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

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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) found neither an excess risk nor any significant trend with distance (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>
<thead>
<tr>
<th>Site and country</th>
<th>Study (reference no.) and year</th>
<th>Study period</th>
<th>Age (years)</th>
<th>Incidence (0/100,000 mortality (M))</th>
<th>Histologic type*</th>
<th>Zone (radius)</th>
<th>Cases</th>
<th>Expected (E)</th>
<th>O/E</th>
<th>95% confidence interval</th>
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<tr>
<td>Sellafield, Great Britain</td>
<td>Black (1), 1984</td>
<td>1955-1984</td>
<td>0-24</td>
<td>I</td>
<td>L</td>
<td>Village of Seascale</td>
<td>5</td>
<td>0.5</td>
<td>10.2</td>
<td>3.3, 23.8</td>
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<tr>
<td></td>
<td>Goldsmith (9), 1992</td>
<td>1971-1980</td>
<td>0-9</td>
<td>I</td>
<td>L</td>
<td>(16 km)</td>
<td>8</td>
<td>4.2</td>
<td>1.9</td>
<td>0.8, 3.8</td>
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<tr>
<td></td>
<td>Draper et al. (11), 1993</td>
<td>1963-1990</td>
<td>0-24</td>
<td>I</td>
<td>LL + NHL</td>
<td>Village of Seascale</td>
<td>6</td>
<td>&lt;1</td>
<td>&gt;10</td>
<td>0.8, 1.9</td>
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<td></td>
<td>Bithell et al. (12), 1994</td>
<td>1966-1987</td>
<td>0-14</td>
<td>I</td>
<td>L + NHL</td>
<td>(25 km)</td>
<td>24</td>
<td>18.5</td>
<td>1.3</td>
<td>0.8, 1.9</td>
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<td></td>
<td>COMARE (13), 1996</td>
<td>1984-1992</td>
<td>0-24</td>
<td>I</td>
<td>LL + NHL</td>
<td>Village of Seascale</td>
<td>3</td>
<td>0.16</td>
<td>19.1</td>
<td>3.8, 55.8</td>
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<td>Hassema et al. (14), 1986</td>
<td>1979-1984</td>
<td>0-24</td>
<td>I</td>
<td>L</td>
<td>(12.5 km)</td>
<td>5</td>
<td>0.5</td>
<td>9.8</td>
<td>3.1, 22.7</td>
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<td>1968-1984</td>
<td>0-24</td>
<td>I</td>
<td>L</td>
<td>(25 km)</td>
<td>6</td>
<td>3.0</td>
<td>2.0</td>
<td>0.7, 4.4</td>
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<td>Black et al. (16), 1994</td>
<td>1968-1991</td>
<td>0-24</td>
<td>I</td>
<td>L + NHL</td>
<td>(25 km)</td>
<td>5</td>
<td>1.5</td>
<td>3.3</td>
<td>1.0, 7.6</td>
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<td></td>
<td>Sharp et al. (17), 1996</td>
<td>1968-1993</td>
<td>0-14</td>
<td>I</td>
<td>L + NHL</td>
<td>(25 km)</td>
<td>4</td>
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<td>2.8</td>
<td>0.7, 7.0</td>
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<td>Aldermaston and Burghfield, Great Britain</td>
<td>Roman et al. (18), 1987</td>
<td>1972-1985</td>
<td>0-14</td>
<td>I</td>
<td>L</td>
<td>(10 km)</td>
<td>41</td>
<td>28.6</td>
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<td>0-4</td>
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<td>1.3, 2.9</td>
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<td>0-9</td>
<td>I</td>
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<td>1.5</td>
<td>1.0, 2.0</td>
</tr>
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<td></td>
<td>Bithell et al. (12), 1994</td>
<td>1966-1987</td>
<td>0-14</td>
<td>I</td>
<td>L + NHL</td>
<td>(25 km)</td>
<td>219</td>
<td>196.7</td>
<td>1.1</td>
<td>1.0, 1.3</td>
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<td></td>
<td>Aldermaston</td>
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<tr>
<td></td>
<td>Bithell et al. (12), 1994</td>
<td>1966-1987</td>
<td>0-14</td>
<td>I</td>
<td>L + NHL</td>
<td>(25 km)</td>
<td>160</td>
<td>145.8</td>
<td>1.1</td>
<td>0.9, 1.3</td>
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<td></td>
<td>Busby and Cato (20), 1997</td>
<td>1981-1995</td>
<td>0-14</td>
<td>M</td>
<td>L</td>
<td>Seven districts</td>
<td>47</td>
<td>33.0</td>
<td>1.4</td>
<td>1.0, 1.9</td>
