Nuclear Regulatory Commission

Protocol for an Analysis of Cancer Risk in Populations Living Near Nuclear-Power Facilities

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OBJECTIVES

The U.S. National Cancer Institute (NCI) report "Cancer in Populations Living Near Nuclear Facilities" has been a valuable, scientifically defensible, risk communication tool for the U.S. Nuclear Regulatory Commission (NRC) staff to use in addressing stakeholder concerns about cancer mortality attributable to the operation of nuclear power facilities and perceived elevated cancer rates in populations near reactors. However, the report is more than 20 years old and is losing its relevance to current populations living near past, present, and possible future licensed nuclear power facilities. Additionally, analyses in the report focus on cancer deaths, and the general public is often also interested in a perceived elevation in cancer incidence. The objective of this project is to provide the Nuclear Regulatory Commission (NRC) with an updated cancer mortality study for populations living near NRC-licensed nuclear power facilities, hereafter referred to as sites. Unlike the initial study, which was completed in 1990, this study will not include Department of Energy (DOE) facilities.

Two different methodologic approaches are outlined. The first is the methodology used in the original study, which compared the cancer mortality in the site county with three counties matched with the site county on demographic characteristics. The second is a spatial analysis in which comparisons of cancer mortality are centered in the geographic area around the site (e.g., within 3 miles versus 3–10 miles). This document contains the proposed protocol for carrying out both of these analyses.

A preliminary protocol for this study has been reviewed and approved by the Oak Ridge Site-wide Institutional Review Board (ORSIRB). Once the study protocol is finalized, the final protocol will be presented to the ORSIRB for review and approval before the start of the study.

LITERATURE REVIEW

The purpose of the literature review is to identify any significant findings, especially additional outcomes of interest, reported since the end of the original study. Literature pertaining to spatial analysis of health outcomes and relevant statistical methods has also been assessed.

Peer-reviewed literature has been searched for relevant publications, concentrating on 1990 and later, including international studies. Special effort has been placed on reviewing major publications on effects of low-dose external radiation exposure from major research organizations that are concerned with radiation health effects: United Nations Scientific Committee on the Effects of Atomic Radiation, National Academy of Sciences, International Commission on Radiation Protection, and NRC. Reports outside of these sources have also been reviewed.

Results of many additional epidemiologic studies regarding the possibility and causes of increased cancer risk in populations living near nuclear facilities have been reported since publication of results of the July 1990 National Cancer Institute (NCI) report (Jablon et al. 1990, 1991). This literature review has addressed sites in additional countries, improvements to study design and data analysis, and continued efforts at identification of causes for confirmed or suspected excess cancer risk in populations located both near to and distant from nuclear facilities. The studies are too numerous to document individually in the main body of this protocol. Appendix A provides summaries of several of the individual studies as published in the available literature. The summaries are listed in chronological order. Topics or publications of particular importance, as they are addressed or included in these summaries, are the following:

- The excess of childhood leukemia observed near the Sellafield, Dounreay, Aldermaston, Burghfield, and Harwell nuclear installations in the United Kingdom (UK); the La Hague nuclear reprocessing plant in France; and the Krümmel nuclear power plant in Germany
- The 1979 United States (U.S.) Three Mile Island nuclear power plant accident, for which radiation exposures to the public were very low and consisted primarily of gamma-emitting noble gases
- The 1986 Union of Soviet Socialist Republics Chernobyl nuclear power plant accident, for which some radiation exposures (from a complex mix of radionuclides) to the public were notably high, with increases in childhood thyroid cancer of particular concern
- The publication in the UK of the report, “The Incidence of Childhood Cancer Around Nuclear Installations in Great Britain,” by the Committee on Medical Aspects of Radiation in the Environment (COMARE) (COMARE 2005)
- The publication in the UK of the COMARE (2006) report, “The Distribution of Childhood Leukaemia and other Childhood Cancers in Great Britain 1969–1993”
- The publication of the German Kinderkrebs in der Umgebung von Kernkraftwerken (KiKK) report, “Leukaemia in Young Children Living in the Vicinity of German Nuclear Power Plants,” (Kaatsch et al. 2008) by the German Childhood Cancer Registry
- The German publication of the Commission on Radiological Protection (Strahlenschutzkommission [SSK]) (2008) assessment of the KiKK report, “Assessment of the Epidemiological Study on Childhood Cancer in the Vicinity of Nuclear Power Plants (KiKK Study)”

- Continued general efforts in the U.S. and other countries to determine if and where excess cancer risks are observed in populations living near nuclear facilities
- The search for patterns of excess cancers that can lead to identification of risk factors and causes
- Improvements to study design and data analysis

COUNTY ANALYSIS

The initial idea was to update the original study completed in 1990 and to exclude the DOE facilities. To accomplish this objective, sites that came on line in 1982 or later would be added along with their control counties, and the comparison of cancer mortality in site counties with control counties would be updated from 1985 through 2006 for all sites. However, the methodology used in the original study cannot be replicated in the updated study because documentation of the details for the methods used in the original study cannot be located. Historic memory at NCI and among authors who participated in the original study has not yielded the level of detail required to replicate the original methods. In addition, the original data files from the study are not available.

Since the original study cannot be directly updated, currently accepted analytic methods are proposed. "Updating" the study will now require that all analyses using newly adopted methods be carried out starting four years before each site came on line rather than starting with 1985. The newly adopted methods will mirror original study methods whenever feasible and in accordance with current scientific practice.

Identification of Study Counties

The following nuclear power sites will be included in the updated study:

- Sites in the original study, whether currently operating or decommissioned
- Two sites that were excluded from the original study because they had ceased operations before 1982 and they were operated under a slightly different category of nuclear power reactor license:
    - Saxton in Pennsylvania, which began operations in 1961 and ceased operations in 1972
    - Vallecitos in California, which began operations in 1957 and ceased operations in 1967
- Sites that came on line since 1982, the cutoff year of the original study, whether currently operating or decommissioned
- New sites for which applications have been submitted to the NRC to establish baseline values for future study

One site that was included in the first study will have a different date for the start of operations than was used in the first study. Beaver Valley, which began operations in 1976, was built on a site adjacent to the Shippingport reactor, which was a DOE site, and ended operations in 1982. A single point will be used for the Beaver Valley facility, with the Shippingport start date of December 1957.

As in the original study, at least one study county will be identified for each site. A study county is defined as the county in which the nuclear power plant is located and certain adjacent counties. For consistency with the original study, an adjacent county will also be classified as a study county only when the adjacent county comprises at least 20% of the area within a 10-mile radius of the site.

Selection of Control Counties

Since the detail necessary to replicate the methodology for selecting control counties used in the original study is not available, much thought has been given to the methods to use in selecting control counties. In selecting the methodology to use, both continuity with the original study and scientific rationale have been considered.

For continuity with the original study, the following decisions were made:

- Three control counties will be selected for each study county.
- A county can be a control for more than one study county.
- A county from an adjoining state is eligible to be a control in this study if that county was a control for a given site in the original study.
- Selection of control counties will be based on a similarity index (SI) calculated for each potential control county.

The initial set of variables chosen for calculation of the SI are similar to those used in the 1990 study and were the same as those used in a study by Boice et al. (2003a) of municipalities near two nuclear material processing facilities. These factors are as follows: population density (total persons divided by county land area), median household income, percent male, percent white, percent rural, percent high school graduates, percent under age 18, percent over age 64, percent employed, percent below poverty level. Factor values for each county are based on the 2000 census. For each factor the absolute value of the difference between study county value and value for each potential control county is calculated and ranked. The SI for a given county is the sum of that county's ranks for each of the 10 factors. The smaller the SI value, the more similar the county is to the study county.

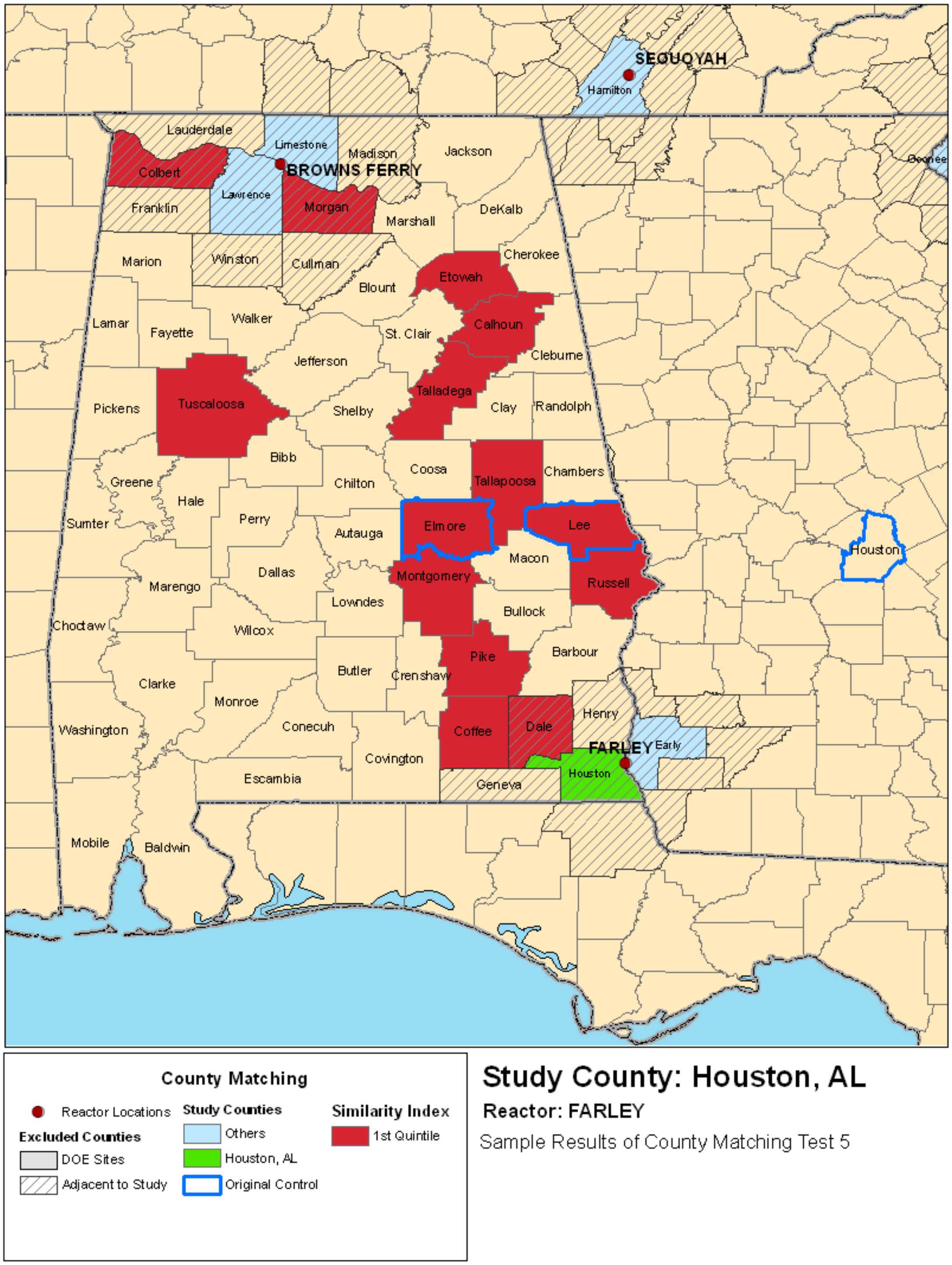
Our goal in county matching is to ensure the best match with respect to cancer risk factors over the entire time period of the operation of the site, which span 50 years. It is a challenge to select control counties that would be appropriate over the long time period because there is potential for substantial change in county characteristics over time. Basing the SI factor values on the most current census data should ensure suitability of control counties for recent time periods. From the scientific perspective, selecting control counties that were also used in the original study whenever reasonable should provide evidence that these counties are suitable for the earlier time periods. Therefore, the focus has been on developing an algorithm, based on data from 2000, that will select a high percentage of original control counties. The original study used 1979 and 1980 data for the matching exercise. This strategy should help minimize the effect on comparisons of cancer mortality among study and control counties that could result in large changes in the matching characteristics over the study period. To implement this strategy a series of tests based on sites in the original study was carried out to examine the percent of original control counties that would be re-selected. Each successive test built on the previous test as issues were revealed and resolved with the algorithm in Test 5 being selected as most suitable for ranking counties by SI.

Decisions made concerning the selection of control counties include restricting control counties to the same state as their study county, exclusion of counties adjacent to nuclear sites from being control counties, and accounting for nonreactor industrial pollution in the SI. Details of the reasons for making these decisions and of the tests carried out appear in Appendix B for each study county three control counties will be selected as follows:

- Any control county from the original study that is in the first quintile of SI ranks and is not among excluded counties is retained as a control county for the site for the current study.
- Any county from the original study that is not in the first quintile or is excluded is replaced by the lowest ranking non-excluded county.

Documentation of the selection of the three control counties for each site will be supported by a state map, with counties identified as illustrated in Figure 1 for the Farley site study county of Houston, AL. In addition, a table will be created that provides, for each site, the original study control counties, the potential control counties ranked by SI and having the first quintile shaded in blue, the counties that are excluded, and the three counties selected as controls. . See Tables 1 and 2 for the two Farley site study counties of Houston, AL, and Early, GA, respectively.

Figure 1: Sample State Map for the Farley, Alabama, Site Study County of Houston Based on Test 5 Results



Study County: Houston, AL

Reactor: FARLEY

Sample Results of County Matching Test 5

Table 1. Farley Site: Finding Control Counties for Study County Houston, AL

Originals	Excluded	FIPS	County	State	Similarity Index	Dist to Pop Centroid (km)	Dist to Geo Centroid (km)
		01031	Coffee	AL	265	77.3	85.8
		01015	Calhoun	AL	280	284.8	290.5
	X	01045	Dale	AL	280	52.3	52.9
		01125	Tuscaloosa	AL	286	316.4	322.8
X		01081	Lee	AL	303	152.0	154.5
		01113	Russell	AL	317	132.8	118.3
		01055	Etowah	AL	322	320.6	324.7
		01121	Talladega	AL	322	258.1	259.0
		01101	Montgomery	AL	331	164.2	151.7
	X	01033	Colbert	AL	336	456.1	460.5
	X	01103	Morgan	AL	342	401.9	393.6
		01123	Tallapoosa	AL	349	193.8	193.0
		01109	Pike	AL	352	100.0	101.6
X		01051	Elmore	AL	359	181.6	181.2
		01095	Marshall	AL	369	359.7	366.2
		01001	Autauga	AL	378	192.5	205.3
		01073	Jefferson	AL	380	300.7	308.3
		01003	Baldwin	AL	382	263.1	259.7
		01021	Chilton	AL	383	235.7	235.6
	X	01077	Lauderdale	AL	392	465.5	472.0
		01097	Mobile	AL	403	297.4	300.8
		01017	Chambers	AL	407	182.1	189.4
		01053	Escambia	AL	413	207.4	195.7
	X	01067	Henry	AL	417	31.8	34.6
		01115	St. Clair	AL	418	294.3	298.7
	X	01043	Cullman	AL	428	363.4	362.2
		01009	Blount	AL	435	333.3	335.0
		01117	Shelby	AL	445	275.3	269.3
		01039	Covington	AL	450	123.8	127.6
		01071	Jackson	AL	450	396.4	403.0
		01099	Monroe	AL	451	215.2	217.8
		01111	Randolph	AL	456	226.5	231.9
		01041	Crenshaw	AL	461	125.8	127.4
	X	01061	Geneva	AL	469	65.4	70.8
		01049	DeKalb	AL	472	363.8	364.8
		01005	Barbour	AL	474	71.0	76.5
		01127	Walker	AL	476	351.5	352.2
		01025	Clarke	AL	481	261.6	263.3
	X	01089	Madison	AL	484	414.4	415.0
		01087	Macon	AL	485	143.9	140.2
X		13153	Houston	GA	496	203.5	193.7
		01007	Bibb	AL	497	275.0	273.7
		01029	Cleburne	AL	511	268.2	274.5
		01013	Butler	AL	513	158.2	160.2
		01037	Coosa	AL	515	218.1	218.2
		01129	Washington	AL	517	292.8	295.4
		01047	Dallas	AL	523	223.7	225.1
		01027	Clay	AL	536	236.3	237.6
		01035	Conecuh	AL	539	180.0	180.6
		01091	Marengo	AL	551	283.1	278.0
	X	01059	Franklin	AL	551	436.9	439.1
		01057	Fayette	AL	564	373.0	371.1
		01011	Bullock	AL	575	113.1	112.9
		01023	Choctaw	AL	576	311.2	311.8
	X	01133	Winston	AL	579	391.0	387.7
		01019	Cherokee	AL	591	331.4	330.7
		01075	Lamar	AL	600	397.5	398.8
		01065	Hale	AL	601	293.3	292.8
		01085	Lowndes	AL	620	176.0	178.7
		01107	Pickens	AL	620	360.2	361.6
		01093	Marion	AL	636	411.6	414.9
		01131	Wilcox	AL	646	231.8	225.1
		01063	Greene	AL	663	319.0	323.5
		01119	Sumter	AL	686	330.1	329.0
		01105	Perry	AL	736	260.5	259.3

Table 2. Farley Site: Finding Control Counties for Study County Early, GA

Originals	Excluded	FIPS	County	State	Similarity Index	Dist to Pop Centroid (km)	Dist to Geo Centroid (km)
		13087	Decatur	GA	389	65.0	63.6
		13273	Terrell	GA	439	89.4	88.8
X		13027	**Brooks**	GA	464	156.3	152.2
	X	13253	Seminole	GA	472	37.8	39.1
		13243	Randolph	GA	481	67.8	68.8
		13287	Turner	GA	488	150.4	151.6
X		13081	**Crisp**	GA	536	150.7	149.3
		13131	Grady	GA	542	94.1	92.2
		13193	Macon	GA	562	158.4	161.5
X		13261	**Sumter**	GA	565	125.4	125.4
		13269	Taylor	GA	603	171.0	168.7
		13155	Irwin	GA	612	179.1	179.5
	X	13007	Baker	GA	623	66.6	64.5
		13093	Dooly	GA	642	164.2	161.9
		13109	Evans	GA	648	322.1	322.8
		13071	Colquitt	GA	650	129.0	128.0
		13205	Mitchell	GA	656	89.7	87.4
		13321	Worth	GA	662	123.8	125.3
		13303	Washington	GA	665	292.5	292.0
		13075	Cook	GA	677	161.5	160.4
		13165	Jenkins	GA	690	345.6	344.6
		13017	Ben Hill	GA	700	186.2	189.3
	X	13107	Emanuel	GA	710	305.6	306.0
		13199	Meriwether	GA	726	201.4	205.5
		13275	Thomas	GA	727	118.9	120.6
		13239	Quitman	GA	740	69.6	72.0
		13175	Laurens	GA	745	251.7	248.7
	X	13005	Bacon	GA	748	254.7	255.5
		13251	Screven	GA	750	368.6	371.6
		13133	Greene	GA	752	317.2	318.9
		13263	Talbot	GA	757	171.6	172.6
		13163	Jefferson	GA	762	326.3	325.3
	X	13201	Miller	GA	762	37.0	36.9
		13189	McDuffie	GA	763	351.9	352.2
		13019	Berrien	GA	780	177.4	179.4
		13259	Stewart	GA	792	101.0	98.4
		13277	Tift	GA	796	154.5	153.1
	X	13033	Burke	GA	811	359.9	357.3
		13301	Warren	GA	813	334.0	333.6
		13197	Marion	GA	816	139.0	137.1
		13249	Schley	GA	824	136.5	137.7
		13271	Telfair	GA	834	227.7	220.6
		13069	Coffee	GA	857	219.4	218.2
	X	13061	Clay	GA	869	46.1	46.4
		13065	Clinch	GA	870	227.5	232.1
		13307	Webster	GA	883	106.0	105.7
	X	13043	Candler	GA	883	316.6	316.0
		13289	Twiggs	GA	891	229.6	225.8
		13293	Upson	GA	896	200.4	199.2
		13319	Wilkinson	GA	898	252.5	253.5
		13023	Bleckley	GA	905	213.3	215.8
		13091	Dodge	GA	906	214.1	212.2
		13095	Dougherty	GA	914	98.3	91.9
		13255	Spalding	GA	915	238.4	239.1
		13317	Wilkes	GA	918	357.5	360.6
	X	13037	Calhoun	GA	919	54.9	57.4
		13167	Johnson	GA	924	281.5	283.9
		13285	Troup	GA	924	200.5	200.9
		13299	Ware	GA	925	260.3	257.0
	X	13283	Treutlen	GA	926	271.9	274.2
		13149	Heard	GA	948	230.3	230.0
		13235	Pulaski	GA	953	194.1	191.2
		13173	Lanier	GA	959	195.9	196.5
		13105	Elbert	GA	974	383.9	385.2
	X	13161	Jeff Davis	GA	983	249.1	243.8
		13315	Wilcox	GA	990	182.3	179.8
		13171	Lamar	GA	1007	224.0	225.1
		13309	Wheeler	GA	1024	245.9	247.1
		13003	Atkinson	GA	1035	212.8	212.7
		13191	McIntosh	GA	1046	354.2	356.7
		13225	Peach	GA	1046	193.2	192.4
		13049	Charlton	GA	1052	300.1	288.2
		13159	Jasper	GA	1054	270.3	268.1
		13143	Haralson	GA	1065	281.4	285.3
		13237	Putnam	GA	1076	285.3	284.6
	X	13229	Pierce	GA	1090	274.6	276.4
		13211	Morgan	GA	1091	305.0	303.5
	X	13267	Tattnall	GA	1107	303.9	303.7
		13021	Bibb	GA	1119	223.7	220.6

(continues)

