentation of acute lymphoid leukaemia. (Letter). Br J Cancer 1998;77:677–8.

175. Kinlen LJ, John SM. Leukaemia and wartime evacuees. (Letter). Nature 1995;373:293.

176. Kinlen LJ, Petridou E. Childhood leukemia and rural population movements: Greece, Italy, and other countries. Cancer Causes Control 1995;6:445–50.

177. IARC monographs on the evaluation of carcinogenic risks to humans: man-made mineral fibres and radon. Lyon, France: International Agency for Research on Cancer, 1988. (IARC monograph no. 43).

178. Richardson RB, Eatough JP, Henshaw DL. Dose to red bone marrow from natural radon and thoron exposure. Br J Radiol 1991;64:608–24.

179. Henshaw DL, Eatough JP, Richardson RB. Radon as a causative factor in induction of myeloid leukaemia and other cancers. Lancet 1990;335:1008–12.

180. Eatough JP, Henshaw DL. Radon exposure and myeloid leukaemia. (Letter). Int J Epidemiol 1994;23:430–1.

181. Darby SC, Whitley E, Howe GR, et al. Radon and cancers other than lung cancer in underground miners: a collaborative analysis of 11 studies. J Natl Cancer Inst 1995;87: 378–84.

182. Lubin JH, Linet MS, Boice JD Jr, et al. Case-control study of childhood acute lymphoblastic leukemia and residential radon exposure. J Natl Cancer Inst 1998;90:294–300.

183. Cartwright RA. Exposition aux produits chimiques et agrégats de leucémie. Symposium sur les agrégats de leucémies. (In French). Ottawa, Ontario, Canada: Atomic Energy Control Board, 1992:29–31.

184. Breslow NE, Day NE. Statistical methods in cancer research. Vol I: The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980. (IARC scientific publications no. 32).

185. Clavel J, Hemon D. Leukaemia near La Hague nuclear plant: bias could have been introduced into study. (Letter). BMJ 1997;314:1553.

186. Schmitz-Feuerhake I, Von Boetticher H, Dannheim B, et al. The cluster of childhood leukemias near the German boiling water reactor Krümmel: ways of elucidation. International Conference on "Radiation and Society: Comprehending Radiation Risk." Vienna, Austria: International Atomic Energy Agency, 1994.

187. Kaatsch P, Kaletsch U, Krummenauer F, et al. Case control study on childhood leukemia in Lower Saxony, Germany: basic considerations, methodology, and summary of results. Klin Padiatr 1996;208:179–85.

188. Crouch D. Science and trans-science in radiation risk assessment: child cancer around the nuclear fuel reprocessing plant at Sellafield, U.K. Sci Total Environ 1986;53:201–16.

189. Gimeno L, Laurier D, Bard D. Le budget temps: intérêt en épidemiologie environnementale et sources disponibles en France. (In French). (Abstract). Rev Epidemiol Sante Publique 1997;45(suppl):S107.

190. Committee on the Biological Effects of Ionizing Radiations, Board on Radiation Effects Research, Commission on Life Sciences, National Research Council. Health effects of exposure to low levels of ionizing radiations (BEIR V). Washington, DC: National Academy Press, 1990.

191. O'Donnell RG, Mitchell PI, Priest ND, et al. Variations in the concentration of plutonium, strontium-90 and total alpha-emitters in human teeth collected within the British Isles. Sci Total Environ 1997;201:235–43.

192. Watson WS, Sumner DJ. The measurement of radioactivity in people living near the Dounreay Nuclear Establishment, Caithness, Scotland. Int J Radiat Biol 1996;70:117–30.

193. Dannheim B, Heimers A, Oberheitmann B, et al. Leukemia in the proximity of a German boiling water nuclear reactor: evidence of population exposure by chromosome studies and environmental radioactivity. In: Low doses of ionizing radiation: biological effects and regulatory control. Sevilla, Spain: International Atomic Energy Agency, 1997:37–43.

194. Inskip H. Childhood leukaemia near nuclear sites re-examined. Lancet 1997;349:969–70.

195. Spira A, Boutou O. Rayonnements ionisants et santé: mesure des expositions à la radioactivité et surveillance des effets sur la santé. Collection des rapports officiels. Rapport aux Ministres de l'Environnement et de la Santé. (In French). Paris, France: La Documentation Française, 1999.