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<td>Aldermaston Burghfield-Harwell</td>
<td>Draper and Vincent (21), 1997</td>
<td>1969-1993</td>
<td>0-14</td>
<td>I</td>
<td>L</td>
<td>Seven districts</td>
<td>173</td>
<td>162.4</td>
<td>1.1</td>
<td>0.9, 1.2</td>
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<td>Hinkley Point, Great Britain</td>
<td>Ewings et al. (22), 1989</td>
<td>1964-1986</td>
<td>0-24</td>
<td>I</td>
<td>L + NHL</td>
<td>(12.5 km)</td>
<td>19</td>
<td>10.4</td>
<td>1.8</td>
<td>1.1, 2.9</td>
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<td>Bithell et al. (12), 1994</td>
<td>1966-1987</td>
<td>0-14</td>
<td>I</td>
<td>L + NHL</td>
<td>(25 km)</td>
<td>57</td>
<td>57.2</td>
<td>1.0</td>
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<td>Amersham, Great Britain</td>
<td>Cook-Mozaftari et al. (24), 1989</td>
<td>1969-1978</td>
<td>0-24</td>
<td>M</td>
<td>L</td>
<td>(16 km)</td>
<td>1.2</td>
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<td></td>
<td>Goldsmith (9), 1992</td>
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<td>0-9</td>
<td>I</td>
<td>L</td>
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<td>40.6</td>
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<td>1.1, 1.9</td>
</tr>
<tr>
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<td>Bithell et al. (12), 1994</td>
<td>1966-1987</td>
<td>0-14</td>
<td>I</td>
<td>L + NHL</td>
<td>(25 km)</td>
<td>388</td>
<td>406.9</td>
<td>1.0</td>
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<td>La Hague, France</td>
<td>Doussot (41), 1989</td>
<td>1970-1982</td>
<td>0-24</td>
<td>M</td>
<td>L</td>
<td>(10 km)</td>
<td>0</td>
<td>0.4</td>
<td>0</td>
<td>0.8, 1.9</td>
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<td></td>
<td>Viel and Richardson (42), 1990</td>
<td>1968-1986</td>
<td>0-24</td>
<td>M</td>
<td>L</td>
<td>(35 km)</td>
<td>21</td>
<td>23.6</td>
<td>0.9</td>
<td>0.6, 1.4</td>
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<td></td>
<td>Hilt and Laplancher (43), 1992</td>
<td>1968-1987</td>
<td>0-24</td>
<td>M</td>
<td>L</td>
<td>(21 km)</td>
<td>12</td>
<td>14.9</td>
<td>0.8</td>
<td>0.4, 1.4</td>
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<tr>
<td></td>
<td>(10 km)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.8</td>
<td>1.2</td>
<td>0.0, 7.0</td>
</tr>
<tr>
<td></td>
<td>Viel et al. (44), 1993</td>
<td>1979-1990</td>
<td>0-24</td>
<td>I</td>
<td>L</td>
<td>(35 km)</td>
<td>23</td>
<td>19.6</td>
<td>1.2</td>
<td>0.7, 1.8</td>
</tr>
<tr>
<td></td>
<td>Hatcchouel et al. (55), 1955</td>
<td>1968-1989</td>
<td>0-24</td>
<td>M</td>
<td>L</td>
<td>(16 km)</td>
<td>5</td>
<td>5.4</td>
<td>0.4</td>
<td>0.1, 7.3</td>
</tr>
<tr>
<td></td>
<td>Viel et al. (45), 1995</td>
<td>1978-1992</td>
<td>0-24</td>
<td>I</td>
<td>L</td>
<td>(35 km)</td>
<td>25</td>
<td>22.8</td>
<td>1.1</td>
<td>0.7, 1.6</td>
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<tr>
<td></td>
<td>(10 km)</td>
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<td></td>
<td>4</td>
<td>1.4</td>
<td>2.8</td>
<td>0.8, 7.3</td>
</tr>
<tr>
<td></td>
<td>Guizard et al. (47), 1997</td>
<td>1993-1996</td>
<td>0-24</td>
<td>I</td>
<td>L</td>
<td>(30 km)</td>
<td>8</td>
<td>7.1</td>
<td>1.1</td>
<td>0.5, 2.2</td>
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<tr>
<td></td>
<td>(10 km)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0.7</td>
<td>0</td>
<td>0.0, 5.5</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Study (reference no.) and year</th>
<th>Country (locale)</th>
<th>No. of sites</th>
<th>Study period</th>
<th>Age (years)</th>
<th>Zone (radius)</th>
<th>Incidence (1)/mortality (M)</th>
<th>Histologic type*</th>
<th>No. of cases</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron (48), 1984</td>
<td>Great Britain</td>
<td>6</td>
<td>1963–1979</td>
<td>0–14</td>
<td>14 local authority areas</td>
<td>M L 33 Global relative risk of 1.5; same risk at start-up and 5–10 years after</td>