Originals	Excluded	FIPS	County	State	Similarity Index	Dist to Pop Centroid (km)	Dist to Geo Centroid (km)
		13115	Floyd	GA	1120	335.7	337.3
		13181	Lincoln	GA	1129	378.7	379.1
		13079	Crawford	GA	1143	198.8	196.6
		13233	Polk	GA	1143	309.1	308.2
		13125	Glascock	GA	1187	324.9	324.1
		13101	Echols	GA	1203	204.4	219.4
		13265	Taliaferro	GA	1203	333.5	334.1
		13031	Bulloch	GA	1207	343.5	344.5
	X	13257	Stephens	GA	1211	406.8	406.7
		13141	Hancock	GA	1241	300.8	301.8
		13207	Monroe	GA	1253	230.7	228.3
		13009	Baldwin	GA	1254	270.4	269.7
	X	13305	Wayne	GA	1258	307.4	306.1
	X	13209	Montgomery	GA	1268	265.9	266.2
		13045	Carroll	GA	1271	264.8	261.7
		13025	Brantley	GA	1274	299.4	298.3
		13297	Walton	GA	1281	310.9	311.9
	X	13147	Hart	GA	1281	401.1	401.0
		13215	Muscogee	GA	1298	140.4	144.4
		13157	Jackson	GA	1301	353.7	353.8
	X	13119	Franklin	GA	1303	393.1	391.5
		13185	Lowndes	GA	1307	180.6	181.3
		13077	Coweta	GA	1311	241.9	238.5
		13221	Oglethorpe	GA	1317	350.8	351.0
		13217	Newton	GA	1320	284.5	284.5
	X	13083	Dade	GA	1321	407.1	404.4
		13169	Jones	GA	1333	241.7	247.7
		13035	Butts	GA	1342	253.6	253.6
		13145	Harris	GA	1343	166.2	168.9
		13059	Clarke	GA	1344	342.8	344.0
	X	13137	Habersham	GA	1344	398.2	405.8
		13013	Barrow	GA	1350	333.1	334.1
		13063	Clayton	GA	1357	267.6	266.7
		13103	Effingham	GA	1373	380.0	378.9
		13177	Lee	GA	1373	103.7	110.9
		13055	Chattooga	GA	1384	362.9	361.3
		13053	Chattahoochee	GA	1386	125.6	128.4
		13123	Gilmer	GA	1386	386.8	389.5
		13231	Pike	GA	1397	218.8	218.2
	X	13295	Walker	GA	1397	400.4	390.0
		13227	Pickens	GA	1406	363.5	364.5
		13129	Gordon	GA	1421	364.0	364.5
		13015	Bartow	GA	1433	331.3	335.3
	X	13241	Rabun	GA	1442	434.9	436.0
		13183	Long	GA	1445	327.1	325.1
		13111	Fannin	GA	1452	414.6	410.5
		13187	Lumpkin	GA	1455	380.9	385.6
		13127	Glynn	GA	1459	347.0	344.7
		13029	Bryan	GA	1472	363.9	359.0
		13195	Madison	GA	1476	364.1	368.3
		13051	Chatham	GA	1483	390.7	390.9
		13247	Rockdale	GA	1487	287.0	288.3
		13011	Banks	GA	1496	378.2	378.7
	X	13245	Richmond	GA	1510	378.1	371.5
		13153	Houston	GA	1527	203.5	193.7
		13121	Fulton	GA	1530	296.9	291.1
		13139	Hall	GA	1533	359.3	363.8
		13097	Douglas	GA	1551	279.2	276.7
		13179	Liberty	GA	1568	341.9	353.2
		13073	Columbia	GA	1574	376.8	371.5
		13219	Oconee	GA	1577	332.9	329.6
		13213	Murray	GA	1593	394.5	396.9
	X	13047	Catoosa	GA	1625	410.0	408.2
		13223	Paulding	GA	1652	297.1	300.0
		13311	White	GA	1653	394.8	400.5
		13113	Fayette	GA	1657	250.1	249.8
		13089	DeKalb	GA	1659	295.1	294.6
		13151	Henry	GA	1679	265.5	263.2
	X	13313	Whitfield	GA	1698	395.8	397.5
		13117	Forsyth	GA	1704	341.4	345.6
		13291	Union	GA	1719	417.6	413.9
		13281	Towns	GA	1722	430.8	429.3
		13039	Camden	GA	1732	335.6	333.3
		13135	Gwinnett	GA	1768	316.8	320.4
		13085	Dawson	GA	1793	364.0	367.9
		13057	Cherokee	GA	1796	329.6	340.3
		13067	Cobb	GA	1802	305.9	305.6

Data for County Analysis

Population Data

Annual county data stratified by age group, gender, and race will be required. Oak Ridge National Laboratory (ORNL) currently has the annual population data from 1970 onward in addition to stratified population data for 1950 and 1960. Age groups will be specified as follows: 0-4, 5-9, 10-14, 15-19, …, 70-74, 75-79, 80-84, and 85 years and older. As in the original study, linear interpolation will be used to estimate the annual age group, gender, and race proportions before 1970.

Mortality Data

Each cancer cause of death stratified by year, state, county of residence, age, gender, and race will be required. Mortality data from 1959 through 1988 have been downloaded from the National Bureau of Economic Research Web site at www.nber.org/data/multicause.html. Robert Anderson, who is chief of Mortality Statistics Branch at National Center for Health Statistics (NCHS), indicated that this was the best source for these data. For years after 1988, the availability of county of death was either limited to counties with 100,000 population (1989-2004) or not available at all (2004+) in the public-use files. Since death data available at the county level lack the detail required for this study, a request was made to and approved by NCHS for micro-data files containing mortality at the county level for all counties regardless of size for years 1989-2006. The micro-data files were requested because of the age groups that will be used in this study. The compressed files of mortality data did not define the age groups narrowly enough for this study. Although the original study included data back to 1950, data from 1950 through 1958 are no longer available in an electronic database. According to Anderson, the only available source of mortality data before 1959 is pdf files that contain the "unit records" used to construct the summarized data. These files are the scanned pages of the published hard-copy volumes of the national mortality data. They are publically available and can be downloaded at www.cdc.gov/nchs/products/pubs/pubd/vsus/vsus.htm. When NCHS moved into a new building around 1990, some of the older electronic media became unavailable. To create an electronic data set of mortality data for the years prior to 1959 would entail manual entry into an electronic file from the pdf files. The start-up date of the earliest NRC-licensed nuclear power facilities was 1957. Since analysis for each site will begin four years before start-up, the earliest year that data would be needed is 1953. Because data before 1959 are not available in electronic files but are only contained within pdf files, complete data for the earliest five-year time period cannot be obtained for seven sites without manual data entry. For these seven sites, the earliest five-year analysis period will be truncated at 1959. Only two sites, Vallecitos and Beaver Valley, will have no pre-five-year start-up period because operations began in 1957 for

Vallecitos and in 1958 for Beaver Valley built approximately on the same site as the Shipping Port reactor, which started operations in 1958."

The mortality data will be selected for all study and control counties by using the county codes included in the annual mortality files. Two different coding schemes were used for county codes in the mortality files. NCHS county codes are included in the files for 1959 through 2002. In the files from 1982 to 2002, both the NCHS codes and the U.S. Census Bureau Federal Information Processing Standard (FIPS) county codes were given. After 2002, only the FIPS codes are available. The overlapping years of 1982–2002 will provide the bridge for identifying a county consistently.

Outcomes of Interest

There has been extensive discussion between the staff at NRC and ORAU concerning the outcomes to include in the analysis. The NRC RFP stated that the analysis should include "all radiogenic cancer types and health endpoints of concern addressed in the original study and others of interest" (p. 3, Task 2) and "any additional cancer sites or health outcomes assessed should be biologically plausible to low-dose radiation exposure as defined in recent reports from authoritative sources" (Task 2(b)). All outcomes in the original study will be included in the update. These are the following:

- Leukemia and aleukemia
- All cancers excluding leukemia
- Hodgkin's disease
- Other lymphoma (including non-Hodgkin's lymphoma)
- Multiple myeloma
- Digestive organs
    - Stomach
    - Colon & rectum
    - Liver (primary)
- Trachea, bronchus, lung
- Breast (female)
- Thyroid
- Bones & joints
- Bladder
- Brain & other central nervous system
- Benign, in situ and unspecified neoplasms

In the review of the recent literature, ORAU concluded that there was no biological plausibility to include any cancers in addition to those included in the original study, NRC has made two proposals to include addition cancer sites.

- Those sites for which cancer risk models were provided in the Biological Effects of Ionizing Radiation VII and those included in a study by Boice, et al. (2003a) of cancer in counties near former nuclear materials processing facilities. Boice notes that he included some of the cancer sites for completeness. These are cancers of the esophagus, pancreas, cervix uteri and corpus uteri, ovary, prostate, malignant melanoma of the skin, Hodgkin's and non-Hodgkin's lymphoma, and multiple myeloma.
- All cancer and to be consistent with the EPA and ICRP,add cancers of the gonads (testis/ovary), esophagus, and all other sites (i.e., pancreas, prostate, uterus, gall bladder, heart, kidneys, lymph nodes, muscle, oral mucosa, small intestine, spleen, thymus, cervix, and skin).

We are seeking the advice of the advisory group to resolve this issue.

When the number of cancers is small for a given outcome, cancers will be aggregated together according to the groupings used in the ICD.

For childhood leukemia, methods will be altered somewhat, using a two-year lag and analyzing only ages under 25 years, allowing time between diagnosis and death. Selected age groups will conform to those in the recent publications concerning childhood leukemia in Germany. In particular, special attention will be given to children under the age of five (Kaatsch et al. 2008).

Since the original study, the Tenth Revision of the International Classification of Diseases (ICD-10) became effective. Since the original study covered only four revisions, the comparability of ICD codes across ICD revisions has been updated to cover five revisions (Appendix C). . With the exception of the outcome benign and unspecified neoplasms, the only change made to the comparability table used in the study by Jablon et al. (1990, volume 1, Appendix Table 1) has been the updating of the table to include the ICD-10. There appears to be an inconsistency in the Jablon et al. (1990) study for the definition used for the benign and unspecified neoplasms between the ICD-8 and the ICD-9. The codes used were 210-239 and 210-234 for the ICD-8 and ICD-9, respectively. The ICD-8 codes included benign (210-228) and unspecified (230-239) neoplasms. The ICD-9 codes include benign neoplasms (210-228) and carcinoma in situ (230-234) but not unspecified neoplasms (235-239). For the current study, the codes used for benign and unspecified neoplasms will be 210-239 for ICD-8, ICD-9, and ICD-10.

Standardized Mortality Ratio Analysis Using County Data

The start-up date of the sites range from 1957 to 1996, and sites will be combined for some analyses (e.g., all sites combined, boiling water reactors [BWR], and pressurized water reactors [PWRs]). Therefore, using established groups of calendar years for each site (1960–1964, 1965–1969, 1970–1974, etc.) as was done in the Jablon et al. (1990) study does not appear to be a good choice of timescale for accumulating individual calendar year values of observed and expected deaths. The authors recommended that the "most appropriate comparison that minimizes to the extent possible biases in changing disease and death coding patterns over time is a relative risk (RR), calculated as the ratio of 'SMR [standardized mortality ratio] After' for the study area to 'SMR After' for the control area" (Jablon et al., 1990, Volume 1, p. 26). In addition, the authors (Jablon et al., 1990, Volume 1, p. 24) pointed out that "[i]f it is assumed that after the plant start-up there were occasional or regularly occurring emissions, then, as time passed, the risk of death from induced cancer, if present, would presumably have increased, because of increasing cumulative exposures and also because it necessarily takes time after a cancer is initiated for it, first, to grow to a point where it is recognizable and, then, to cause death." Based on this input, an appropriate timescale is "years since start of site," which would be combined into five-year time periods, with the first period beginning four years before start-up or 1959, whichever is later, and the last period including the year 2006. This timescale is similar to the second set of analyses used in the original study, although in that study the five-year periods began in 1950 and ended in 1984 and no RRs were calculated. Because there are nearly 50 years of follow-up for some sites, calculating RRs for five-year periods after start-up is more meaningful and will allow examination of the risk trend over time.

Expected deaths will be calculated separately by year based on the county population stratified by age, gender, and race. Race stratification finer than white and nonwhite will not be possible because of lack of stratification in data collected for earlier years. Observed deaths and expected deaths will be combined into five-year time periods. For each site, observed and expected deaths will be pooled as follows: when a site spans more than one county, data from the multiple study counties will be combined, and data for all control counties matched to the study county/counties will be combined.

Statistical Methods

In the original study SMRs were calculated for the study and control counties before and after the beginning of site operation for each cancer of interest. The expected deaths were based on U.S. rates. In this study grouped data Poisson regression methods (Frome, 1983) that include deaths based on external standard rates will be used for the analysis of the cancer mortality – see Breslow and Day, 1987, chapter 4 and Frome et.a. (1997) for further details. External standard rates based on U.S. vital statistics will be used to calculate age adjusted "expected deaths" for the site and control counties for each year. In addition to SMRs, Poisson regression provides standard errors and flexibility in analysis.

For each cause of death the general form of the regression function is: log $E(d_{ij})$ = $\log(\mu^*_{ij}) + \alpha_i + x_{ij}\beta$, where i indexes strata formed by gender, race, and county, j indexes the exposure variable of interest, μ^*_{ij} is the expected number of deaths based on the external standard rates, x_{ij} is a row vector that defines the "exposure" variables, and β is a vector of risk parameters. The μ^*_{ij} are calculated as follows: for age group a and year t let λ^*_{at} be the U.S. rate and n_{iat} the number in county i age group a and year t. Then $\mu^*_{ik} = \Sigma_a \Sigma_t n_{iat} \lambda^*_{at}$ where k represent five year time intervals based on t^0, which is the year that the power plant began operation, e.g. for k = 0, $t = t^0 - 4, t^0 - 3, \ldots, t^o$; for k = 1, $t = t^0 + 1, \ldots, t^0 + 5$; for k = 2, $t = t^0 + 6, \ldots, t^0 + 10$.

To test for a trend in RR over time, a line will be fit through the RRs calculated for each five-year time period of analysis. The null hypothesis will be that the slope of the line is zero, and the alternative hypothesis will be the two-sided alternative of an increasing or decreasing trend in risk over time. A result will be considered statistically significant for p-value < 0.05. Secured results will be presented electronically. Clicking on the link for each site will lead to a page that shows the graph of the RR trend over time (when data are sufficient to calculate this trend), along with associated statistics and SMRs for study and control counties. Further links will be available to view similar results for the combined analyses. In addition, links to tables of results will be available to show SMRs by time period and other details of interest. Examples of statistical results for two sites in Alabama can be found in Appendix D.

R functions are being developed for using Poisson regression to calculate and present the results for the SMR and RR analyses. These functions will require input data files that are structured according to specific criteria. Fields Included in the analysis files are site ID, county FIPS code ID, study or control county, five-year time period, observed deaths for each cause of interest, expected deaths for each cause of interest, site start year, gender, and race.

Comparing SMRs to Results of the Original Study

This comparison will be done only qualitatively since details of the original methodology are not available. The original study SMR will be compared to the SMR from the updated study to determine if the former SMR lies within the confidence intervals produced by the new methods for a selected subset of the large number of analyses conducted in the original study.

SPATIAL ANALYSIS

In addition to the original study approach of comparing cancer risk among study and control counties, additional analyses are proposed with the comparisons taking place among geographic areas centered at the site. Because these analyses will require obtaining residence addresses from death certificates for cancer deaths within the selected areas and population data at the census tract level, spatial analyses will be carried out for sites located in states that agree to supply the address data for individuals deceased from 1990 onward. The year 1990 was chosen because this is the earliest year for which census data are granular enough to carry out this type of analysis.

ArcGIS© software from Environmental Systems Research Institute, Inc., will be used to produce maps and carry out comparisons. Geographic information system (GIS) is an integrated collection of computer software and data used to view and manage information about geographic places, analyze spatial relationships, and model spatial processes. GIS provides a framework for gathering and organizing spatial data and related information so that it can be displayed and analyzed. Statistical analyses will be carried out by using R functions.

Obtaining Data for Spatial Analysis

Population Data

ORNL currently has access to census tract and census block population data for 1990 through 2006. Information on the distributions of age, race, and gender for these data are available for the census years of 1990 and 2000. For intervening years the age, race, and gender distributions will be interpolated from county data.

Mortality Data

Mortality data linked to address of residence are required. It was determined that they are not available on the national level through communications with Robert Anderson, chief, NCHS Mortality Statistics Branch; Robert Bilgrad, director of the National Death Index; and Garland Land, executive director of National Association for Public Health Statistics Information Systems(NAPHSIS), the national association of state vital records and public health statistics offices. Mortality data with addresses must be obtained from individual states and will require contacting each state and following the state procedure for data access. Not all states have electronic data for the entire period 1990–2006, and some states have never captured address data electronically. However, it should be possible to obtain from many states the address and demographic data necessary to carry out the study.

States fall into the following four general categories with respect to providing data with addresses and corresponding demographic information:

- Open states in which sharing mortality information is permitted by law
- States in which the health statistics director alone can give permission

- States in which the health statistics director can give permission but must adhere to certain restrictions
- States in which Instituional Review Board approval is required and strict guidelines are invoked

Land is willing to seek NAPHSIS endorsement of the study and communicate with states if he is provided with a write-up that includes the purpose of the study and the reason that addresses are required to geo-code the residence location for the cancer deaths. For states unwilling to release mortality data with addresses, an alternative standard approach is to obtain cancer deaths aggregated to the census tract if these states already have census tract information for each death or are willing to acquire and use that information to assign cases to census tracts.

Since states will release only data required for the study, one potential problem is determining how to specify exactly which mortality records match the geographic areas of the state that will be included in the analysis. A possible solution is to receive from the state File 1, which contains only pseudo-identifications and addresses; geo code the addresses and determine which are within the geographic area to be covered by the analysis; return File 1 to the state and receive File 2 containing demographic information and cause of death for only the pseudo-identifications required for analysis. File 2 could be aggregated by cause of death and the spatial distance from the site.

Because mortality records belong to the state where the death occurred but analysis is to be carried out by residence address, another issue is to make sure that out-of-state cancer deaths are retrieved and included in analysis with correct residence address. To meet this goal, the existence of interstate transfer agreements for death certificates will be investigated, particularly if a cancer treatment center is near a site but in an adjoining state. Also, since many cancer treatments take place in Houston, Texas, agreements with the State of Texas will also be sought. It should be noted that there is a possibility of backlogs in the transfer of death certificates from state of death to state of residence when interstate transfer agreements are in place. This possibility will be acknowledged.

To obtain the required data from states, requests will be made for mortality records of residents as opposed to records for individuals who died in the state. Required information includes age at death, year of death, gender, race, residence address, the underlying cause of death restricted to cancer and to benign, in situ, and unspecified neoplasms. States will be offered compensation for employees' time to put together the files in the required format. In addition, an offer will be made to aggregate the data if there is an NRC requirement to retain the data for future review and specify that the state will be notified if/when data are brought up for review.

Availability of Mortality Data

Because each state must be queried for availability of address data for mortality records, the NRC will have to get approval from the Office of management and Budget (OMB) to send out questionnaires to the state cancer registries and vital statistics offices requesting this information. The approval process takes about 6 months. Although approval would not be obtained in time for this protocol, OMB rules allow nine questionnaires to be sent without OMB approval. In order to get an indication of the availability of these data, we developed the questionnaire that will be used for all 35 states from which data will be required and sent it to 9 of these states. The states were chosen to try to get a representative sample of what might be encountered in all 35 states: Arizona, California, Connecticut, Georgia, Illinois, Minnesota, Mississippi, New Jersey, and Tennessee.

Of the 7 states that have replied to date, all have residence address at death in electronic form. However, the first year for which these electronic data are available varies greatly: 1980, 1985, 1992, 2003, 2005, 2006 and 2008. Six of the seven states require IRB approval before data will be released and four of these six require submission of additional documents before data will be released. After approval, the turn-around time on the request for data is 2 to 5 months for the five states that provided a time estimate. Five states charge a fee for the data.

Using these results it is possible to extrapolate what the likely results will be for all 35 states. In summary, all states will have residence address in electronic form with 10 states having data for the whole period of interest 1990+, 5 states for the period 1991-1999, and 20 states for 2000+. Approval by the IRB will be required in 30 states with 20 of these states requiring submission of additional documents. The turn-around time on the data request will be 2-5 months. Twenty-five states will request a fee to provide the data but an estimate of the magnitude of the fee cannot be determined since it is dependent on what is requested.

SMR Analysis Using Spatial Data

Spatial analysis will be limited to sites in certain states during certain years in or after 1990 due to limitations in obtaining cancer mortality data with addresses and age/race/gender from some states and population data at the census tract or census block level.

Analysis Regions

Cancer mortality in a circle with a 3-mile radius centered at a site will be compared with cancer deaths in sequential annular geographic areas defined by 10-mile radius, 30-mile radius, and 50-mile radius circles drawn from the same center point, as seen in

Figure 2. The circle with a three-mile radius was selected to correspond to the 5 km area within which a recent study found an elevated risk of childhood leukemia for children younger than five (Kaatsch et al. 2008). The 10-mile and 50-mile circles correspond to NRC emergency pathway zones for the 10-mile plume exposure pathway and 50-mile ingestion exposure pathway. The 30-mile circle is midway between the 10 and the 50 and was chosen to facilitate trending of risk over distance.

Adapted analysis regions will be required when the circles from two or more sites overlap because of the proximity of the sites to one another. In these cases the sites with overlapping circles will be analyzed as a group rather than individually since it is impossible to separate the “exposure” emanating from each site in the group. Cancer mortality data for the combined three-mile inner circle regions will be compared to deaths in the appropriately combined rings. Figure 3 provides an example of how such regions will be derived. For geographic areas in the overlapping region, mortality will be assigned to time periods based on possible exposure from the earliest opening site.