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<tr>
<td>Forman et al. (23), 1987</td>
<td>Great Britain</td>
<td>14</td>
<td>1959–1980</td>
<td>0–24</td>
<td>(10 km)</td>
<td>M LL 44 Global relative risk of 2</td>
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</tr>
<tr>
<td>Cook-Mozaffari et al. (24), 1989</td>
<td>Great Britain</td>
<td>15 (+ 8 possible)</td>
<td>1969–1978</td>
<td>0–24</td>
<td>(16 km)</td>
<td>M L 635 Excess mortality of 15% around sites; similar excess found around possible sites</td>
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<tr>
<td>Jablon et al. (52), 1991</td>
<td>United States</td>
<td>62</td>
<td>1950–1984</td>
<td>0–9</td>
<td>107 counties</td>
<td>M + I 1,390 No overall significant excess; no difference before and after start-up</td>
<td></td>
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<tr>
<td>Grosche (37), 1992</td>
<td>Germany (Bavaria)</td>
<td>5</td>
<td>1983–1989</td>
<td>0–14</td>
<td>(10 km)</td>
<td>I L 16 No overall excess except in towns where sites are located</td>
<td></td>
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<tr>
<td>Goldsmith (9), 1992</td>
<td>Great Britain</td>
<td>14</td>
<td>1971–1980</td>
<td>0–9</td>
<td>(16 km)</td>
<td>I L 200 No excess for power plants; excess at Sellafield, Aldermaston, and Amersham</td>
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<tr>
<td>Hill and Laplanche (43), 1992</td>
<td>France</td>
<td>6</td>
<td>1968–1987</td>
<td>0–24</td>
<td>(16 km)</td>
<td>M L 58 No significant excess</td>
<td></td>
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<tr>
<td>McLaughlin et al. (54), 1993</td>
<td>Canada (Ontario)</td>
<td>5</td>
<td>1950–1987</td>
<td>0–14</td>
<td>(25 km)</td>
<td>M L 54 No overall excess</td>
<td></td>
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<tr>
<td>Michaelis et al. (58), 1992</td>
<td>Germany</td>
<td>20 (+ 6 possible)</td>
<td>1980–1990</td>
<td>0–14</td>
<td>(15 km)</td>
<td>I AL 274 No excess, except for 0–4 years living &lt;5 km from sites where operations began before 1970</td>
<td></td>
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<tr>
<td>Bithell et al. (12), 1994</td>
<td>Great Britain</td>
<td>23 (+ 6 possible)</td>
<td>1966–1987</td>
<td>0–14</td>
<td>(25 km)</td>
<td>I L + NHL 4,100 No overall excess, except around Sellafield and Burghfield</td>
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<tr>
<td>Iwasaki et al. (50), 1995</td>
<td>Japan</td>
<td>44</td>
<td>1973–1987</td>
<td>0–14</td>
<td>18 municipalities</td>
<td>M L 33 No overall excess risk</td>
<td></td>
<td></td>
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<tr>
<td>Waller et al. (61), 1995</td>
<td>Sweden</td>
<td>4</td>
<td>1980–1990</td>
<td>0–14</td>
<td>Entire country</td>
<td>I ALL 656 Risk of leukemia not higher at the four sites than elsewhere</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hattchouel et al. (55), 1995</td>
<td>France</td>
<td>13</td>
<td>1968–1992</td>
<td>0–24</td>
<td>(16 km)</td>
<td>M L 69 No significant excess risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharp et al. (17)</td>
<td>Scotland</td>
<td>6</td>
<td>1968–1993</td>
<td>0–14</td>
<td>(25 km)</td>
<td>I L + NHL 399 No overall excess, except around Dounreay</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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 taken 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 uncertainty 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 procedural 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.
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 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

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

* 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 lymphoblastic 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-
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 comprehensive 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.

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