Figure 2: Spatial Analysis Example of 3-, 10-, 30-, and 50-Mile Analysis Regions

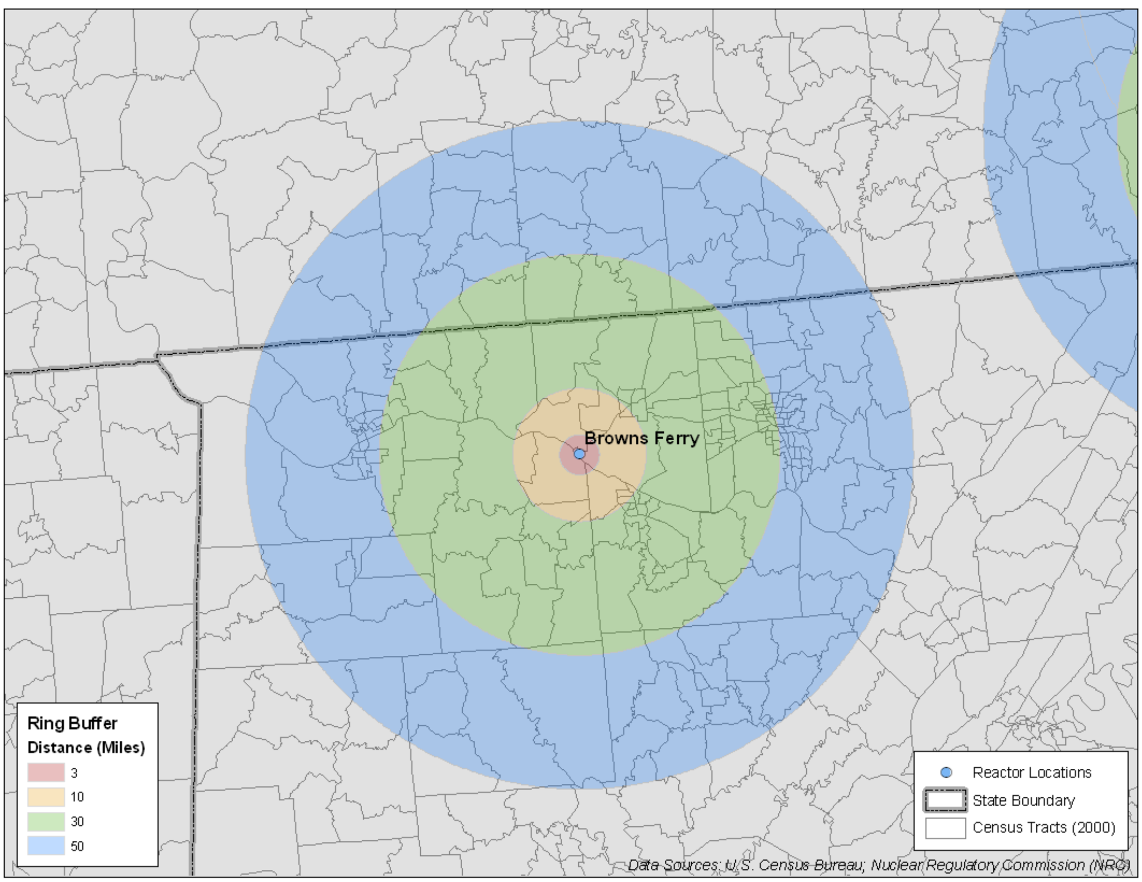
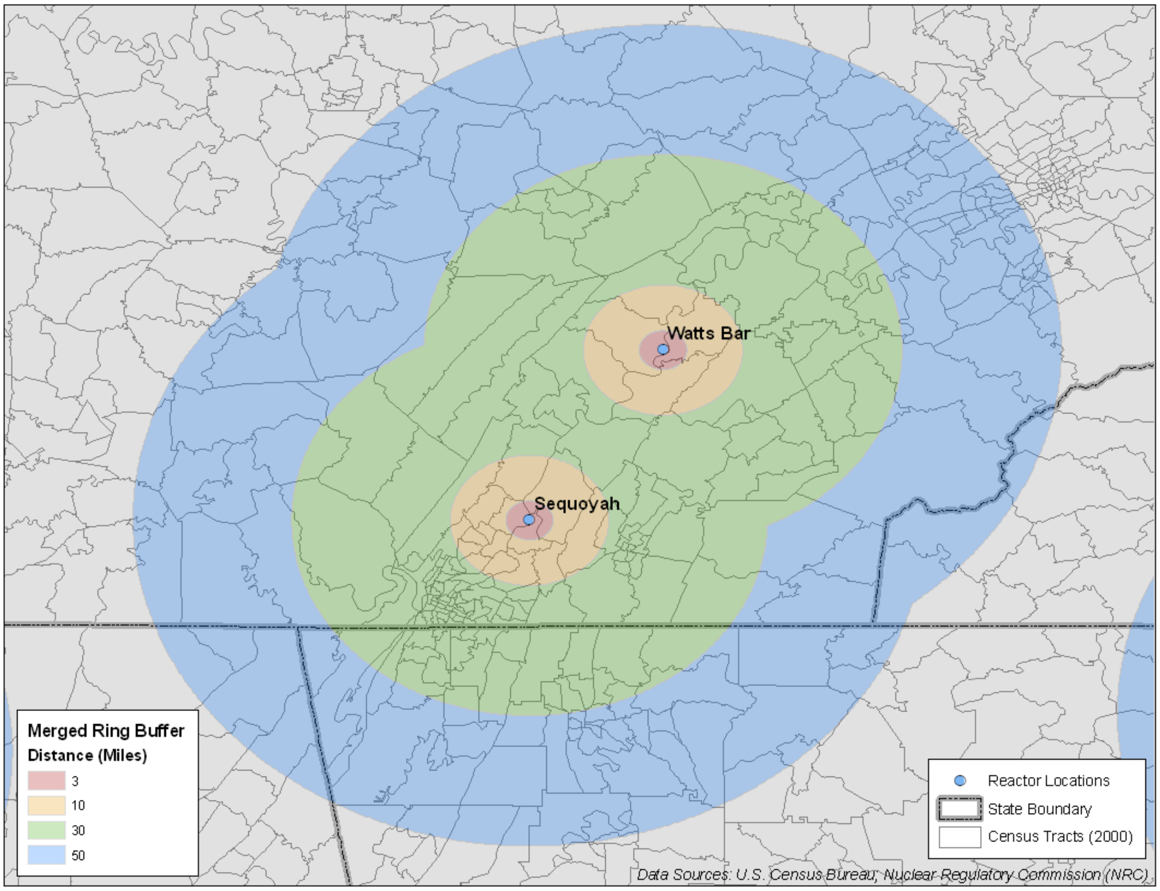


Figure 3: Spatial Analysis Example of Combining Analysis Regions for Sites Closer than 100 Miles Apart: Watts Bar and Sequoyah Sites in Tennessee



Analytic Approach

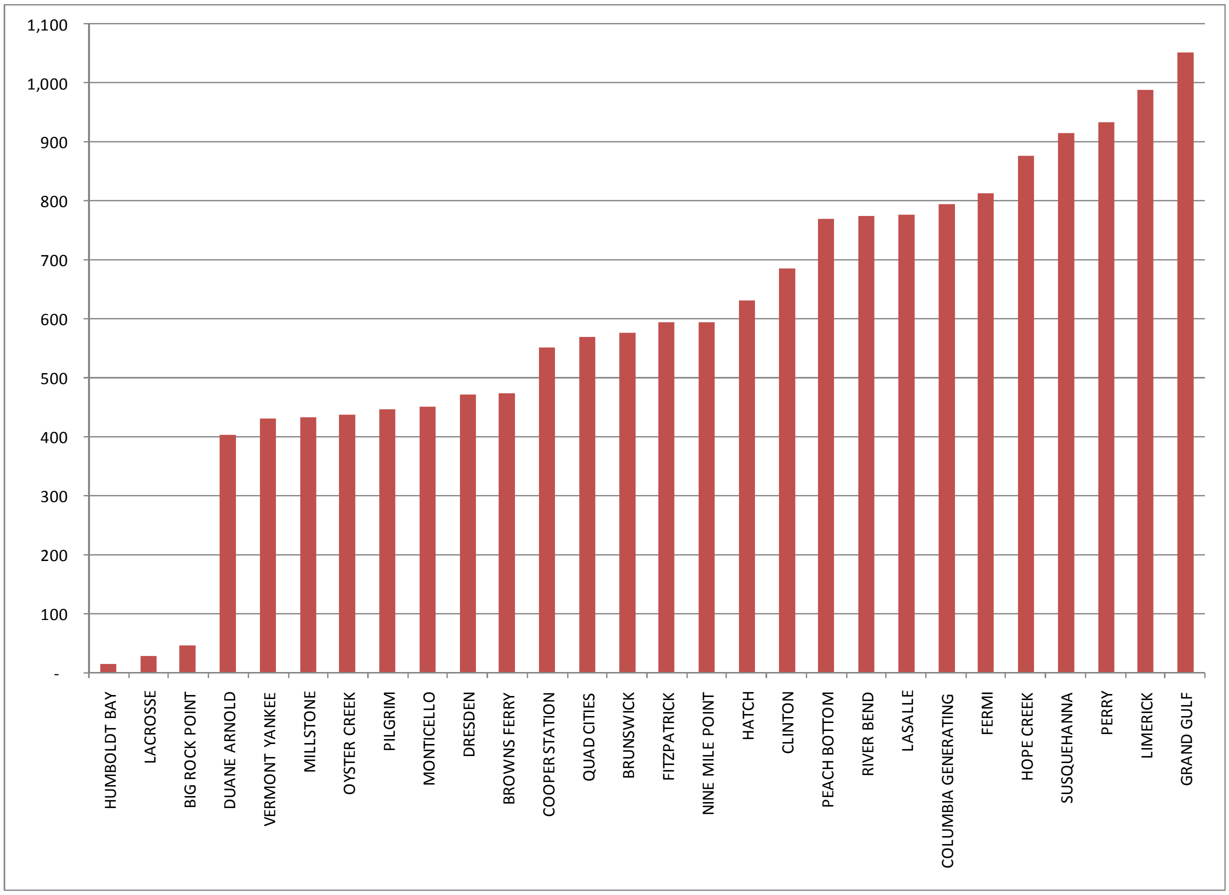
SMRs will be calculated for the inner circle and for rings between the 3- and 10-, the 10- and 30-, and the 30- and 50-mile circles or for the adapted regions in cases where circles from nearby sites overlap (see Figure 3). RRs will be calculated for the inner circle compared to each of the rings or adapted regions.

For sites where few or no deaths occurred within the three-mile circle for a given cancer cause-of-death, data from multiple sites will be aggregated. Because there is currently no objective procedure for aggregating sites spatially, initial spatial analysis will be conducted on a comprehensive level. That is, for all sites in states providing address data, combined cancer deaths within 3 miles of these sites will be compared to cancer deaths in the 3-10 mile ring around these sites. A similar comparison will be made with the 10-30 mile and the 30-50 mile ring. RRs will be calculated in this manner for all causes of death of interest. The next step in spatial analysis will involve partitioning the sites into subgroups. The degree of partitioning will be dependent on the cause of death since, for example, there will be more lung cancer than thyroid cancer deaths. Subgroups for aggregation will be determined by factors such as reactor type (BWR and PWR), years since site start-up, average power generation, or other applicable factors. Two sites will be excluded from any BWR or PWR analyses: St. Vrain and Millstone. St. Vrain was the only high-temperature, gas-cooled reactor, and Millstone had both a BWR and a PWR on the site.

Grouping the reactors by type and size would be a logical aggregation as it reflects the magnitude of operations at the site. Figures 4 and 5 present for BWRs and PWRs, respectively, the magnitude of operations expressed as the average megawatt (MW)-year output over the years of operation by summing the site's actual MW-year power output from 1973–2007 for the years of commercial operation divided by the number of reactor unit-years. Because the earliest year for which a site's actual MW-year power output is available is 1973, sites shut down before that year do not appear in the figures. These figures show that there are three small BWRs and one small PWR. The PWRs seem to have a clear group of large reactors above 900 MW-years, while large BWRs appear to be over 750 MW-years.

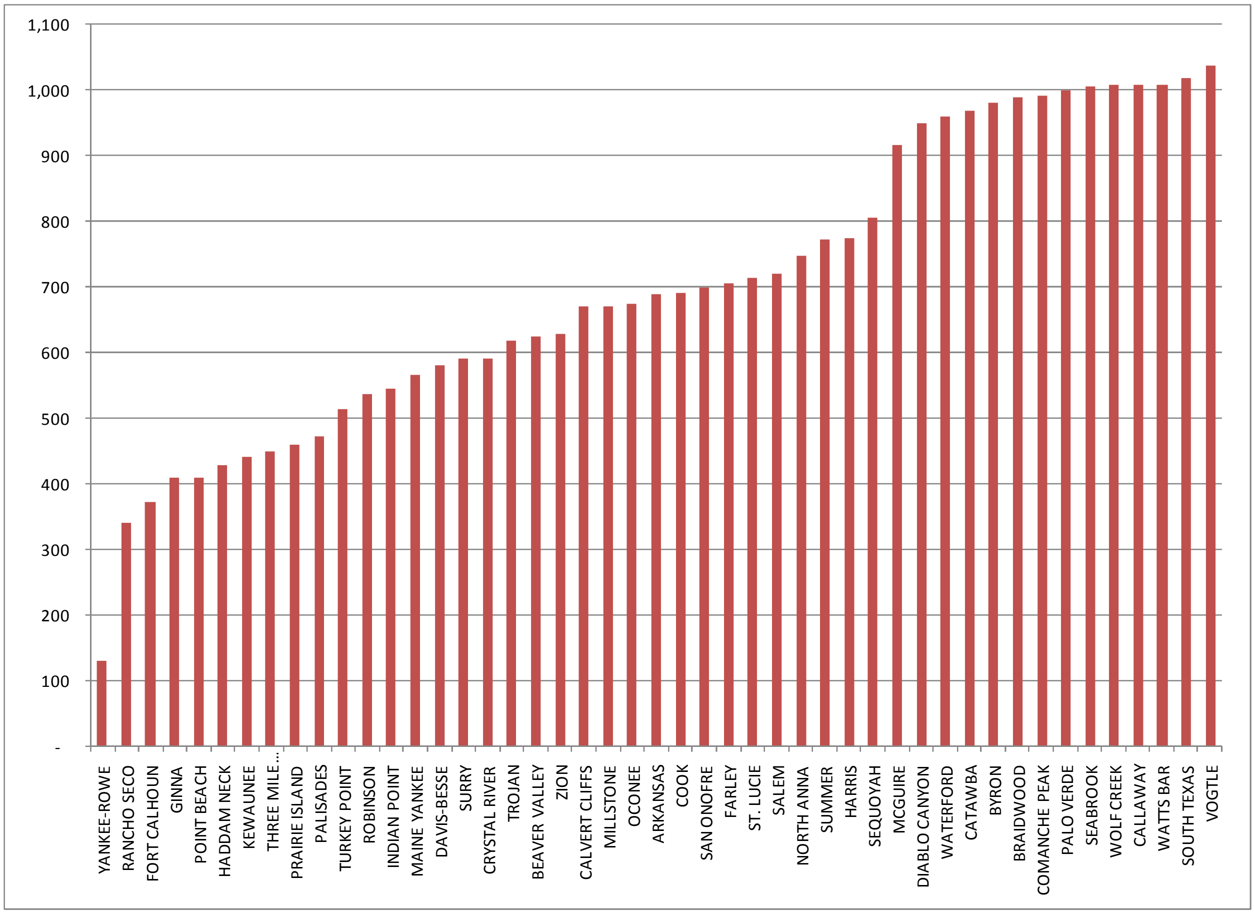
Figure 6 shows the number of years of operation for each site by BWR and PWR as information for an alternative method of aggregation of sites for spatial analysis. Groupings of less than 25, 25–34, and 35 or more years appear to be reasonable for both BWRs and PWRs.

Figure 4. Average Megawatt-years per Years of Reactor Operation for BWRs*



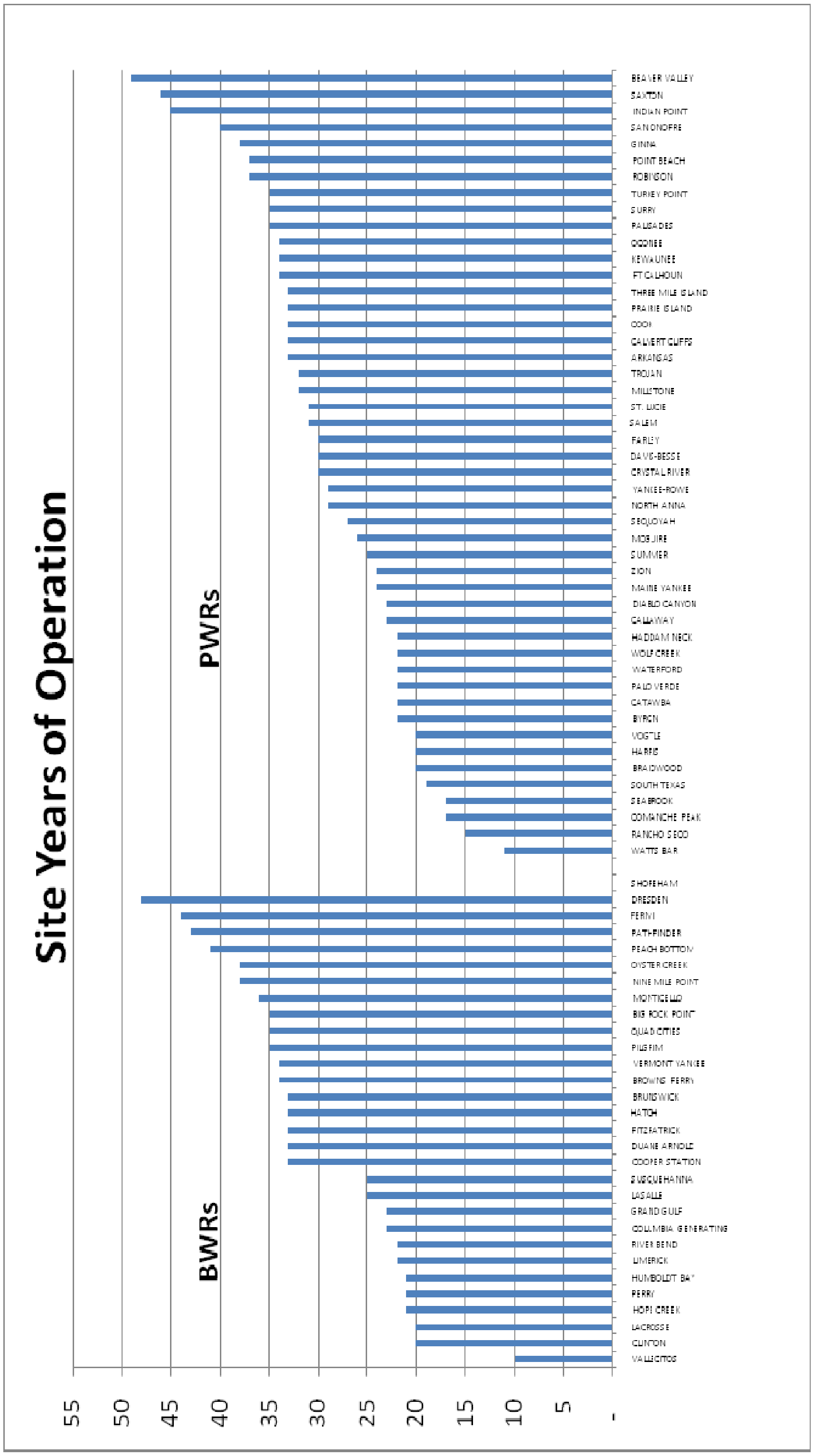
* Based on data collected by the NRC from 1973 (or the first year of commercial operation for each reactor if after 1973) through 2007.

Figure 5. Average Megawatt-years per Years of Reactor Operation for PWRs*



* Based on data collected by the NRC from 1973 (or the first year of commercial operation for each reactor if after 1973) through 2007.

Figure 6: Years of Reactor Operation at Each Site*



* Based on data collected by the NRC from 1973 (or the first year of commercial operation for each reactor if after 1973) through 2007.

Additional Spatial Analysis for Childhood Leukemia

An additional analysis is proposed that employs spatial analysis methods to investigate childhood leukemia. Because childhood leukemia is a very rare cause of death, it will likely be necessary to pool data from many, if not all, sites. Pooling geographic data in a credible manner will be accomplished according to a procedure that will be developed a priori. Methods comparable to those used in the German study of childhood leukemia (Kaatsch et al. 2008) and approved by the German SSK will be utilized for this analysis insofar as possible. Additional details are being formulated, with special attention being directed at methodology issues discussed in Bithell et al. (2008).

Study Products

The study will be summarized in several ways. An extended executive summary similar to *Volume 1 Report and Summary* from the 1990 study will be prepared. A manuscript suitable for submission to a peer-reviewed journal and similar in content to the paper by Jablon et al. (1991) will be prepared. Possible journals to which the manuscript may be submitted include Journal of the American Medical Association, Health Physics, American Journal of Epidemiology, and American Journal of Public Health. Other publications are possible including application of GIS methods to spatial analysis. Levels of detailed study results will be prepared for electronic viewing as outlined in Appendix D.

Archiving the Study Materials

At the outset, we intended to use the software and data files from the study done in 1991. However, both the software and the data could not be located. In addition, a detailed accounting of the methods used was not available. As a result, the current study had to be constructed from original data sources. Even some of the national data that were available for use in the first study were no longer available in electronic form (i.e., national mortality data prior to 1959). As a result of these issues, it is recommended that all the materials from this study be archived for future use in a national repository. The National Archives and Records Administration is one possible repository. Another possibility is the Department of Energy's (DOE) Comprehensive Epidemiologic Data Resource (CEDR). CEDR, which was established in 1990, is a DOE public-sue repository of data from occupational and environmental health studies of workers at DOE facilities and nearby community residents. While this study did not include DOE facilities, the study's focus is parallel to the that of data in CEDR, namely the potential health risks resulting from exposure to ionizing radiation.

Abbreviations and Acronyms

BWR	boiling water reactor
COMARE	Committee on Medical Aspects of Radiation in the Environment
DOE	Department of Energy
EPA	Environmental Protection Agency
FIPS	Federal Information Processing Standard
ICD	International Classification of Diseases
IRB	Institutional Review Board
KiKK	Kinderkrebs in der Ungebung von Kernkraftwerken
MW	megawatt
NAPHSIS	National Association for Public Health Statistics Information Systems
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NRC	Nuclear Regulatory Commission
ORNL	Oak Ridge National Laboratory
ORSIRB	Oak Ridge Site-wide Institutional Review Board
PWR	pressurized water reactor
RR	relative risk
SI	similarity index
SMR	standardized mortality ratio
SSK	Strahlenschutzkommission (Commission on Radiological Protection)
UK	United Kingdom
U.S.	United States

Bibliography

Antonelli, A., *et al.* “Epidemiologic and Clinical Evaluation of Thyroid Cancer in Children from the Gomel Region (Belarus).” *World Journal of Surgery*. Vol. 20: pp. 867–871. 1996.

Aylin, P., *et al.* “A National Facility for Small Area Disease Mapping and Rapid Initial Assessment of Apparent Disease Clusters Around a Point Source: The UK Small Area Health Statistics Unit.” *Journal of Public Health Medicine*. Vol. 21, No. 3: pp. 289–298. 1999.

Baker, P.J. and D. Hoel. “Meta-Analysis of Standardized Incidence and Mortality Rates of Childhood Leukaemia in Proximity to Nuclear Facilities.” *European Journal of Cancer Care*. Vol. 16, No. 4: pp. 355–363. 2007.

Bhaduri, B., *et al.* “LandScan USA: A High-Resolution Geospatial and Temporal Modeling Approach for Population Distribution and Dynamics.” *GeoJournal*. Vol. 69: pp. 103–117. 2007.

Bithell, J.F. and R.A. Stone. “On Statistical Methods for Analysing the Geographical Distribution of Cancer Cases Near Nuclear Installations.” *Journal of Epidemiology and Community Health*. Vol 43: pp. 79–85. 1989.

Bithell, J.F., *et al.* “Distribution of Childhood Leukaemias and Non-Hodgkin’s Lymphomas Near Nuclear Installations in England and Wales.” *BMJ*. Vol. 309: pp 501–505. 1994.

Bithell, J.F., *et al.* “Childhood Leukaemia Near British Nuclear Installations: Methodological Issues and Recent Results.” *Radiation Protection Dosimetry.* Vol. 132, No. 2: pp. 191–197. 2008.

Black D. “Investigation of the Possible Increased Incidence of Cancer in West Cumbria. Report of the Independent Advisory Group.” London: HMSO. 1984.

Black, R.J., *et al.* “Leukaemia and Non-Hodgkin’s Lymphoma: Incidence in Children and Young Adults Resident in the Dounreay Area of Caithness, Scotland 1968–91.” *Journal of Epidemiology and Community Health*. Vol. 48: pp. 232–236. 1994.

Blackwell Publishing Ltd. “Children And Young People Show Elevated Leukaemia Rates Near Nuclear Facilities.” *ScienceDaily* 18 July 2007. <http://www.sciencedaily.com /releases/2007/07/070718113939.htm>. (04 November 2008).

Boice Jr., J.D. “Nuclear Energy: Relationship to Cancer Incidence.” *Cancer Prevention*. pp. 1–9. January 1991.

Boice Jr., J.D., *et al.* “Cancer Incidence in Municipalities Near Two Former Nuclear Materials Processing Facilities in Pennsylvania.” *Health Physics*. Vol. 85, No. 6: pp. 678–690. 2003a.

Boice Jr., J.D., *et al.* “Cancer Mortality in Counties Near Two Former Nuclear Materials Processing Facilities in Pennsylvania, 1950–1995.” *Health Physics*. Vol. 85, No. 6: pp. 691–700. 2003b.

Boice Jr., J.D., *et al.* “Childhood Cancer Mortality in Relation to the St. Lucie Nuclear Power Station.” *Journal of Radiological Protection*. Vol. 25: pp. 229–240. 2005.

Boice Jr., J.D., M.T. Mumma, and W.J. Blot. “Cancer Mortality Among Populations Residing in Counties Near the Hanford Site, 1950–2000.” *Health Physics*. Vol. 90, No. 5: pp. 431–445. 2006.

Boice Jr., J.D., M.T. Mumma, and W.J. Blot. “Cancer and Noncancer Mortality in Populations Living Near Uranium and Vanadium Mining and Milling Operations in Montrose County, Colorado, 1950–2000.” *Radiation Research*. Vol. 167: pp. 711–726. 2007.

Boutou, O., *et al.* “Population Mixing and Leukaemia in Young People Around the La Hague Nuclear Waste Reprocessing Plant.” *British Journal of Cancer*. Vol. 87: pp. 740–745. 2002.

Breslow, N.E. and N.E. Day. “Indirect Standardization and Multiplicative Models for Rates, with Reference to the Age Adjustment of Cancer Incidence and Relative Frequency Data.” *Journal of Chronic Diseases*. Vol. 28: pp. 289–303. 1975.

Breslow, N.E. and N.E. Day. *Statistical Methods in Cancer Research*, *Volume II – The Design and Analysis of Cohort Studies.* Oxford University Press: New York. 1987. Chapter 4. <http://www.iarc.fr/en/publications/pdfs-online/stat/sp82/>.

Bruske-Hohlfeld, I., *et al.* “A Cluster of Childhood Leukaemias Near Two Neighbouring Nuclear Installations in Northern Germany: Prevalence of Chromosomal Aberrations in Peripheral Blood Lymphocytes.” *International Journal of Radiation Biology*. Vol. 77, No. 1: pp. 111–116. 2001.

Busby, C. and M.S. Cato. “Death Rates from Leukaemia Are Higher Than Expected in Areas Around Nuclear Sites in Berkshire and Oxfordshire [letter to editor].” *BMJ*. Vol. 315: p. 309. 1997.

Cai, Q. “Appendix Three. A Methodology for Estimating Small-Area Populations by Age and Sex Based on Methods of Spatial Interpolation and Statistical inference.” In: *Development of High Resolution Population Distribution Data to Enhance Cancer Prevention and Control Research*. SEER Special Project #08. RFP No. NCI-PC-25014-20. Final Report [Contains Final Report by subcontractor, Oak Ridge National Laboratory]. Iowa City, Iowa: Iowa Cancer Registry, The University of Iowa. June 7, 2004. <http://www.uiowa.edu/~gishlth/UIORNL/4_Appendix%20Three%20Cai.pdf>.

Cai, Q., *et al.* “Estimating Small-Area Populations by Age and Sex Using Spatial Interpolation and Statistical Inference Methods.” *Transactions in GIS*. Vol. 10, No. 4: pp. 577–598. 2006.

Cardis, E., *et al.* “Risk of Thyroid Cancer After Exposure to ^{131}I in Childhood.” *Journal of the National Cancer Institute*. Vol. 97, No. 10: pp. 724–732. 2005.

Cartwright, R. A., *et al.* “The Onset of the Excess of Childhood Cancer in Seascale, Cumbria.” *Journal of Public Health Medicine*. Vol. 23, No. 4: pp. 314–322. 2001.

Centers for Disease Control and Prevention, National Center for Health Statistics. “A Guide to State Implementation of ICD-10 for Mortality.” July 16, 1998. <http://www.cdc.gov/nchs/about/major/dvs/icd10des.htm> (12 March 2009).

Centers for Disease Control and Prevention, National Center for Health Statistics. “A Guide to Implementation of ICD-10 for Mortality Part II: Applying Comparability Ratios.” December 4, 2000. <http://www.cdc.gov/nchs/about/major/dvs/icd10des.htm> (12 March 2009).

Committee on Medical Aspects of Radiation in the Environment (COMARE). “The Incidence of Childhood Cancer Around Nuclear Installations in Great Britain. Tenth Report.” London: Health Protection Agency for the Committee on Medical Aspects of Radiation in the Environment. 2005.

Committee on Medical Aspects of Radiation in the Environment (COMARE). “The Distribution of Childhood Leukaemia and Other Childhood Cancers in Great Britian 1969–1993. Eleventh Report.” London: Health Protection Agency for the Committee on Medical Aspects of Radiation in the Environment. 2006.

Commission on Radiological Protection (SSK). “Assessment of the Epidemiological Study on Childhood Cancer in the Vicinity of Nuclear Power Plants (KiKK Study): Statement of the Commission on Radiological Protection (SSK).” In: *Reports of the Commission on Radiological Protection, Issue 57*. Berlin: H. Hoffmann Fachverlag. 2008.

Cragle, D.L. and A. Fetcher. “Risk Factors Associated with the Classification of Unspecified and/or Unexplained Causes of Death in an Occupational Cohort.” *American Journal of Public Health*. Vol. 82, No. 3: pp. 455–457. 1992.

Davis, S., *et al.* “Risk of Thyroid Cancer in the Bryansk Oblast of the Russian Federation After the Chernobyl Power Station Accident.” *Radiation Research*. Vol. 162: pp. 241–248. 2004.

Dickinson, H. O. and L. Parker. “Quantifying the Effect of Population Mixing on Childhood Leukaemia Risk: The Seascale Cluster.” *British Journal of Cancer*. Vol. 81, No. 1: pp. 144–151. 1999.

Doll, R. “The Seascale Cluster: A Probable Explanation.” *British Journal of Cancer*. Vol. 81, No. 1: pp. 3–5.1999.

Draper, G. J., *et al.* “Cancer in Cumbria and in the Vicinity of the Sellafield Nuclear Installation, 1963–90.” *BMJ*. Vol. 306: pp. 89–94. 1993.

Evard, A.-S., *et al.* “Childhood Leukaemia Incidence Around French Nuclear Installations Using Geographic Zoning Based on Gaseous Discharge Dose Estimates.” *British Journal of Cancer*. Vol. 94, No. 9: pp. 1342–1347. 2006.

Fairlie, I. “Comment: Let’s Take Cancer Clusters Seriously This Time.” *New Scientist*. No. 2653: p. 18. 26 April 2008.

Forman, D., et al. “Cancer Near Nuclear Installations,” *Nature.* Vol. 329: pp. 499-505. 1987.

Frome, E. L., et al. “A Mortality Study of Employees of the Nuclear Industry in Oak Ridge, Tennessee,” *Radiation Research*. Vol. 148: pp. 64-80. 1997.

Frome, E. L., D. L. Cragle, and R. W. McClain. “Poisson Regression Analysis of the Mortality Among a Cohort of World War II Nuclear Industry Workers.” *Radiation Research*. Vol. 123: pp. 138-152. 1990.

Gardner, M.J., *et al.* “Follow up Study of Children Born Elsewhere but Attending Schools in Seascale, West Cumbria (Schools Cohort).” *British Medical Journal*. Vol. 295: pp. 819–822. 1987a.

Gardner, M.J., *et al.* “Follow up Study of Children Born to Mothers Resident in Seascale, West Cumbria (Birth Cohort).” *British Medical Journal*. Vol. 295: pp. 822–827. 1987b.

Gardner, M.J., *et al.* “Methods and Basic Data of Case-Control Study of Leukaemia and Lymphoma Among Young People Near Sellafield Nuclear Plant in West Cumbria.” *British Medical Journal*. Vol. 300: pp. 429–434. 1990a.

Gardner, M.J., *et al.* “Results of Case-Control Study of Leukaemia and Lymphoma Among Young People Near Sellafield Nuclear Plant in West Cumbria.” *British Medical Journal*. Vol. 300: pp. 423–429. 1990b.

Goldsmith, J.R. “Nuclear Installations and Childhood Cancer in the UK: Mortality and Incidence for 0–9-Year-Old Children 1971–1980.” *The Science of the Total Environment*. Vol. 127: pp. 13–35. 1992.

Grosche, B., *et al.* “Leukaemia in the Vicinity of Two Tritium-Releasing Nuclear Facilities: A Comparison of the Kruemmel Site, Germany, and the Savannah River Site, South Carolina, USA.” *Journal of Radiological Protection*. Vol. 19, No. 3: pp. 243–252. 1999.

Guizard, A.-V., *et al.* “The Incidence of Childhood Leukaemia Around the La Hague Nuclear Waste Reprocessing Plant (France): A Survey for the Years 1978–1998.” *Journal of Epidemiology and Community Health*. Vol. 55: pp. 469–474. 2001.

Hatch, M. and M. Susser. “Background Gamma Radiation and Childhood Cancers Within Ten Miles of a U.S. Nuclear Plant.” *International Journal of Epidemiology*. Vol. 19, No. 3: pp. 546–552. 1990.

Hatch, M. C., *et al.* “Cancer Near the Three Mile Island Nuclear Plant: Radiation Emissions.” *American Journal of Epidemiology*. Vol. 132, No. 3: pp. 397–412; discussion: pp. 413–417. 1990.

Hattchouel, J.-M., A. Laplanche, and C. Hill. “Cancer Mortality Around French Nuclear Sites.” *Annals of Epidemiology*. Vol. 6: pp. 126–129. 1996.

Hattchouel, J.-M., A. Laplanche, and C. Hill. “Leukaemia Mortality Around French Nuclear Sites.” *British Journal of Cancer*. Vol. 71: pp. 651–653. 1995.

Hill, C. and A. Laplanche. “Overall Mortality and Cancer Mortality Around French Nuclear Sites.” *Nature*. Vol. 347: pp. 755–757. 1990.

Hjalmars, U., *et al.* “Childhood Leukaemia in Sweden: Using GIS and a Spatial Scan Statistic for Cluster Detection.” *Statistics in Medicine*. Vol. 15: pp. 707–715.1996.

Hoffmann, W., C. Terschueren, and D.B. Richardson. “Childhood Leukemia in the Vicinity of the Geesthacht Nuclear Establishments Near Hamburg, Germany.” *Environmental Health Perspectives*. Vol. 115, No. 6: pp. 947–952. 2007.

Hoffmann, W., *et al.* “A Cluster of Childhood Leukemia Near a Nuclear Reactor in Northern Germany.” *Archives of Environmental Health*. Vol. 52, No. 4: pp. 275–280. July–August 1997.

Illinois Department of Public Health. “Pediatric Cancer Incidence and Proximity to Nuclear Facilities in Illinois.” In: “Health and Hazardous Substances Registry Newsletter (Illinois Department of Public Health).” Fall 2000. <www.idph.state.il.us/cancer/pdf/article.pdf> (04 November 2008).

Inskip H. “Childhood Leukaemia Near Nuclear Sites Re-examined.” *The Lancet*. Vol. 349, No. 9057: pp. 969–970. 1997.

Iowa Cancer Registry. “Development of High Resolution Population Distribution Data to Enhance Cancer Prevention and Control Research.” SEER Special Project #08. RFP No. NCI-PC-25014-20. Final Report [Contains Final Report by subcontractor, Oak Ridge National Laboratory]. Iowa City, Iowa: Iowa Cancer Registry, The University of Iowa. June 7, 2004.

Iwasaki, T., *et al.* “Leukaemia and Lymphoma Mortality in the Vicinity of Nuclear Power Stations in Japan, 1973–1987.” *Journal of Radiological Protection*. Vol. 15, No. 4: pp. 271–288. 1995.

Jablon, S., *et al.* “Cancer in Populations Living Near Nuclear Facilities. Volume 1, Report and Summary.” NIH Publication No. 90-874. Washington, DC: U.S. Department of Health and Human Services. July 1990.

Jablon, S., Z. Hrubec, and J.D. Boice Jr. “Cancer in Populations Living Near Nuclear Facilities: A Survey of Mortality Nationwide and Incidence in Two States.” *Journal of the American Medical Association*. Vol. 265, No. 11: pp. 1403–1408. 1991.

Jacob P., *et al.* “Childhood Exposure Due to the Chernobyl Accident and Thyroid Cancer Risk in Contaminated Areas of Belarus and Russia.” *British Journal of Cancer*. Vol. 80, No. 9: pp. 1461–1469. 1999.

Kaatsch, P., *et al.* “An Extended Study on Childhood Malignancies in the Vicinity of German Nuclear Power Plants.” *Cancer Causes and Control*, Vol. 9: pp. 529–533. 1998.

Kaatsch, P., *et al.* “Leukaemia in Young Children Living in the Vicinity of German Nuclear Power Plants.” *International Journal of Cancer*, Vol. 1220: pp. 721–726. 2008.

Kinlen, L.J. “Infection and Childhood Luekaemia Near Nuclear Sites.” *The Lancet*. Vol. 349: p. 1702. 1997.

Kinlen, L.J. “The Relevance of Population Mixing to the Aetiology of Childhood Leukaemia.” In: Crosbie, W. A. and J. H. Gittus, editors. *Medical Response to Effects of Ionising Radiation.* London: Elsevier. pp. 272–278. 1989.

Kinlen, L.J. and A. Balkwill. “Infective Cause of Childhood Leukaemia and Wartime Population Mixing in Orkney and Shetland, UK.” *The Lancet*. Vol. 357: p. 858. 2001.

Kinlen, L.J. and P. Tiplady. “The ‘Seascale Cluster’.” *Journal of Public Health Medicine*. Vol. 24, No. 4: pp. 342–343. 2002.

Kinlen, L.J., *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*. Vol. 306: pp. 743–748. 1993.

Laurier, D. “Clusters of Leukaemia Among Young People Living Near Nuclear Sites, with a Focus on Studies Performed in the Nord-Cotentin (France).” In: *Low-Dose Ionizing Radiation and Cancer Risk. Radiation Protection 125*. Luxembourg: European Commission. 2001. pp. 39–60.

Laurier, D. and D. Bard. “Epidemiologic Studies of Leukemia Among Persons Under 25 Years of Age Living Near Nuclear Sites.” *Epidemiologic Reviews*. Vol. 21, No. 2: pp. 188–206. 1999.

Laurier, D., B. Grosche, and P. Hall. “Risk of Childhood Leukaemia in the Vicinity of Nuclear Installations.” *Acta Oncologica*. Vol. 41, No. 1: pp. 14–24. 2002.

Laurier, D., D. Hemon, and J. Clavel. “Childhood Leukaemia Incidence Below the Age of 5 Years Near French Nuclear Power Plants.” *Journal of Radiological Protection*. Vol. 28: pp. 401–403. 2008.

Lopez-Abente, G., *et al.* “Leukemia, Lymphomas, and Myeloma Mortality in the Vicinity of Nuclear Power Plants and Nuclear Fuel Facilities in Spain.” *Cancer Epidemiology, Biomarkers & Prevention*. Vol. 8: pp. 925–934. 1999.

Lopez-Abente, G., N. Aragones, and M. Pollan. “Solid-Tumor Mortality in the Vicinity of Uranium Cycle Facilities and Nuclear Power Plants in Spain.” *Environmental Health Perspectives*. Vol. 109, No. 7: pp. 721–729. 2001.

Mangano, J.J., *et al.* “Elevated Childhood Cancer Incidence Proximate to U.S. Nuclear Power Plants.” *Archives of Environmental Health*. Vol. 58, No. 2: pp. 74–82. 2003.

McLaughlin, J.R., *et al.* “Childhood Leukemia in the Vicinity of Canadian Nuclear Facilities.” *Cancer Causes and Control*. Vol. 4: pp. 51–58. 1993.

Michaelis, J. “Recent Epidemiological Studies on Ionizing Radiation and Childhood Cancer in Germany.” *International Journal of Radiation Biology*. Vol. 73, No. 4: pp. 377–381. 1998.

Michaelis, J., *et al.* “Incidence of Childhood Malignancies in the Vicinity of West German Nuclear Power Plants.” *Cancer Causes and Control*. Vol. 3: pp. 255–263. 1992.

Morris, M. S. and R. S. Knorr. “Adult Leukemia and Proximity-Based Surrogates for Exposure to Pilgrim Plant’s Nuclear Emissions.” *Archives of Environmental Health*. Vol. 51, No. 4: pp. 266–274. 1996.

Muirhead, C.R. “Childhood Cancer and Nuclear Installations: A Review.” Nuclear Energy. Vol. 37, No. 6: pp. 371–379. 1998.

Pobel, D. and J.-F. Viel. “Case-Control Study of Leukaemia Among Young People Near La Hague Nuclear Processing Plant: The Environmental Hypothesis Revisited.” *BMJ*. Vol. 314: pp. 101–106. 1997.

Qiao, B., M. Lehnherr, and T. Shen. “Pediatric Cancer Incidence and Mortality in the Vicinity of Nuclear Power Plants in Illinois. Epidemiologic Report Series 06:01.” Springfield, Illinois: Illinois Department of Public Health. January 2006.

Rushton G. and Q. Cai. “Appendix Five. The Congruence of LandScan USA Boundaries with U.S. Census Block Boundaries.” In: “Development of High Resolution Population Distribution Data to Enhance Cancer Prevention and Control Research. SEER Special Project #08. RFP No. NCI-PC-25014-20. Final Report [Contains Final Report by subcontractor, Oak Ridge National Laboratory].” Iowa City, Iowa: Iowa Cancer Registry, The University of Iowa. June 7, 2004. <http://www.uiowa.edu/~gishlth/UIORNL/6_Rushton%20Cai%20Appendix%20Five%20Pop%20Grid%20Congruence.pdf>.

Rushton G. and Q. Cai. “Appendix Four. Errors in Spatial Coverage When Zip Code Areas (ZCTAs) Are Assigned to Spatial Filters Based on Their Centroids—Implications for Cancer Maps.” In: “Development of High Resolution Population Distribution Data to Enhance Cancer Prevention and Control Research. SEER Special Project #08. RFP No. NCI-PC-25014-20. Final Report [Contains Final Report by subcontractor, Oak Ridge National Laboratory].” Iowa City, Iowa: Iowa Cancer Registry, The University of Iowa. June 7, 2004. <http://www.uiowa.edu/~gishlth/UIORNL/5_Rushton%20Cai%20Appen%20four.pdf>.

Rushton, G., *et al.* “Geocoding in Cancer Research: A Review.” *American Journal of Preventive Medicine*. Vol. 30, No. 2: pp. S16–S24. February 2006.

Rushton, G., Q. Cai, and M. West. “Appendix Two. A Comparison of the Expected Number of Colorectal Cancer Incidences in Circular Areas with Populations Defined from Interpolated Block Group Data with Populations Defined with LandScan USA Data.” In: “Development of High Resolution Population Distribution Data to Enhance Cancer Prevention and Control Research. SEER Special Project #08. RFP No. NCI-PC-25014-20. Final Report [Contains Final Report by subcontractor, Oak Ridge National Laboratory].” Iowa City, Iowa: Iowa Cancer

Registry, The University of Iowa. June 7, 2004.
<http://www.uiowa.edu/~gishlth/UIORNL/3_Rushton%20Cai%20West%20Appen%202.pdf.>

Schmitz-Feuerhake, I., *et al.* “Leukemia in the Proximity of a German Boiling-Water Nuclear Reactor: Evidence of Population Exposure by Chromosome Studies and Environmental Radioactivity.” *Environmental Health Perspectives*. Vol. 105, Supplement 6: pp. 1499–1504. 1997.

Schmitz-Feuerhake, I., *et al.* “The Elbmarsch Leukemia Cluster: Are There Conceptual Limitations in Controlling Immission from Nuclear Establishments in Germany?” *Archives of Environmental Contamination and Toxicology*. Vol. 49: pp. 589–600. 2005.

Sharp, L., *et al.* “Incidence of Childhood Brain and Other Non-haematopoietic Neoplasms Near Nuclear Sites in Scotland, 1975–94.” *Occupational and Environmental Medicine*. Vol. 56: pp. 308–314. 1999.

Sharp, L., *et al.* “Incidence of Childhood Leukaemia and Non-Hodgkin’s Lymphoma in the Vicinity of Nuclear Sites in Scotland, 1968–93.” *Occupational and Environmental Medicine*. Vol. 53: pp. 823–831. 1996.

Silva-Mato, A., *et al.* “Cancer Risk Around the Nuclear Power Plants of Trillo and Zorita (Spain).” *Occupational and Environmental Medicine*. Vol. 60, No. 7: pp. 521–527. 2003.

Sofer, T., *et al.* “Geographical and Temporal Trends of Childhood Leukemia in Relation to the Nuclear Plant in the Negev, Israel, 1960–1985.” *Public Health Review*. Vol. 19: pp. 191–198. 1991/1992.

Spix, C., *et al.* “Case-Control Study on Childhood Cancer in the Vicinity of Nuclear Power Plants in Germany 1980–2003.” *European Journal of Cancer*, Vol. 44, No. 2: pp. 275–284. 2008.

Steenland, K., *et al.* “Individual- and Area-Level Socioeconomic Status Variables as Predictors of Mortality in a Cohort of 179,383 Persons.” *American Journal of Epidemiology*. Vol. 159, No. 11: pp. 1047–1056. 2004.

Terry, G. A. “A Look at Life on the Job for Mortality Data Reporters.” *Journal of AHIMA*. Vol. 72, No. 8: pp. 48–56. 2001.

Turnbull, B. W., *et al.* “Monitoring for Clusters of Disease: Application to Leukemia Incidence in Upstate New York.” *American Journal of Epidemiology*. Vol. 132, No. 1: pp. S136–S143. 1990.

Urquhart, J. D., *et al.* “Case-Control Study of Leukaemia and Non-Hodgkin’s Lymphoma in Children in Caithness Near the Dounreay Nuclear Installation.” *BMJ*. Vol. 302: pp. 687–692. 1991.

Viel, J. F. and S. T. Richardson. “Childhood Leukaemia Around the La Hague Nuclear Waste Reprocessing Plant.” *BMJ*. Vol. 300: pp. 580–581. 1990.

Viel, J.-F., *et al.* “Childhood Leukemia Incidence in the Vicinity of La Hague Nuclear-Waste Reprocessing Facility (France).” *Cancer Causes and Control*. Vol. 4: pp. 341–343. 1993.

Wakeford, R. “Childhood Cancer in Seascale.” *Journal of Public Health Medicine*. Vol. 24, No. 4: pp. 343–344. 2002.

Waller, L.A. and G.M. Jacquez. “Disease Models Implicit in Statistical Tests of Disease Clustering.” *Epidemiology*. Vol. 6, No. 6: pp. 584–590. 1995.

White-Koning, M.L., *et al.* “Incidence of Childhood Leukaemia in the Vicinity of Nuclear Sites in France, 1990–1998.” *British Journal of Cancer.* Vol. 91: pp. 916–922. 2004.

Yasui, Y. and J. Whitton. “Problems in Using Age-Stratum-Specific Reference Rates for Indirect Standardization.” *Journal of Clinical Epidemiology*. Vol. 52, No. 5: pp. 393–398. 1999.

Appendix A: Literature Update

Antonelli et al. (1996) reviewed the epidemiology of childhood thyroid cancer in the area of Gomel, Belarus, and the clinical data of 64 children aged 4 to 16 years from the area who had been diagnosed with differentiated thyroid carcinoma following the Chernobyl nuclear accident. The authors found significant increases in thyroid cancer rates during successive five-year periods from 1986 to 1994 when compared with the pre-accident period 1981–1985 and no indication that the rate had leveled off. The latency period was constant with time after the accident, regardless of age at the time of exposure. The Gomel cancer data showed differences when compared with data from previous elevated thyroid radiation exposures in other populations with regard to female/male ratio, latency period, and metastasis to other tissues. [Antonelli, A., *et al.* "Epidemiologic and Clinical Evaluation of Thyroid Cancer in Children from the Gomel Region (Belarus)." *World Journal of Surgery*. Vol. 20: pp. 867-871. 1996]

Aylin et al. present methods for estimating relative risks for defined areas around a point source relative to a local reference region and producing corresponding maps. To minimize the effect of shrinking the boundaries closer to the reported cluster, *a priori* bands of 0-2 km and 2-7.5 km are used. Standardized Mortality Ratios (SMRs) are adjusted for age, gender, and **quintile** of the Carstairs index, which is a small area deprivation measure. Also described is a method for smoothed risk estimates for areas with small populations that are a compromise between raw SMRs and the mean risk across the region as a whole. [Aylin, P. et al. "A national facility for small area disease mapping and rapid initial assessment of apparent disease clusters around a point source: the UK Small Area Health Statistics Unit." *Journal of Public Health Medicine*. Vol. 21, No. 3: pp. 289-298. 1999.]

Baker and Hoel (2007) conducted a multinational meta-analysis that combined and statistically analyzed studies of childhood leukemia and nuclear facilities, including only studies that calculated standardized incidence or mortality rates for individual facilities. Seventeen published studies addressing 136 nuclear sites in nine current or former countries (East Germany) met the criteria for at least one of the eight analyses performed. Five sites in the U.S. were excluded due to zero observed deaths, and expected could not be calculated because only observed and standardized mortality ratio were reported. Unadjusted, fixed effects and random effects models were used. Meta-rates greater than one were found in all models at all stratification levels, and often these rates were significant at the 95% confidence level. The authors comment that dose-response studies do not support excess rates found near nuclear facilities, and the reason for the elevated incidence and mortality rates is unknown. [Baker, P. J. and D. Hoel. "Meta-Analysis of Standardized Incidence and Mortality Rates of Childhood Leukaemia in Proximity to Nuclear Facilities." *European Journal of Cancer Care*. Vol. 16, No. 4: pp. 355-363. 2007]

Bithell and Stone develop locational methods for analyzing data such as leukemia risk near a nuclear installation. The Poisson maximum statistic, which is very sensitive to cases near a source of risk, was presented as an improvement over the SMR. This statistic can be interpreted as the maximum observed SRM that would be obtained if SMRs were calculated for expanded ordered regions around the risk source. The Poisson maximum statistic assumes only that risk is monotonically decreasing with increasing distance from the source. The Kolmogorov-Smirnov test was also suggested as a suitable locational test, but it requires adjustment for the discreteness of the data. [Bithell, JF and Stone, RA. On the statistical methods for analyzing the geographical distribution of cancer cases near nuclear installations. *Journal of Epidemiology and Community Health*, 43:79-85. 1989.]

Bithell et al (2008) conducted a study as similar as possible to the KiKK study of childhood leukemia in Germany. The Poisson regression estimate from this study and conditional logistic regression estimate from the KiKK study both estimated the change in log(RR) per km^{-1}. Results from the primary analysis, Poisson regression on the reciprocal of distance over a 50 km circle and the KiKK study were not statistically significantly different at the 0.05 level of significance, although the p-value for the hypothesis test of difference was 0.063. The primary analysis followed the portion of the KiKK methodology that has been criticized by the German Commission on Radiological Protection (SSK) in their recent assessment (2008). Supplemental analyses calculated the Poisson regression estimate in a circle with a 5 km radius, the area approved of by the Assessment Committee, and obtained a negative association of leukemia cases with proximity to site. Additional analyses calculated SIRs within circles of 5, 10, 25, and 50 km with all results less than one except for the 5 km circle [1.23(0.73:1.95)]. [Bithell, J. F. et al. “Childhood Leukaemia near British Nuclear Installations: Methodological Issues and Recent Results.” *Radiation Protection Dosimetry Advance Access*. Oxford University Press. pp. 1-7. October 20, 2008.]

Bithell et al. (2008) described a recent study of childhood cancer and leukemia around German nuclear power stations conducted by the Kinderkrebs in der Umgebung von Kernkraftwerken (KiKK) and published by the German Childhood Cancer Registry (Kaatsch et al. 2008; Spix et al. 2008). The positive findings of this study appeared to conflict with the results of a recent British analysis carried out by the Committee on Medical Aspects of Radiation in the Environment (COMARE, 2005). The British study showed no evidence of a raised risk of childhood leukemia or any other cancer around nuclear power stations. The German study results found an approximately doubled risk of leukemia in children under the age of five within 5 km of the power stations. The discrepancies in results prompted the British researchers to look again at their study data from the National Registry of Children’s Tumours, specifically to examine possible associations by using more nearly the same methods as in the German study. The British analyses were of areal data, in contrast to the German case-control approach. It was not possible in the reanalysis to use a case-control design, as there was not a suitable population register available in the UK. The previous methodology based on electoral wards was followed. It was concluded that there was no evidence of an elevated incidence of acute leukemia in children less than five years of age and living within 5 km of nuclear power stations in Britain. The discrepancy with the KiKK result was considered in light of the considerable sampling errors in both estimates. Although the calculations comparing the KiKK and the revisited COMARE studies suggested the possibility of a real underlying difference in the risk estimates, the difference was on the margins of statistical significance at the 5% level. [Bithell, J. F., *et al.* “Childhood Leukaemia near British Nuclear Installations: Methodological Issues and Recent Results.” *Radiation Protection Dosimetry.* Vol. 132, No. 2: pp. 191-197. 2008]

Bithell et al. (1994) examined the incidence risk of childhood (age less than 15 years) leukemia and non-Hodgkin's lymphoma with regard to the proximity of residence to nuclear installations in England and Wales for the period 1966–1987. The authors found no evidence of a general increase of childhood leukemia or non-Hodgkin's lymphoma around 23 nuclear installations and six control sites that had been investigated for suitability for generating stations but never used. Study areas were within 25 km radii around the installations. Cases were assigned based on address at the time of cancer registration. The authors calculated observed and expected numbers of cases and used both standard analytical methods and a new statistical test, the linear risk score test, based on ranks and designed to be sensitive to excess incidence near a putative risk and addressing small area statistics. The authors concluded that "apart from Sellafield, the evidence for distance related risk is very weak." [Bithell, J.F., *et al.* "Distribution of Childhood Leukaemias and Non-Hodgkin's Lymphomas Near Nuclear Installations in England and Wales." *BMJ*. Vol. 309: pp 501-505. 1994]

Black et al. (1994) reviewed the incidence of leukemia and non-Hodgkin's lymphoma in children and young adults within an area less than 25 km from the Dounreay nuclear reprocessing plant and the remainder of the plant's postcode area for the period 1968 to 1991. Observed numbers of cases and observed-to-expected ratios based on Scottish national expected rates were determined for subjects aged 0–24 years. Consistent with a similar, previous study, there was no adjustment for socioeconomic variables or urban-rural status. In the study period 1968–1991 for the 0–14 years and the 0–24 years age groups, observed cases exceeded expected cases within a 0–12.5 km area and a 12.5–25 km area, although only the inner area showed statistical significance. Similar results were seen also for the subperiod 1985–1991 but without statistical significance. [Black, R.J., *et al.* "Leukaemia and Non-Hodgkin's Lymphoma: Incidence in Children and Young Adults Resident in the Dounreay Area of Caithness, Scotland 1968-91." *Journal of Epidemiology and Community Health*. Vol. 48: pp. 232-236. 1994]

Blackwood Publishing Ltd. (2008) in *Science Daily* reports on the meta-analysis conducted by Baker and Hoel (2007) of standardized incidence and mortality rates of childhood leukemia in proximity to nuclear facilities. The authors evaluated data from 17 research papers covering 136 nuclear sites in the UK (four studies plus another three for Scotland only), Canada (two), France (three), U.S. (one), former East and West Germanys (one each), Japan (one), and Spain (one). Death rates were elevated by between 5 and 24%, depending on proximity to the facilities, for children 0–9 years of age and by 2 to 18% for the 0–25 year age group; incidence rates were increased by 14 to 21% and 7 to 10%, respectively. Dose-response studies showed no excess rates near nuclear facilities. [Blackwell Publishing Ltd.. "Children And Young People Show Elevated Leukaemia Rates Near Nuclear Facilities." ScienceDaily 18 July 2007. <http://www.sciencedaily.com /releases/2007/07/070718113939.htm>. (04 November 2008)]

Boice et al. (2007) compared cancer and noncancer standardized mortality rates (SMRs) between 1950 and 2000 among residents of Montrose County, Colorado, which has a history of extensive uranium and vanadium mining and milling, to SMRs among five demographically similar counties in Colorado. The SMRs were calculated by using expected numbers of deaths in the general populations of Colorado and the U.S.. There was no difference between the mortality rates in the study county and those in the comparison counties for total cancers, childhood cancer, or cancers of the breast, kidney, liver, bone, leukemia, as well as non-Hodgkin's lymphoma, renal disease, or female lung cancer or for nonmalignant respiratory disease.   An increase in male lung cancer, tuberculosis, and accidental deaths and decreases in male kidney cancer, liver, and kidney cancer and leukemia were seen at the 95% significance level. No significant differences in cancer mortality for different time intervals were seen. The authors suggest that the increase in male lung cancer was most likely due to prior occupational exposure to radon and cigarette smoking among underground miners, which would be consistent with previous cohort studies of this area. [Boice Jr., J. D., M. T. Mumma, and W. J. Blot. "Cancer and Noncancer Mortality in Populations Living Near Uranium and Vanadium Mining and Milling Operations in Montrose County, Colorado, 1950-2000." *Radiation Research*. Vol. 167: pp. 711-726. 2007]

Boice et al. (2006) conducted a descriptive epidemiologic study of cancer mortality among residents of counties near the DOE Hanford nuclear facility near Richland, Washington, extending by 16 years a previous study conducted by the National Cancer Institute (Jablon et al. 1990) that included this site. Unlike the previous study, information on release patterns and wind direction were used in the selection of study and comparison counties. The authors compared cancer standardized mortality ratios (SMRs) from 1950 through 2000 in four counties with the highest estimated exposure to I-131, with cancer SMRs in five demographically similar counties in the state having had minimal I-131 exposure. In general, cancer rates in the study counties were slightly below those in the comparison counties due mainly to a low risk for lung cancer. There was no significant increase in risk in the study counties for thyroid cancer, female breast cancer, leukemia other than chronic lymphocytic leukemia, or childhood leukemia at the 95% level of significance. There was no evidence of a difference in cancer rates, including for thyroid cancer only, over time between study and comparison counties. [Boice Jr., J. D., M. T. Mumma, and W. J. Blot. "Cancer Mortality Among Populations Residing in Counties Near the Hanford Site, 1950-2000." *Health Physics*. Vol. 90, No. 5: pp. 431-445. 2006]

Boice et al. (2005) extended by 17 years for St. Lucie County, Florida, a previous case-control study (Jablon et al. 1990, 1991) of county mortality conducted by the National Cancer Institute. In a descriptive study, mortality rates of total cancer, leukemia, and cancer of brain and other nervous tissue in children under the age of 20 years and across all ages in St. Lucie County were compared with rates in two similar Florida counties and evaluated for the years before and after the 1976 start-up of the St. Lucie nuclear power station. Over the period 1950–2000, there were no significant differences in mortality rates between the study and comparison counties for any cancer post 1976 start-up. Relative rates for all childhood cancers and for childhood leukemia were higher before the start-up than after; rates of brain and other nervous tissue cancer were slightly lower in St. Lucie County than in the comparison counties for both before and after start-up. [Boice Jr., J. D., *et al.* "Childhood Cancer Mortality in Relation to the St. Lucie Nuclear Power Station." *Journal of Radiological Protection*. Vol. 25: pp. 229-240. 2005]

Boice et al. (2003a) performed a descriptive epidemiologic correlation study to assess cancer incidence rates for the Apollo and Parks former uranium and plutonium nuclear fuel processing facilities located in Armstrong County, Pennsylvania, nearly 40 years after the facilities began operation. Cancer incidence rates were evaluated for the period 1993–1997 among approximately 17,000 persons living in one of eight municipalities encompassing or near the facilities using numbers of cancers and mailing addresses obtained from the Pennsylvania Department of Health. Each of the 935 cancer-related addresses was validated and corrected when necessary; 40% were found to be outside the boundaries of the study municipalities and were excluded. No significant excesses were noted within the study municipalities for lung, kidney, non-Hodgkin's lymphoma, liver, bone, female breast and thyroid, and leukemia. No increase in cancer risk could be attributed to living near the facilities overall. The authors note, however, that misleading elevations in cancer risks would have been suggested if the non-applicable mailing addresses had not been excluded. [Boice Jr., J. D., *et al.* "Cancer Incidence in Municipalities Near Two Former Nuclear Materials Processing Facilities in Pennsylvania." *Health Physics*. Vol. 85, No. 6: pp. 678-690. 2003a]

Boice et al. (2003b) studied cancer mortality rates during the period 1950–1995 in Armstrong and Westmoreland Counties of western Pennsylvania for the Apollo and Parks former uranium and plutonium nuclear fuel processing facilities. Each of the two study counties was matched for comparison to three control counties in the same region on the basis of age, race, urbanization, and socioeconomic factors available from the 1990 U.S. Census. There were no significant mortality increases in the study counties for any cancer or for all cancers combined when comparisons were made with either the U.S. population or the control counties. Estimated relative risks of cancer mortality (the ratio of the standard mortality ratio [SMR] in the study counties with the SMR in the control counties) before facility operation (1950–1964), during operations (1965–1980), and after facility closure (1980–1995) were similar. For childhood leukemia mortality, the estimated relative risks decreased successively before, during, and after plant start-up, although no relative risk was significantly different than 1.0. The authors note that "the study is limited by the correlational approach and the relatively large size of the geographic areas of the counties studied." [Boice Jr., J. D., *et al.* "Cancer Mortality in Counties Near Two Former Nuclear Materials Processing Facilities in Pennsylvania, 1950-1995." *Health Physics*. Vol. 85, No. 6: pp. 691-700. 2003b]

Boutou et al. (2002) conducted a geographical study for 1979 to 1998 in Nord Cotentin, France, to determine if an association was evident between population mixing as a result of worker influx for the construction of a nuclear power plant and a nuclear waste reprocessing unit and the incidence of childhood leukemia. The highest risk of leukemia in people less than 25 years of age was observed in rural communes (villages or towns) with high population mixing. Incidence rate ratios were significantly increased for study areas with higher population mixing. The effects of population mixing on acute lymphocytic leukemia were strongest among younger children one to six years. The authors' findings supported a possible infective basis for childhood leukemia. [Boutou, O., *et al.* "Population Mixing and Leukaemia in Young People Around the La Hague Nuclear Waste Reprocessing Plant." *British Journal of Cancer*. Vol. 87: pp. 740-745. 2002]

Brüske-Hohlfeld et al. (2001) determined the frequency of dicentric and ring chromosomes in lymphocytes of the peripheral blood in 42 children in Elbmarsch, Germany, located near the combined site of the Kernkraftwerk Krümmel nuclear power plant and the Forschungszentrum GKSS nuclear research facility, and 30 children in Plön, located more than 100 km from a nuclear facility. A leukemia cluster had been reported for Elbmarsch in 1990 and 1991. The chromosome changes in circulating human T-lymphocytes are a sensitive indicator of radiation damage. All of the children volunteered for the study, and there was no parental history of occupational radiation exposure. No significant difference in frequencies was observed. For a single exposure event from an accidental release of radionuclides in the mid 1980s, a dose of several hundred mSv would have been required to provide a significantly increased aberration yield in 1992. [Bruske-Hohlfeld, I., *et al.* "A Cluster of Childhood Leukaemias Near Two Neighbouring Nuclear Installations in Northern Germany: Prevalence of Chromosomal Aberrations in Peripheral Blood Lymphocytes." *International Journal of Radiation Biology*. Vol. 77, No. 1: pp. 111-116. 2001]

Busby and Cato (1997) found elevated observed/expected relative risks for leukemia mortality in children 14 years and younger from 1981 to 1996 in the Newbury area, England, near nuclear facilities compared with nearby county districts. The authors note that "…the districts with significantly higher relative risks are those that contain the outfalls for licensed releases of radioisotopes from the nuclear sites at the Atomic Energy Research Establishment, Harwell; the Atomic Weapons Establishment, Aldermaston; and the Royal Ordnance Factory, Burghfield." Environmental concentrations of plutonium-239 and -240 in the area are reported to be 10 times the highest levels that would be expected from weapons testing fallout. The authors express concern that risk factors developed from the studies of Hiroshima, which are of short-term, high-dose external exposure, might not be appropriate when applied to long-term, low-dose internal exposure. [Busby, C. and M. S. Cato. "Death Rates from Leukaemia Are Higher than Expected in Areas Around Nuclear Sites in Berkshire and Oxfordshire [Letter to Editor]." *BMJ*. Vol. 315: p. 309. 1997]

Cardis et al. (2005) conducted a population-based case-control study of thyroid cancer in Belarus and the Russian Federation to evaluate the risk of thyroid cancer after childhood exposure to radioactive iodine and the environmental and host factors that might modify that risk. Two hundred seventy-six children with thyroid cancer diagnosed from 1992 through 1998 were matched to 1,300 control subjects, all less than 15 years of age at the time of the Chernobyl accident. Individual radiation doses were estimated as was the subjects' likely stable iodine status at the time of the accident. The authors observed a strong dose-response relationship between radiation dose to the thyroid received in childhood and thyroid cancer risk. The risk was three times higher in iodine-deficient areas than elsewhere; the risk was reduced by the consumption of potassium iodide. [Cardis, E., *et al.* "Risk of Thyroid Cancer After Exposure to ^{131}I in Childhood." *Journal of the National Cancer Institute*. Vol. 97, No. 10: pp. 724-732. 2005]

Cartwright et al. (2001) conducted a mortality study within the Whitehaven, UK, registration district for 1906–1970 to investigate when Seascale childhood and young persons' excess cancer cases originated and how they might be correlated in time with known industrial (including nuclear) and population changes in the area. Death records were abstracted for deaths categorized as from leukemias, lymphomas, other cancers, and all other causes in persons aged 0–14 (childhood), 0–24 (young persons), and 25–84 years. The number of deaths, death rates, and standardized mortality ratios were calculated. The authors found no cancer deaths in persons aged 0–24 years in the Gosforth civil parish during 1906–1970, six cancer deaths in persons aged 0–24 years (all occurring within 0–14 years) in the Seascale civil parish beginning in 1954, and no unremarkable cancer deaths in persons aged 25–84 years when compared with national data for 1906–1970. The authors found no clear temporal associations of the case excesses with either periods of significant nuclear activity on the Sellafield site or with the main periods of population growth in the area. [Cartwright, R. A., *et al.* "The Onset of the Excess of Childhood Cancer in Seascale, Cumbria." *Journal of Public Health Medicine*. Vol. 23, No. 4: pp. 314-322. 2001]

The Committee on Medical Aspects of Radiation in the Environment (COMARE) (2006) examined the spatial and space-time distribution of childhood leukemia and other childhood cancers in Great Britain for the period 1969–1993 to identify any characteristic patterns of occurrence for these cancers and any relation to socio-demographic factors. Results indicated that, at the geographical levels of country, county, county district and electoral ward, each cancer type showed variation in rates, which are thought not to be random. The nonrandom distribution was seen at very local levels or within short time periods (under five years) and very close (under 5 km), but the causes are unknown. Many childhood cancer rates, including but not limited to leukemia, were slightly higher in affluent areas. The non-leukemia childhood cancers had not been linked to population mixing, infectious agents, or immune incompetence as leukemia appeared to be. There appeared to be some weak acute lymphoblastic leukemia (ALL) spatial clustering, but the average number of cases was too low for a strong indication. Space-time clustering (cases occurring within a few years and a few kilometers of each other) also was evident for ALL and some other solid childhood cancers. Additional confirmation was needed for non-leukemia tumors. There was no evidence for unusual clustering of childhood cancer cases in populations living near nuclear power plants in Great Britain. For clusters identified near nuclear installations, there was no consistency regarding the type of nuclear facility, the time span involved, or the nature of the excess cases involved. The committee cautioned about the potential for spurious positive levels of association because of multiple statistical testing. The results of this study were consistent with a rare and unusual response to an infective process (including immature immune competence) during one of multiple steps in the development of childhood cancer. Further research is needed to address this possibility. The committee recommended additional, specific study areas and update and validation of the database of the National Registry of Childhood Tumours for use in these studies. [Committee on Medical Aspects of Radiation in the Environment (COMARE). "The Distribution of Childhood Leukaemia and Other Childhood Cancers in Great Britian 1969-1993. Eleventh Report." London: Health Protection Agency for the Committee on Medical Aspects of Radiation in the Environment. 2006]

The Committee on Medical Aspects of Radiation in the Environment (COMARE) (2005) reviewed earlier evidence and presented new data with regard to childhood cancers around nuclear installations in Great Britain. The committee focused on the results of a series of updated analyses concerning the incidence of childhood cancers in the vicinity of nuclear sites in England, Wales, and Scotland. Results confirmed excess childhood cancer in the village of Seascale near Sellafield, in Thurso near Dounreay, and near Aldermaston, Burghfield, and Harwell, and there was a trend in risk with distance from the Rosyth plant for childhood leukemia and non-Hodgkin's lymphoma. However, the authors noted the anomalies between some of the studies, such as the longevity of the excess in Seascale and apparently transient nature of the Thurso excess. Doses to the general public around Aldermaston, Burghfield, and Harwell would have been lower from the nuclear sites than from the local coal-fired power station at Didcot. The committee found no evidence of excess within any local 25 km area of a nuclear power site. The committee recommended more general studies of variations in incidence and clustering of cancers in Britain as a whole and further investigation for the Rosyth site. [Committee on Medical Aspects of Radiation in the Environment (COMARE). "The Incidence of Childhood Cancer Around Nuclear Installations in Great Britain. Tenth Report." London: Health Protection Agency for the Committee on Medical Aspects of Radiation in the Environment. 2005]

The Commission on Radiological Protection (SSK) (2008) assessed the reported results of the epidemiological study on childhood cancer in the vicinity of nuclear power plants (KiKK Study) (Kaatsch et al. 2008; Spix et al. 2008) to answer the question of whether the radiation emitted by nuclear power plants could be responsible for the positive correlation that the KiKK Study found between the proximity of a child's residence to the nearest German power plant at the time of diagnosis and the child's risk of contracting cancer (or leukemia) before the fifth birthday. The SSK appointed a working group of experts in epidemiology, radioecology, and children's radiology to conduct the assessment. The SSK concluded that, while it could not determine the cause of the results reported in the KiKK Study, it was able to rule out certain causes. Of particular importance, the SSK concluded that no conclusions regarding ionizing radiation dose could be drawn from the residential distance to the plant; the doses attributable to the nuclear power plants were orders of magnitude lower than those that would have been received from natural background and medical sources, orders of magnitude less than even the variability of the natural background and medical sources, and themselves varied by orders of magnitude from plant site to plant site and over time at the individual plants. In addition, the SKK found that radiobiological findings indicate that a causal role for ionizing radiation does not provide a plausible explanation for the KiKK Study's results with regard to children; the nuclear power plant doses would be too low to generate observable results of the magnitude seen by the KiKK Study. Regarding causality of radioactive emissions from the plants, only the Bradford Hill criterion of "timeliness" returned a positive result, and that result was borderline positive. Regarding causality of residential proximity, the Bradford Hill criteria returned either positive or no results for all except "biological plausibility," "experiments/animal testing," and "lack of plausible alternative explanations." [Commission on Radiological Protection (SSK). "Assessment of the Epidemiological Study on Childhood Cancer in the Vicinity of Nuclear Power Plants (KiKK Study): Statement of the Commission on Radiological Protection (SSK)." In: *Reports of the Commission on Radiological Protection, Issue 57*. Berlin: H. Hoffmann Fachverlag. 2008]

Davis et al. (2004) conducted a population-based case-control study to determine if exposure to radiation from the Chernobyl Power Station accident is associated with an increased risk of thyroid cancer in children and adolescents aged 0–19 years at the time of the accident who resided in the more highly contaminated areas of Bryansk Oblast in the Russian Federation. Twenty-six cases were diagnosed with thyroid cancer before 1 October 1997; two matched controls per case were identified from the Russian State Medical Dosimetrical Registry. Individual radiation doses to the thyroid were estimated using a semiempirical model and data collected primarily from the participants' mothers. The authors observed a statistically significant increased risk with dose at the highest dose range quartile level with increasing (but not statistically so) risk with dose for the second and third dose range quartiles. [Davis, S., *et al.* "Risk of Thyroid Cancer in the Bryansk Oblast of the Russian Federation After the Chernobyl Power Station Accident." *Radiation Research*. Vol. 162: pp. 241-248. 2004]

Dickinson and Parker (1999) developed a statistical model to predict the number of cases of childhood (less than 15 years at diagnosis) leukemia and non-Hodgkin's lymphoma (NHL) in children born 1950–1989 in the Seascale village near the Sellafield nuclear facility and diagnosed anywhere in the UK before 1993. The model is based on Poisson regression of cancer and NHL incidence in relation to population mixing among all children born 1969–1989 to mothers living in Cumbria, northwest England, excluding the Seascale ward. After allowing for age, the incidence of acute lymphoblastic leukemia (ALL) and NHL was significantly higher among children born in areas with the highest levels of population mixing and was highest among children of newcomers. The authors concluded that "population mixing is a significant risk factor for ALL/NHL, especially in young children, accounting for over 50% of cases in Cumbria and most cases in Seascale." The magnitude of the association is much greater than reported in other studies, and the authors suggest that the reason might be the smaller areal units used (electoral wards, rather than larger areas such as counties), studying the area of residence at birth, not diagnosis, using individual records for accurate populations counts, rather than interpolation, and using characteristics of the parents, rather than the area, to reflect population mixing. [Dickinson, H. O. and L. Parker. "Quantifying the Effect of Population Mixing on Childhood Leukaemia Risk: The Seascale Cluster." *British Journal of Cancer*. Vol. 81, No. 1: pp. 144-151. 1999]

Doll (1999) summarizes the identification and related studies of the Seascale cluster prior to 1999 and highlights the importance of the quantitative, predictive model developed by Dickinson and Parker (1999) and its apparent corroboration of the Kinlen (1997) hypothesis of the effect of population mixing on childhood lymphatic leukemia. [Doll, R. "The Seascale Cluster: A Probable Explanation." *British Journal of Cancer*. Vol. 81, No. 1: pp. 3-5. 1999]

Draper et al. (1993) tested the findings of the 1984 Advisory Group report (Black 1984) by using more comprehensive data sets and analyses that had become available. The authors calculated cancer incidence by using data from population-based cancer registries and special surveys to determine whether there was an observable excess among those aged 0–24 years in the Seascale ward of the Copeland district compared with the incidence in the two Cumbria county districts (Allerdale and Copeland but excluding Seascale) closest to the Sellafield nuclear facility and in Cumbria county (excluding Allerdale and Copeland) for the years 1984–1990, following the publication of the Black (1984) report. Draper et al. (1993) confirmed an increased incidence of cancer, especially leukemia, in young people during the period 1963 through 1993, as well as an increase in the incidence of cancer, but not of leukemia, during the years 1984–1990. [Draper, G. J., *et al.* "Cancer in Cumbria and in the Vicinity of the Sellafield Nuclear Installation, 1963-90." *BMJ*. Vol. 306: pp. 89-94. 1993]

Evard et al. (2006) performed an epidemiologic study of the incidence of childhood leukemia for the period 1990–2001 around French nuclear installations by using geographic zoning based on estimated doses to the red bone marrow from airborne radioactive releases. The authors studied residential areas ("communes") located in 40 km squares centered on 23 installations, including 18 nuclear power plant sites. Red bone marrow doses were estimated based on modeling of atmospheric dispersion and deposition of reported airborne emissions, uptake and contamination of foodstuffs, and the dose pathways of inhalation, ingestion, and external exposure from air and water plumes and ground and sediment deposition. The study found no evidence of an increased incidence of childhood leukemia around the nuclear sites. [Evard, A.-S., *et al.* "Childhood Leukaemia Incidence Around French Nuclear Installations Using Geographic Zoning Based on Gaseous Discharge Dose Estimates." *British Journal of Cancer*. Vol. 94, No. 9: pp. 1342-1347. 2006]

Fairlie (2008) cites study results in the United States and Europe indicating an observed increase in childhood cancer with proximity to nuclear power plants. The author notes that the recent German studies, in particular Kaatsch et al. (2008), found higher incidences of cancers and a stronger association with nuclear installations than all previous reports. Fairlie (2008) indicates that these studies ruled out coincidence, an infectious agent, and radioactive discharges from the nuclear installations as causes. Postulating a possible causal link to tritium emissions of pressurized water reactors, the author advocates consideration of recommendations to populations near nuclear facilities to reduce exposures and of rethinking decisions to build more reactors. [Fairlie, I. "Comment: Let's Take Cancer Clusters Seriously This Time." *New Scientist*. No. 2653: pp. 18. 26 April 2008]

Gardner et al. (1990a) conducted a case-control study to examine whether the observed excess of childhood (0–14 years) leukemia and lymphoma near the Sellafield nuclear plant is associated with established risk factors or with factors related to the plant. Factors examined included antenatal abdominal x-ray examinations, viral infections, habit factors, and proximity to and employment characteristics of parents at Sellafield. The authors reported in this methods and data paper that overall the collected data were sufficiently reliable for detailed analysis and careful interpretation. [Gardner, M. J., *et al.* "Methods and Basic Data of Case-Control Study of Leukaemia and Lymphoma Among Young People Near Sellafield Nuclear Plant in West Cumbria." *British Medical Journal*. Vol. 300: pp. 429–434. 1990a]

Gardner et al. (1990b) conducted a case-control study to examine whether the observed excess of childhood (0–14 years) leukemia and lymphoma near the Sellafield nuclear plant is associated with established risk factors or with factors related to the plant. Factors examined included antenatal abdominal x-ray examinations, viral infections, habit factors, and proximity to and employment characteristics of parents at Sellafield. The authors concluded that "the raised incidence of leukaemia, particularly, and non-Hodgkin's lymphoma among children near Sellafield was associated with paternal employment and recorded external dose of whole body penetrating radiation during work at the plant before conception. The association can explain statistically the observed geographical excess [also observed for Seascale children living near the plant at conception]. This result suggests an effect of ionizing radiation on fathers that may be leukaemogenic in their offspring, though other, less likely, explanations are possible."

[Gardner, M. J., *et al.* “Results of Case-Control Study of Leukaemia and Lymphoma Among Young People Near Sellafield Nuclear Plant in West Cumbria.” *British Medical Journal*. Vol. 300: pp. 423-429. 1990b]

Goldsmith (1992) examined incidence and mortality rates in the UK for the period 1971–1980 for observed childhood (0–9 years) leukemia or other cancers versus an expected rate based on regional data and an expected rate based on comparison areas for nuclear power plants, other nuclear installations, and coastal areas postulated to have been impacted by the Sellafield facility. There was no evidence of any excess leukemia or other cancer risk (incidence or mortality) in the vicinity of the nuclear power plants, individually or combined, nor in the coastal communities. There was considerable evidence of excess leukemia incidence (but not mortality nor incidence or mortality for other cancers) in the vicinity of the non-power nuclear installations (most of which were constructed before 1955), which included nuclear research, nuclear fuel production, nuclear weapons manufacture, and radionuclide reagent manufacture and marketing. [Goldsmith J. R. “Nuclear Installations and Childhood Cancer in the UK: Mortality and Incidence for 0-9-Year-Old Children 1971-1980.” *The Science of the Total Environment*. Vol. 127: pp. 13-35. 1992]

Grosche et al. (1999) tested the hypothesis that, if the increased number of childhood leukemia cases observed around the Krümmel nuclear power plant in Germany was induced by tritium releases, an increase should be detected around other facilities that release substantial quantities of tritium. The authors compared tritium releases and childhood leukemia incidence rates at the DOE Savannah River Site (SRS) with those at the Krümmel plant for the period 1991 to 1995. The incidence rates of childhood leukemia near SRS was less, but not significantly so, than expected; the incidence rates near the Krümmel site were significantly higher than expected. However, tritium releases from SRS exceeded those from the Krümmel site by several orders of magnitude, suggesting that environmental tritium is not associated with the Krümmel site increase. The authors point out limitations to the study, including but not limited to dissimilarities in population densities, distributions, and demographics; study area sizes; and predominant exposure pathways. There is no attempt to estimate exposures to the study populations; only tritium air and water releases are given. The differences in population distribution relative to the sites existed for other comparison studies between nuclear sites in the US and Europe. [Grosche B., *et al.* “Leukaemia in the Vicinity of Two Tritium-Releasing Nuclear Facilities: A Comparison of the Kruemmel Site, Germany, and the Savannah River Site, South Carolina, USA.” *Journal of Radiological Protection*. Vol. 19, No. 3: pp. 243-252. 1999]

Guizard et al. (2001) conducted a geographical study of leukemia incidence among those diagnosed with leukemia from 1978 to 1998 at ages less than 25 years and residing at the time of diagnosis within three zones defined by their distance (0–10 km, 10–20 km, and 20–35 km) from the La Hague nuclear waste reprocessing plant in France. Cases from 1978 to 1993 were identified by a retrospective survey of doctors practicing in the study area at some time during the period, local hospital files, and death certificate data. Cases for the period from 1994 to 1998 were identified from data of the La Manche cancer register. Data for Alderney, a UK channel island about 15 km from the plant, were collected from the two general practitioners on the island. Available blood and/or bone marrow samples were examined by the authors to confirm diagnosis. For the entire study area, cases of childhood leukemia observed were consistent with those expected. With regard to the individual zones, the highest standardized incidence ratio was observed in the 0–10 km zone among children in the five- to nine-year age group and diagnosed with acute lymphoblastic leukemia. No cases within the study period were observed on Alderney. The authors cautioned that, because of prior partial analysis of the data increasing the risk of erroneously concluding that there is an excess, the calculated confidence limits cannot be used as an indicator of statistical significance. [Guizard, A.-V., *et al.* "The Incidence of Childhood Leukaemia Around the La Hague Nuclear Waste Reprocessing Plant (France): A Survey for the Years 1978-1998." *Journal of Epidemiology and Community Health*. Vol. 55: pp. 469-474. 2001]

Hatch and Susser (1990) examined rates of cancer in children in relation to outdoor background gamma-ray exposure for 69 small geographical subunits within 10 miles of the U.S. Three Mile Island nuclear power plant. The gamma-ray exposure rates were available from a 1976 aerial survey. Incident cases of cancer for the period 1 January 1975 through 31 December 1985 were obtained through review of patient charts at all 19 hospitals within 30 miles of Three Mile Island. The authors also reviewed the records of six referral hospitals in the nearby cities of Philadelphia, Pittsburgh, and Baltimore. Cancer mortality was identified from review of the state of Pennsylvania death certificates. The authors observed significant elevated odds ratios for incidence of all cancers comparing highest with lowest quartile exposure levels for children less than 15 years at diagnosis, with the highest ratio for those aged 10–14 years. A nonsignificant association with background gamma exposures was seen for mortality from all cancers. The association between exposure to outdoor background gamma radiation and childhood cancer would not be expected on the basis of current radiobiology. The authors noted that the magnitude of the increase seen for portions of the study area at annual background gamma exposures of 1 mGy (odds ratio = 2.4) compares with a risk of childhood cancer from prenatal x-ray exposures of 10 mGy or more. [Hatch, M. and M. Susser. "Background Gamma Radiation and Childhood Cancers Within Ten Miles of a U.S. Nuclear Plant." *International Journal of Epidemiology*. Vol. 19, No. 3: pp. 546-552. 1990]

Hatch et al. (1990) conducted an ecologic study of cancer, particularly leukemia and childhood malignancies, among the 159,684 residents living within a 10-mile (16-kilometer) radius of the Three Mile Island nuclear plant for the period 1975–1985. Cancer incidence was evaluated relative to the pattern of radiation dose from estimated airborne radioactivity releases from the 28 March 1979 plant accident and from routine operations, as modeled by using a Gaussian dispersion model modified to account for terrain and wind shifts. For both accident and routine emissions, the authors observed an elevated, but not statistically significant, incidence for childhood leukemia and a significantly elevated incidence for non-Hodgkin's lymphoma. The latter trended with estimated exposure for routine emissions from 1979–1985 and for accident emissions from 1984–1985. The authors noted that for non-Hodgkin's lymphoma no such association was seen with background gamma radiation (also assessed), and non-Hodgkin's lymphoma is thought to not be a radiosensitive cancer. For both accident and routine emissions, lung cancer was also found to show an elevation trending with exposure, although the elevation was not significant for accident emissions when adjustment was made for background gamma radiation. It was noted that lung cancer has a latency period longer than the period since the site accident. The authors concluded that, "[o]verall, the pattern of results does not provide convincing evidence that radiation releases from the [TMI] facility influenced cancer risk during the limited period of follow-up." [Hatch, M. C., *et al.* "Cancer Near the Three Mile Island Nuclear Plant: Radiation Emissions." *American Journal of Epidemiology*. Vol. 132, No. 3: pp. 397-412; discussion: pp. 413-417. 1990]

Hattchouel et al. (1996) studied leukemia and solid tumor mortality between 1968 and 1989 in the population living in 503 administrative units ("communes") within 16 km of 13 nuclear reprocessing and power installations in France for the age groups 0 to 24 and 25 to 64 years. Observed cancer mortality rates were compared with expected rates based on national rates. The study showed no excess mortality in the population aged 0–64 years residing near the French nuclear sites and no excess mortality in the population aged 0 to 24 years at the 95% level of significance. For males, the number of leukemia deaths among those under age 25 years was significantly lower than expected; the total number of cancers in the 25–64 age group was higher than expected but with borderline significance. For females, the number of observed lung and pleura and breast cancers for both age groups separately and for the age groups combined were significantly less than expected. The authors note that there was no control in the study for confounders, such as smoking habits, and the follow-up time from beginning of operation of the sites varied between 5 and 22 years, possibly insufficient for full expression of long-term effects. [Hattchouel, J.-M., A. Laplanche, and C. Hill. "Cancer Mortality Around French Nuclear Sites." *Annals of Epidemiology*. Vol. 6: pp. 126-129. 1996]

Hattchouel et al. (1995) extended a previous study (Hill and Laplanche 1990) to examine leukemia mortality in the population under the age of 25 years residing near the 13 main French nuclear sites operating in 1985. The authors identified 503 exposed communes in four geographical zones around the sites (0–5 km, 5–10 km, 10–13 km, and 13–16 km from the sites). Observed (O) mortality was compared with the expected (E) mortality on the basis of national rates and standardized mortality ratios (100 × O/E) were calculated. No excess of leukemia mortality was observed in the population aged 0–24 residing around French nuclear sites between 1968 and 1989. Results were similar when leukemia and non-Hodgkin's lymphoma deaths were considered together. Two of the 13 standardized mortality ratios were significantly lower than expected. After correcting for multiple testing, no effect was observed of sex and age, no difference was seen between reprocessing plants and reactors, and there was no linear trend with increasing distance from the site. [Hattchouel, J.-M., A. Laplanche, and C. Hill. "Leukaemia Mortality Around French Nuclear Sites." *British Journal of Cancer*. Vol. 71: pp. 651-653. 1995]

Hill and Laplanche (1990) compared observed mortality in the population aged 0–24 years between 1968 and 1987 in zones of French communes at distances of <5 km, 5–10 km, 10–13 km, and 13–16 km (and for the La Hague site, 16–21 km) from nuclear power and reprocessing plants in operation during 1975 or before with mortality expected based on national rates. A second comparison was made with control communes in the same "Département" having the closest total population figure. The number of leukemia deaths in the exposed population was slightly less than that expected from national mortality statistics. A statistically significant (for both $p = 0.02$, two-sided test) excess of Hodgkin's disease and a deficit of malignant brain tumors were observed for the study populations. Following correction for multiple tests due to consideration of several causes of death, these results were not significant. No significant differences were observed when comparing the standardized mortality ratios in the exposed and control areas. There was no observed effect of sex, age, or type of plant (reprocessing or other) and no trend with increasing distance from installation. There was no observed excess in leukemia mortality for those aged 0–24 years residing near French nuclear sites. The results confirmed the Viel and Richardson (1990) study of leukemia mortality around La Hague, which used geographical units seven times larger than the Hill and Laplanche (1990) study. [Hill, C. and A. Laplanche. “Overall Mortality and Cancer Mortality Around French Nuclear Sites.” *Nature*. Vol. 347: pp. 755-757. 1990]

Hjalmars (1996) conducted a population-based investigation of clusters of acute childhood leukemia in Sweden using combined cases from 1973-93. A spatial span statistics assuming Poisson distributed cases and calculated from parish (I.e., county) centroids and an *a prior* 10% population border for the circles did not uncover any significant clusters. Individual address would have been required for analysis of disease clusters related to local risk factors such as electric power lines or background radiation. [Hjalmars, U. “Childhood Leukaemia in Sweden: Using GIS and a Spatial Span Statistic for Cluster Detection.” *Statistics in Medicine.* Vol. 15, pp. 707-715. 1996.]

Hoffmann et al. (2007) identified all incidents of childhood (<15 years at diagnosis) leukemia during the period 1990-2005 within a 5 km radius of the Krümmel nuclear power plant, located near an adjacent nuclear research facility and on the Elbe River southeast of Hamburg, Germany. Standardized incidence ratios (SIRs) were calculated for comparison by using county (for 1990–1998) and national (1990–2005) leukemia incidence rates as referents. Analyses were stratified by calendar period and attained age and by subdividing the study region by areas north and south of the bordering Elbe River. The authors found the incidence in the study area to be significantly higher than for the comparison counties and for Germany as a whole, with elevated rates that have persisted in the study area for over 15 years. The highest SIRs were observed for children zero to four years (SIR = 4.9; 95% confidence interval: 2.4–9.0) and for residents south of the Elbe (SIR = 7.5; 95% confidence interval: 2.8–16.4), when comparisons were made with national data. [Hoffmann, W., C. Terschueren, and D. B. Richardson. “Childhood Leukemia in the Vicinity of the Geesthacht Nuclear Establishments Near Hamburg, Germany.” *Environmental Health Perspectives*. Vol. 115, No. 6: pp. 947-952. 2007]

Hoffmann et al. (1997) examined data regarding six cases of childhood leukemia diagnosed between February 1990 and December 1995 among residents of the small rural community of Elbmarsch in Northern Germany. Five of the cases were diagnosed in the 16-month period between February 1990 and May 1991. All lived within 4,500 m of the Krümmel nuclear boiling water reactor, which is itself adjacent to the nuclear research institute Gesellschaft für Kernenergieverwertung in Schiffbau and Schiffahrt. The authors calculated childhood (less than 15 years) leukemia standardized incidence ratios and 95% confidence intervals (CIs) for the periods 1990–1995 and 1990–1991 for a 5 km radius area around the nuclear plant. For the period 1990–1995, the standardized incidence ratio (SIR) for the region was 460 (95% CI: 210–1,030); for the period 1990–1991, the SIR was 1,180 (95% CI: 490–2,830). No established or putative risk factors could be identified to explain the cluster of childhood leukemia cases in follow-up studies commissioned by governments of the two adjacent federal states. The authors noted that, since submission of their manuscript, three additional childhood leukemia cases were identified in the study region: two diagnosed in 1995 and 1996 and the third diagnosed in 1994 that missed in the original data assessment. [Hoffmann, W., *et al.* "A Cluster of Childhood Leukemia Near a Nuclear Reactor in Northern Germany." *Archives of Environmental Health*. Vol. 52, No. 4: pp. 275-280. July-August 1997]

The Illinois Department of Public Health (2000) tested the hypothesis that infants and children living near seven nuclear power plants in Illinois have worse health outcomes than those living elsewhere. Study counties with nuclear facilities and comparison counties without were matched for population density, proportion of children ages 0 to 19 years, racial composition, and, after these initial criteria were met and to the extent feasible, geographic distance from any facility counties. For the eight years examined (1990–1997), the evaluation failed to find significant cancer incidence rate differences among facility and comparison counties for age groupings of 0–19 years and 0–4 years. In addition, no dose-response effect could be detected when comparing counties with nuclear facilities in operation for long and short periods of time. [Illinois Department of Public Health. "Pediatric Cancer Incidence and Proximity to Nuclear Facilities in Illinois." In: Health and Hazardous Substances Registry Newsletter (Illinois Department of Public Health). Fall 2000. <www.idph.state.il.us/cancer/pdf/article.pdf > (04 November 2008)]

Iwasaki et al. (1995) examined the standardized mortality ratios (SMRs) and relative risks for five malignant neoplasms for two age groups (0–14 years and all ages) during four different periods (1973–1977, 1978–1982, 1983–1987, and 1973–1987) in 18 site municipalities and four matched control municipalities selected for the 44 nuclear power station sites in Japan at the beginning of 1993. Reactor types included gas-cooled reactors, pressurized water reactors, and boiling water reactors. The five malignant neoplasms studied were leukemia, malignant lymphoma, non-Hodgkin's lymphoma, multiple myeloma, and acute non-lymphatic leukemia. These neoplasms were chosen due to their short latency from exposure to appearance (especially leukemia) and a previous finding of an increase in childhood leukemia near nuclear facilities in Britain. The study showed higher or lower SMRs for certain malignant neoplasms at some nuclear sites and their control groups, either before or after the facilities came into operation. The SMRs for malignant neoplasms in the municipalities of some nuclear facilities was only slightly greater than what would have been expected based on the control groups. For some control groups, it was found that the SMRs were substantially higher than expected. The numbers of leukemia cases in the 0–14 age group were small, and for both age groups the authors could determine no discernable pattern of significant excess risk associated with the reactor sites. It was concluded that leukemia and lymphoma mortality in the Japanese municipalities containing nuclear power stations was not significantly different from SMRs of the control areas. [Iwasaki , T., *et al.* "Leukaemia and Lymphoma Mortality in the Vicinity of Nuclear Power Stations in Japan, 1973-1987." *Journal of Radiological Protection*. Vol. 15, No. 4: pp. 271-288. 1995]

Jacob et al. (1999) utilized two methods of risk analysis, Poisson regression and Monte Carlo calculations, in their study of thyroid doses during the period 1991–1995 due to ^{131}I release during the May 1986 Chernobyl accident. The thyroid dose due to ^{131}I releases was reconstructed for children and adolescents in two cities and 2,122 settlements in Belarus and in one city and 607 settlements in the Bryansk district of the Russian Federation, addressing the two high contamination spots in the two countries following the accident. Poisson regression was used for results for the single settlements and Monte Carlo calculations were used for results in the larger areas or subpopulations. Best estimates of both methods agreed well. The study calculated excess absolute risk per unit thyroid dose (EARPD) and excess relative risk per unit thyroid dose. No significant differences between countries or cities and rural areas were found. The EARPD for those born 1971–1985 (2.1 cases per 10^4 person-year Gy; 95% confidence interval: 1.0–4.5) was statistically elevated in all five dose groups (≤0.1, 0.1–0.5, 0.5–1.0, 1.0–2.0, >2.0), including the lowest, which had an average thyroid dose of 0.05 Gy. Average thyroid doses of small children were about a factor of 5 higher than average doses of adults. Dependencies of risks on age at exposure and on gender were consistent with findings after external exposures. [Jacob P., *et al.* "Childhood Exposure Due to the Chernobyl Accident and Thyroid Cancer Risk in Contaminated Areas of Belarus and Russia." *British Journal of Cancer*. Vol. 80, No. 9: pp. 1461-1469. 1999]

Kaatsch et al. (2008) reported on a childhood (less than five years at diagnosis) leukemia incidence subset of the Spix et al. (2008) case-control study of childhood cancer in children living near German nuclear power plants between 1980 and 2003. In the subset, 593 cases of children diagnosed with leukemia between 1980 and 2003 were each matched to three controls (1,766 total) from the corresponding registrar's office on the basis of age, sex, and nuclear power plant area at the date of diagnosis. Proximity of residence to the nearest nuclear power plant at the time of diagnosis was determined for each subject with a precision of about 25 m. Kaatsch et al. (2008) concluded that "cases live closer to nuclear power plants than the randomly selected controls." A significant trend for 1/distance was seen for all leukemia at the 95% level of significance. A categorical analysis showed a statistically significant odds ratio of 2.19 (lower 95% confidence limit: 1.51) for residential proximity within 5 km compared to residence outside this area. This result is largely attributed to cases in the previous studies of the German Childhood Cancer Registry (particularly in the inner 0–5 km zone), as there is some overlap between the studies. The strength of the current study is the availability of individual measurements of residential proximity to nuclear power plants, and, whereas the previous studies were based on incidence rates only, this study provides a case-control approach. This study confirmed the previous German findings regarding leukemia in the 5 km zone of nuclear power plants. Regarding the study period not covered in the previous studies (basically independent data), a tendency toward an increased risk with closer residential proximity also was seen. No conclusions on the impact to study results of potential confounders could be drawn. The authors indicate that radiation dose from nuclear power plant emissions is a factor of 1,000–100,000 less than from natural and medical sources and that the observed positive trend with 1/distance could not be explained. [Kaatsch, P., *et al.* "Leukaemia in Young Children Living in the Vicinity of German Nuclear Power Plants." *International Journal of Cancer*, Vol. 1220: pp. 721-726. 2008]

Kaatsch et al. (1998) compared incidence rates of childhood (less than 15 years at diagnosis) cancer for children living within 15 km of German nuclear power plants between 1991 and 1995 to rates in control regions in order to evaluate and validate results from a previous exploratory study (Michaelis 1992) conducted with data from the German Childhood Cancer Registry for the 1980–1990 period. Evaluating the previously confirmatory results with the combined data from the two study periods showed that incidence rates were not increased for all malignancies or for acute leukemia in children younger than 15 years living near German nuclear installations. Children younger than five years with acute leukemia, living within a 5 km radius of a West German nuclear installation, showed only a nonsignificant tendency (relative risk, 1.39, 95% confidence interval: 0.69–2.57), dominated by cases observed near the Krümmel nuclear power plant. [Kaatsch, P., *et al.* “An Extended Study on Childhood Malignancies in the Vicinity of German Nuclear Power Plants.” *Cancer Causes and Control*, Vol. 9: pp. 529-533. 1998]

Kinlen (1997) responded to a commentary by H. Inskip in a previous issue of *The Lancet* (Inskip 1997) regarding childhood leukemia near nuclear sites in the UK. Kinlen says Inskip could have taken further the question of an infective etiology. It was the high rate of childhood leukemia at these sites (Sellafield and Dounreay) that led to the population mixing (infective) hypothesis that the bringing together of rural and urban groups, or different socioeconomic groups, can increase the frequency of childhood leukemia through increased contact between susceptible and infected individuals. The population mixing hypothesis has been supported by 11 studies in the UK, Greece, and Hong Kong, explaining more than 200 excess cases of childhood leukemia. Kinlen states that Inskip referred to Seascale in a restrictive way, only in relation to Sellafield, although Seascale is the southwest segment of the Sellafield immediate vicinity, resulting in bias. The whole of the immediate vicinity of Sellafield should also be studied. When this was done, the excess was similar to that reported in other studies of rural population mixing that included small areas with an incidence of childhood leukemia similar to that in Seascale. [Kinlen, L. J. “Infection and Childhood Luekaemia Near Nuclear Sites.” *The Lancet*. Vol. 349: p. 1702. 1997]

Kinlen and Balkwill (2001) explored evidence for an association between childhood leukemia and an infective cause through comparisons of childhood leukemia mortality in wartime and postwar cohorts of the Orkney and Shetland islands’ children, aged 0–14 years. During wartime, local residents were outnumbered by the servicemen stationed there to guard against an invasion from Norway after its occupation by Germany in 1940. Childhood leukemia mortality increased by a factor of 3.6 (P = 0.001) in the wartime cohort but not in the postwar cohort compared with national Scottish rates. Of the nine deaths observed (compared with 2.5 expected), five of the cancers were described as lymphatic, two as monocytic, and two as leukemia of unspecified type; only three occurred in the childhood leukemia peak ages of two to six years. All deaths were of local children. [Kinlen, L. J. and A. Balkwill. “Infective Cause of Childhood Leukaemia and Wartime Population Mixing in Orkney and Shetland, UK.” *The Lancet*. Vol. 357: pp. 858. 2001]

Kinlen and Tiplady (2002) responded by letter to the Cartwright et al. (2001) paper with factual corrections to the paper’s data and with continued support for an infective cause resulting from population mixing as the most likely explanation for the cluster of leukemia and lymphomas in

Seascale. [Kinlen, L. J. and P. Tiplady. “The ‘Seascale Cluster’.” *Journal of Public Health Medicine*. Vol. 24, No. 4: pp. 342-343. 2002]

Kinlen et al. (1993) studied examples of population mixing in rural Scotland produced by the North Sea oil industry to determine if it was associated with any excess of childhood leukemia and non-Hodgkin’s lymphoma. The authors concentrated on the three largest groups of workers in the oil industry in northern Scotland in the late 1970s. Home addresses of the 17,160 Scottish residents were postcoded, integrated with census data, and classified as urban or rural. The incidence of leukemia and non-Hodgkin’s lymphoma in young people below age 25 was examined in the rural and urban categories for the periods 1974–1978, 1979–1983, and 1984–1988. A significant excess of leukemia and non-Hodgkin’s lymphoma was found for 1979–1983 in the group of rural home areas with the largest proportion of oil workers, following closely on large increases in the workforce. The area near the Dounreay nuclear installation, for which an excess of leukemia has been reported, was within the rural high oil worker category. The findings supported the infection hypothesis that population mixing can increase the incidence of childhood leukemia in rural areas and suggest that the Dounreay-Thurso area excess is due to population mixing, promoted by some unusual local demographic factors. [Kinlen, L. J., *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*. Vol. 306: pp. 743-748. 1993]

Laurier et al. (2008) presented additional results from a previously reported French study (White-Koning et al. 2004) in response to a recent German study (Kaatsch et al. 2008) that showed a significant excess risk of all leukemias and of acute lymphoblastic leukemia among children less than five years living within 5 km of one of the 16 nuclear power plants in western Germany during the period 1980–2003. The additional data of Laurier et al. (2008) from intermediate analyses performed at the time of the French study, but not included in the White-Koning et al. (2004) final publication, allow direct comparison with the results of the German study. The analyses addressed leukemia incidence among children aged 0–4 years living near 1 of the 19 nuclear power plants in France between 1990 and 1998. The results indicated neither excess risk in any of the defined 5 km distance zones (0–5, 5–10, 10–15, and 15–20 km) nor a decreasing trend of risk with increasing distance from the plants. The observed to expected ratio for leukemia cases below age five years and living within 5 km of a French nuclear power plant is 0.96 (95% confidence interval: 0.31–2.25). Laurier et al. (2008) note that the small number of cases result in wide confidence intervals for observed to expected ratios; however, the results can rule out an increased risk in young children living near French nuclear power plants that is greater than two. [Laurier, D., D. Hemon, and J. Clavel. “Childhood Leukaemia Incidence Below the Age of 5 Years Near French Nuclear Power Plants.” *Journal of Radiological Protection*. Vol. 28: pp. 401-403. 2008].

Laurier et al. (2002) reviewed studies that examined the risk of leukemia among young people near nuclear installations. An excess incidence of leukemia did exist near some nuclear installations, at least for the reprocessing plants at Sellafield and Dounreay and the nuclear power plant at Krümmel. However, excesses of leukemia had also been identified far away from any nuclear installations, and the results from multisite studies had invalidated the hypothesis of an increased risk of leukemia related to radioactive discharge. The authors stated that the hypothesis of an infectious etiology associated with population mixing needed further investigation. Response to a local excess of cancer cases should include recalling the current epidemiologic knowledge and using systematic recording of cases. Communication with the general population should include a variety of experts. [Laurier, D., B. Grosche, and P. Hall. “Risk of Childhood Leukaemia in the Vicinity of Nuclear Installations.” *Acta Oncologica*. Vol. 41, No. 1: pp. 14-24. 2002]

Laurier (2001) summarizes the literature regarding childhood leukemia and nuclear sites, concluding that “[c]luster studies show that an excess of childhood leukaemia exists near some nuclear sites (at least, for the reprocessing plants at Sellafield and Dounreay). Nonetheless, the results of the multi-site studies invalidate the hypothesis whereby the frequency of leukaemia generally increases among young people living near nuclear sites. Moreover, excesses of leukaemia have also been identified far from any nuclear site.” The author lists weaknesses of cluster studies in both the analytic methodology and the interpretation of results and recommendations made to help overcome them and discusses the hypotheses proposed regarding the cause of clusters. At the time of publication, the strongest association appeared to be with population mixing and an infectious agent. The author goes on to discuss in more detail the status of information regarding the Nord-Contentin in France and the La Hague cluster of leukemia cases. The author concluded that “the existence of an excess of leukaemia cases among young people in the vicinity of the La Hague reprocessing plant suggested in 1995 has not been confirmed. Follow-up of the incidence is still ongoing. … the inclusion of experts from environmental associations in the GRNC has been an important element in the construction of the credibility in the final results.” [Laurier, D. “Clusters of Leukaemia Among Young People Living Near Nuclear Sites, with a Focus on Studies Performed in the Nord-Cotentin (France).” In: *Low-Dose Ionizing Radiation and Cancer Risk. Radiation Protection 125*. Luxembourg: European Commission. 2001. pp. 39-60]

Laurier and Bard (1999) reviewed the studies that had been conducted in prior years regarding an excess risk of leukemia among young people living near nuclear sites. At the time of this literature review (1999), there were 13 years of accumulated results and the existence of an excess risk of leukemia among young people living near nuclear sites was still controversial. The authors discussed two types of studies, descriptive “cluster” studies and analytical studies (primarily case-control studies). The descriptive studies of the frequency of leukemia near nuclear sites showed that an excess of leukemia did exist near some nuclear sites (e.g., the reprocessing plants at Sellafield and Dounreay); however, the results of the multisite studies did not support the hypothesis. In addition, excesses of leukemia had been shown far from any nuclear site and around sites only considered for nuclear facilities, and studies of the geographic distribution of leukemia showed that incident cases tend toward spatial clustering. The analytical studies carried out to search for the causes of leukemia clusters did not uncover any definite risk factor but allowed the rejection of several hypotheses, in particular those related to paternal pre-conceptual exposure to radiation and to environmental exposure to ionizing radiation. The validity of the hypothesis of an infectious etiology had not been proven on an individual level. The authors advocated an honest, comprehensive, and clear response to public concern about cancer clusters near nuclear sites that includes facts about received doses and risk levels. Another recommendation was to implement systematic and rigorous surveillance of leukemia incident cases around nuclear sites through the use of registries. Finally, the authors advocate the development of research on individual sensitivity, exposure, or effect biomarkers that might provide more sensitive tools in the future and useful information for epidemiologic purposes. [Laurier, D. and D. Bard. "Epidemiologic Studies of Leukemia Among Persons Under 25 Years of Age Living Near Nuclear Sites." *Epidemiologic Reviews*." Vol. 21, No. 2: pp. 188-206. 1999]

Lopez-Abente et al. (2001) conducted a mortality study based on 12,245 cancer deaths from 1975 to 1993 in 283 towns located within a 30 km radius of Spain's four nuclear power plants and four nuclear fuel facilities. The nonexposed areas used were 275 towns lying within a 50 to 100 km radius of each installation, matched by population and socio-demographic characteristics. Relative risk (RR) for each area and trends in risk with increasing proximity to an installation were examined. The results revealed a pattern of solid tumor mortality in the vicinity of uranium cycle facilities, basically excess lung (RR: 1.37; 95% confidence interval: 1.02–1.25) and renal cancer mortality (RR: 1.37, 95% confidence interval: 1.07–1.76). No such pattern appeared in the vicinity of nuclear power plants. The authors recommend monitoring cancer incidence and mortality in areas surrounding nuclear fuel facilities and power plants, with more specific studies recommended for areas in which installations have been fully operational for longer periods. Future studies should use dosimetric information. [Lopez-Abente, G., N. Aragones, and M. Pollan. "Solid-Tumor Mortality in the Vicinity of Uranium Cycle Facilities and Nuclear Power Plants in Spain." *Environmental Health Perspectives*. Vol. 109, No. 7: pp. 721-729. 2001]

Lopez-Abente et al. (1999) studied mortality due to hematologic tumors in towns near Spain's seven nuclear power plants and five nuclear fuel facilities during the period 1975–1993. The study was based on 610 leukemia-, 198 lymphoma-, and 122 myeloma-induced deaths in 489 towns located within a 30 km radius of the installations. For control areas, they used 477 towns lying within a 50 to 100 km radius of each installation, matched by population size and several socio-demographic characteristics. Relative risk (RR) for each area and trends in risk with increasing proximity to an installation were analyzed by using log-linear models. None of the nuclear power plants registered an excess risk of leukemia-induced mortality in any of the surrounding areas. Excess risk of leukemia mortality was observed in the vicinity of the uranium processing facilities in Andujar (RR: 1.30; 95% confidence interval: 1.03–1.64) and Ciudad Rodrigo (RR: 1.68; 95% CI: 0.92–3.08). An excess risk of multiple myeloma mortality was found in the area surrounding the Zorita nuclear power plant. Statistical testing revealed that, with the exception of multiple myeloma, none of the tumors studied showed evidence of a rise in risk with proximity to the installation. The only area to register a high RR was Garona, but the excess risk failed to attain statistical significance. No study area yielded evidence of a raised risk of leukemia mortality among persons under the age of 25 years. The authors say more specific studies are called for in areas near installations that have been fully operational for longer periods. They stress the importance of using dosimetric information in all future studies. [Lopez-Abente, G., *et al.* "Leukemia, Lymphomas, and Myeloma Mortality in the Vicinity of Nuclear Power Plants and Nuclear Fuel Facilities in Spain." *Cancer Epidemiology, Biomarkers & Prevention*. Vol. 8: pp. 925-934. 1999]

Mangano et al. (2003) analyzed childhood (less than 10 years at time of diagnosis) cancer incidence and mortality during the years 1988 to 1997 for 49 counties located mostly or completely within 30 miles (48 km) of 24 nuclear reactors at 14 locations in the eastern U.S. Mangano reported a statistically significant excess incidence of all childhood cancers for counties near 3 of the 14 reactor locations and “borderline” significance for two more when compared with national rates estimated by using data from the U.S. Surveillance, Epidemiology and End Results (SEER) Program. Combined childhood cancer incidence for all 14 reactor counties was 12.4% above a comparison SEER-based incidence rate ($P < 0.00001$). The total excess incidence from comparing the counties near reactors with those in the rest of the state, or state combinations in the case of less populated states, was 5.0% ($P< 0.04$). The incidence of childhood leukemia in the 23 counties near five nuclear reactor sites in Pennsylvania “…exceeded the U.S. rate by 10.8%; the rate for the remainder of the state was 11.5% below the U.S. rate ([P] < 0.01). For all other cancers, virtually no difference was seen between nuclear and nonnuclear counties, even though both exceeded the national rate (by 2.6 and 3.2%, respectively).” Cancer mortality for children less than 10 years was higher, but not significantly so, than the U.S. rate in 7 of the 14 study areas. [Mangano, J. J., *et al.* “Elevated Childhood Cancer Incidence Proximate to U.S. Nuclear Power Plants.” *Archives of Environmental Health*. Vol. 58, No. 2: pp. 74-82. 2003]

McLaughlin et al. (1993) conducted an ecologic study to determine whether leukemia rates among children aged 0–14 years born to mothers residing in the vicinity of Ontario, Canada, nuclear facilities differed from the provincial average. Childhood leukemia mortality and incidence ratios for the period 1950 to 1987 were examined for five regions within 25 km of a nuclear facility. Nuclear facilities studied included a research development facility, a uranium refinery, a uranium mining and milling facility, and two nuclear power-generating stations. For all facilities combined, there was a slight, nonsignificant excess of childhood leukemia. There was no consistent pattern of a greater than expected risk among children who were born in the vicinity of a nuclear facility as opposed to those who resided there at the time of death. When the authors analyzed individual facilities, the risk of childhood leukemia ranged from being less than expected to being greater than expected; however, none of the differences was statistically significant. Among children born within 25 km of the two nuclear power plants, the slight excess of leukemia deaths (observed/expected: 1.4; 95% confidence interval: 0.98–1.9) was close to being statistically significant. At one facility, where it was possible to examine periods before and after the initial operation of the facility, the mortality ratio was slightly but not significantly greater after the facility opened than before. [McLaughlin, J. R., *et al.* “Childhood Leukemia in the Vicinity of Canadian Nuclear Facilities.” *Cancer Causes and Control*. Vol. 4: pp. 51-58. 1993]

Michaelis (1998) summarized the results from recent epidemiologic studies based on the German Childhood Cancer Registry. A previously published German study (Michaelis et al. 1992) was comparable to the largest English and Wales study by Forman et al. (1987). In contrast to the English study, the German study did not show an increase of childhood leukemia within the 15 km radius regions around nuclear installations. However, for children below five years of age living within 5 km radius regions and for children living close to old installations started prior 1970, increased relative risk had been observed. The original study covered

11 years from 1980 to 1990 and was extended for an additional 5 years. The analysis of the new study period still showed a nonsignificantly increased relative risk of leukemia in the younger age group and in the inner 5 km zone around nuclear installations as a whole, due mainly to four cases in the vicinity of the nuclear power plant at Krümmel, Germany. Relative risks for regions around the installations started prior to 1970 were not elevated in the new time period. All the calculations showed that there was no statistically increased risk and that the upper bounds of the corresponding confidence intervals were rather low. Apart from the 5 km area around the Krümmel plant, there was no other region around a nuclear power plant in West Germany that showed a significant increase of incidence of all malignancies or acute leukemia. The new study also extended to areas surrounding installations in Eastern Germany and to additional areas in West Germany. These analyses also did not show any significant effects. The author noted that the observed clusters close to Sellafield and Krümmel are still puzzling and a basis for public concern. Two population-based case-control studies exploring potential risk factors of childhood leukemia in the state of Lower Saxony and in all western states of Germany were also considered. The author concluded that the population-based epidemiologic studies showed that under current conditions exposure to ionizing radiation in Germany did not constitute risks of childhood malignancies relevant to public health. [Michaelis, J. "Recent Epidemiological Studies on Ionizing Radiation and Childhood Cancer in Germany." *International Journal of Radiation Biology*. Vol. 73, No. 4: pp. 377-381. 1998]

Michaelis et al. (1992) performed an incidence study based on the Federal Republic of Germany (West German) registry of childhood malignancies, which included so many observations that a 10% increase of risk for the incidence of childhood malignancies near nuclear installations could be detected at the 1% level of significance with a probability of more than 95%. The incidence of childhood malignancies in 20 areas surrounding nuclear installations was compared with the incidence in matched control regions. The study was based on 1,610 childhood malignancies that were diagnosed before 15 years of age from 1980 to 1990. The study gave no evidence for an increased risk of childhood leukemia or all childhood malignancies in the vicinity of nuclear installations. Subgroup analyses, which were not specified beforehand but were reasonable in the given context, revealed increased relative risks for acute leukemia in early childhood (less than five years) for children living within areas approximately 5 km distant from the installations, especially ones that began operating before 1970. The authors attributed most of this increase to an unexpected low incidence in the matched control regions for which no explanation could be found. By using the same control regions, a comparable and even more pronounced increase in relative risk was observed in areas where nuclear power plants had been planned but were not existing. [Michaelis, J., *et al.* "Incidence of Childhood Malignancies in the Vicinity of West German Nuclear Power Plants." *Cancer Causes and Control*. Vol. 3: pp. 255-263. 1992]

Morris and Knorr (1996) presented the results of the Southeastern Massachusetts Health Study, a case-control study conducted by the Massachusetts Department of Public Health. The study was designed to test the hypothesis that leukemia incidence between 1978 and 1986 near the Pilgrim nuclear plant in Plymouth, Massachusetts, was related to residential proximity to the plant and to other proximity-based surrogate measures of potential for exposure to the plant's radioactive emissions. There were 105 nonchronic, lymphocytic leukemia cases from 22 towns near Pilgrim and 208 population controls. The odds ratios relating leukemia risk for all subjects to residential proximity to Pilgrim were consistently greater than 1.0 and tended to increase as proximity to Pilgrim increased. The small group of subjects that had resided within four miles of Pilgrim had 3.88 (95% confidence interval: 0.81–10.64) times the leukemia risk of those who had lived 23 miles or more from Pilgrim. The exposure score was used as an index of exposure potential. All odds ratios exceeded 1.0 when effects of higher exposure potential were compared with effects of lower exposure potential. Data for all males and females combined showed a statistically significant linear trend in the odds ratios and the 95% confidence intervals for odds ratios excluded 1.0. All relative risk estimates for males exceeded 2.0 and confidence intervals excluded or nearly excluded 1.0; however, a linear trend was not obvious. The odds ratios estimated for female subjects exhibited a strong linear trend, and individuals with the highest exposure scores had a statistically significantly greater risk of leukemia (odds ratio = 5.19, 95% confidence interval = 1.83–15.70) than did individuals with the lowest scores. [Morris, M. S. and R. S. Knorr. "Adult Leukemia and Proximity-Based Surrogates for Exposure to Pilgrim Plant's Nuclear Emissions." *Archives of Environmental Health*. Vol. 51, No. 4: pp. 266-274. 1996]

Pobel and Viel (1997) performed a case-control study to investigate the association between childhood (less than 25 years) leukemia and established or other risk factors related to the La Hague nuclear waste reprocessing plant. Twenty-seven cases of leukemia diagnosed during the period 1978–1993 and 192 controls were matched for sex, age, place of birth, and residence at time of diagnosis. Risk factors that were investigated included ante- and postnatal exposure to X rays and viral infections, occupational exposure of the parents (particularly to ionizing radiation), living conditions, and lifestyle of the parents and children. Increased trends were observed for use of local beaches by mothers and children ($P \le 0.01$) as well as for consumption of local fish and shellfish ($P = 0.01$). A relative risk of 1.18 a year (95% confidence interval = 1.03 to 1.42) was observed for length of residence in a granite-built house or in a granitic area. No association was observed with parental occupational exposure. The authors concluded that some lifestyle risk factors are associated with the development of childhood leukemia, suggesting an environmental route for contamination with radioactive material. [Pobel, D. and J.-F. Viel. "Case-Control Study of Leukaemia Among Young People Near La Hague Nuclear Processing Plant: The Environmental Hypothesis Revisited." *BMJ*. Vol. 314: pp. 101-106. 1997]

Qiao et al. (2006) updated and expanded a previous study that examined pediatric cancer risk in relation to the proximity of nuclear power plants in Illinois. Age-adjusted cancer incidence and mortality rates for children aged from 0–14 for years 1990 to 2002 were calculated for a nuclear facility county group and a nuclear facility ZIP code group and compared with those for a matched nonnuclear facility county group or a nonnuclear facility ZIP code group, respectively. Rates based on state and National Cancer Institute's Surveillance, Epidemiology and End Results Program national registry levels were also used for comparisons. A Poisson regression analysis was performed on proximity to nuclear power plants versus cancer incidence, adjusting for race, gender, and age. Based on the 95% confidence intervals for rate ratios, there was no significant difference between pediatric cancer incidence and mortality rates for the nuclear facility groups and their comparison groups. There was no evidence of increased trend in cancer incidence rate after start-up of the nuclear power plants. Proximity to nuclear power plants was not a significant indicator of variation of cancer incidence. [Qiao, B., M. Lehnherr, and T. Shen. "Pediatric Cancer Incidence and Mortality in the Vicinity of Nuclear Power Plants in Illinois. Epidemiologic Report Series 06:01." Springfield, Illinois: Illinois Department of Public Health. January 2006].

Rushton et al. (2006) reviewed the practice of assigning geographic identifiers to cancer records for many purposes and discusses methods to improve the accuracy of geo-coded cancer data. The authors identify a common source of error from using digital boundary files of dubious quality to place addresses into areas of interest. Demographic, environmental, and health services geo-coded data have unique accuracy considerations associated with each. Statistical methods must be adjusted for the locational uncertainty of geo-coded data when masking methods are used for protected private information. The authors suggest use of longitude and latitude for basic geo-coding; all other geo-codes of interest could be derived from this basic identifier. The authors also suggest using census block group data as the smallest area for which both cancer data and demographic data are available. [Rushton, G., *et al.* "Geocoding in Cancer Research: A Review." *American Journal of Preventive Medicine*. Vol. 30, No. 2: pp. S16-S24. February 2006].

Rushton et al (2006) reviewed the practice of assigning geographic identifiers to cancer records and discussed methods to improve the accuracy of geocoded cancer data. The authors recommend use of longitude and latitude for basic geocoding; all other geocodes of interest could be derived from this basic identifier. They also suggest using census block group data as the smallest area for which both cancer data and demographic data are available. They stress that when short distances may associated with health effects, sufficient accuracy in location is required to resolve whether such effects exist. Use of ZIP codes is rejected and and ZIP Code Tabulation Areas are said to be useful only when cancers are first geocoded to census blocks. An extensive table of questions and answers on geocoding quality is provided. [Rushton, G. et al. "Geocoding in Cancer Research." *American Journal of Preventive Medicine*. Elsevier Inc. Vol. 30, Issue 2: pp. S16-S24. February 2006.]

Schmitz-Feuerhake et al. (2005) summarize investigations regarding a cluster of childhood leukemia that had been identified in the proximity of the German nuclear establishments of Geesthacht, beginning in 1990 and continuing to publication of this article. Blood samples from local residents showed an increase in dicentric chromosomes in lymphocytes, indicating exposures that exceeded dose limits. Analysis of "immission" (environmental monitoring) data revealed several unexpected deliveries of fission and activation radionuclides to the environment but provided no explanation of the source. It was believed that the dicentric chromosomes could possibly be explained by a contribution of densely ionizing emitters. The routine environmental surveillance programs at that time did not include alpha emitters. These were measured in specific studies that proved contamination by transuranic nuclides. The discussion highlights limitations of the immission control concept of environmental monitoring, which is predominantly based on gamma radiation monitoring. [Schmitz-Feuerhake, I., *et al.* "The Elbmarsch Leukemia Cluster: Are There Conceptual Limitations in Controlling Immission from Nuclear Establishments in Germany?" *Archives of Environmental Contamination and Toxicology*. Vol. 49: pp. 589-600. 2005]

Schmitz-Feuerhake et al. (1997) investigated the radiation exposures of the population living near the Krümmel nuclear power plant (Kernkraftwerk Krümmel), which is located near the nuclear research institute Gesellschaft für Kernenergieverwertung in Schiffbau und Schiffahrt. Elevation of leukemia cases in children living in Elbmarsch near the Krümmel plant was observed in 1989 to 1991, five years after the 1983 start-up of the power plant. A retrospective investigation by chromosome aberration analysis was conducted on 21 individuals, all current or former residents within 5 km of the plant. The rate of dicentric chromosomes in peripheral blood lymphocytes was significantly elevated and indicated ongoing exposures from the plant during its operation. It was hypothesized that chronic reactor leakages had occurred. Analyses of data on environmental radioactivity measurements also were conducted. Artificial radioactivity in air, rainwater, soil, and vegetation was identified by the environmental monitoring program at the nuclear power plant, which supported the hypothesis. The authors concluded that calculations of corresponding source terms showed that emissions must have been well above authorized annual limits. [Schmitz-Feuerhake, I., *et al.* "Leukemia in the Proximity of a German Boiling-Water Nuclear Reactor: Evidence of Population Exposure by Chromosome Studies and Environmental Radioactivity." *Environmental Health Perspectives*. Vol. 105, Supplement 6: pp. 1499-1504. 1997]

Sharp et al. (1999) examined the risk of cancers other than leukemia and non-Hodgkin's lymphoma in children (less than 15 years at diagnosis) living in the vicinity of nuclear sites in Scotland during the period 1975–1994. The cases were analyzed in two groups: tumors of the central nervous system and other malignant tumors (excluding leukemia and non-Hodgkin's lymphoma). Expected cases for each site were calculated. Stone's maximum likelihood ratio test was used to determine whether there was any evidence of increased risk of the neoplasms among children living within 25 km of the sites investigated. More tumors of the central nervous system were observed (O) than expected (E) within 25 km of Dounreay (O/E: 1.14), Hunterston (O/E: 1.14), and Rosyth (O/E: 1.22), based on 2, 26, and 136 observed cases, respectively. The unconditional maximum likelihood ratio test was significant only for Rosyth ($P = 0.006$); the conditional application of the test for Rosyth was not significant ($P = 0.771$). Among the cases of other malignant neoplasms, the unconditional maximum likelihood ratio test was not significant for any of the sites. The authors found no evidence for generally increased risk of either neoplasms of the central nervous system or other solid tumours and Hodgkin's disease in children living near nuclear sites in Scotland during the period 1975–1994. A significant excess risk of central nervous system tumors was found in the study zone around Rosyth dockyard. This was likely due to an unexplained high incidence of tumors of the central nervous system in that part of the country, which warrants further investigation. [Sharp, L., *et al.* "Incidence of Childhood Brain and Other Non-haematopoietic Neoplasms Near Nuclear Sites in Scotland, 1975-94." *Occupational and Environmental Medicine*. Vol. 56: pp. 308-314. 1999]

Sharp et al. (1996) investigated the incidence of leukemia and non-Hodgkin's lymphoma in children living near seven nuclear sites in Scotland and determined whether there was a gradient in risk with distance from the sites. The authors also assessed the power of statistical tests for increased risk of disease near a point source using census data for Scotland. The study data set included 1,287 cases of leukemia and non-Hodgkin's lymphoma diagnoses in children under 15 years of age during 1968–1993. A study zone within 25 km was constructed around each site. Expected numbers were calculated and six statistical tests were evaluated. Stone's maximum likelihood ratio was applied as the main test for general increased incidence across a study zone. The linear risk score based on enumeration districts was used as a secondary test for declining risk with distance from each site. More cases were observed (O) than expected (E) in the study zones around Rosyth naval base (O/E: 1.02), Chapelcross electricity generating station (O/E: 1.08), and Dounreay reprocessing plant (O/E: 1.99). The maximum likelihood ratio reached significance only for Dounreay (P = 0.030). The linear risk score test did not indicate a trend in risk with distance from any of the sites. The most important conclusion from the evaluation exercise was that the power of the tests is dependent on the characteristics of the population under study, including population density, distribution of the population, number of units of analysis, and overall expected number of cases. There was no evidence of a generally increased risk of childhood leukemia and non-Hodgkin's lymphoma around nuclear sites in Scotland and no evidence of a trend of decreasing risk with distance from any of the sites. There was a significant excess risk in the zone around Dounreay, which was only partially accounted for by the socio-demographics of the area. [Sharp, L., *et al.* "Incidence of Childhood Leukaemia and Non-Hodgkin's Lymphoma in the Vicinity of Nuclear Sites in Scotland, 1968-93." *Occupational and Environmental Medicine*. Vol. 53: pp. 823-831. 1996].

Silva-Mato et al. (2003) investigated the association between cancer incidence risk and residency within 10, 20, and 30 km of two Guadalajara nuclear power plants, Zorita and Trillo, which began operations in 1968 and 1987, respectively. In a case-control study, patients admitted with non-secondary cancer and non-tumorous patients, both admitted to Guadalajara Hospital during 1988–1999, were compared after stratifying by gender and age group (<40, 40–59, 60–79, ≥80 years). The odds ratio for all cancers and the entire study period comparing the 10 and 30 km residency areas around Trillo was 1.71 (95% confidence interval: 1.15 to 2.53), increasing in magnitude in the subgroup of more radiogenic tumors and in the period considered to be post-latency (1997–1999). Risk increased linearly with proximity to the two plants, significantly for Trillo (P < 0.01) but not for Zorita (P = 0.19). Differences were not significant for other comparisons. [Silva-Mato, A., *et al.* "Cancer Risk Around the Nuclear Power Plants of Trillo and Zorita (Spain)." *Occupational and Environmental Medicine*. Vol. 60, No. 7: pp. 521-527. 2003]

Sofer et al. (1991/1992) studied spatial and temporal trends of leukemia incidence over the period 1960–1985 for the age group 0–24 years at the time of diagnosis in the Negev, Israel, where the Dimona nuclear plant has operated since 1960. The authors divided the Negev into an eastern part, where plant employees were likely to live, and a western part, where this was unlikely. Leukemia cases were identified from the Israel Cancer Registry and verified against data from hospitals in the area. Jewish and Bedouin cases were studied separately. The authors observed no excess of childhood leukemia among the population who lived near, and might be employed in, the Dimona nuclear plant. Leukemia rates were consistently higher over time in the western Negev among children aged 0–9 years, especially for acute lymphatic leukemia (ALL). There was an unexplained sudden increase, especially of ALL, among girls aged 0–4 years at diagnosis, born during the period 1970–1979, in the northern part of the western Negev, which was not noticed among boys. The authors recommended that case referent studies be performed. [Sofer, T., *et al.* “Geographical and Temporal Trends of Childhood Leukemia in Relation to the Nuclear Plant in the Negev, Israel, 1960-1985.” *Public Health Review*. Vol. 19: pp. 191-198. 1991/1992]

Spix et al. (2008) conducted a matched case-control study for preselected areas around all 16 major nuclear power plants in Germany. Cases (1,592 total) were all cancers and nonmalignant brain tumors for children less than five years diagnosed between 1980 and 2003. All cases were matched with three controls each (a total of 4,735 for the analysis) for date of birth, age, sex and nuclear power plant area at the date of diagnosis. Comparisons were made of inverse distance of location of residence to the nearest nuclear power plant at the time of diagnosis by using a conditional logistic regression model. Study cases showed an increased risk for cancer in children less than five years of age and living within 5 km (odds ratio of 1.47; lower one-sided 95% confidence limit: 1.16), with the effect largely restricted to leukemia (OR: 1.76; lower one-sided 95% confidence limit: 1.24). No conclusions on the impact to study results of potential confounders could be drawn. The authors note that radiation dose from nuclear power plant emissions is a factor of 1,000–100,000 less than from natural and medical sources and that the observed positive trend with 1/distance could not be explained. [Spix, C., *et al.* “Case-Control Study on Childhood Cancer in the Vicinity of Nuclear Power Plants in Germany 1980-2003.” *European Journal of Cancer*, Vol. 44, No. 2: pp. 275-284. 2008]

Steenland et al (2004) studied whether area-level socioeconomic status predicts mortality independently of individual-level socioeconomic status in 179,383 persons in the American Cancer Society Nutrition Cohort, followed for mortality from 1992 to 2000. The area-level variable based on census blocks was an average of home value, income, education, and occupation. The individual-level socioeconomic status variable was education. The authors studied socioeconomic status-mortality trends with each socioeconomic status variable adjusted for the other. For all causes, an individual’s education was strongly and inversely associated with mortality and with all-vascular disease; area-level socioeconomic status was weakly but significantly associated with both mortality and all-vascular disease. For all cancers, there was a significant inverse trend with education, but no such trend with area-level socioeconomic status. A weaker association of education with mortality was seen for women following adjustment for conventional risk factors in multivariate analyses. Results indicated that the predictive value of area-level socioeconomic status variables varies by cause of death, but is less important than individual-level socioeconomic status variables. Multivariate models that consider socioeconomic status as a potential confounder might not need to consider area-level socioeconomic status if data are available on individual-level education. [Steenland, K. et al. “Individual- and Area-Level Socioeconomic Status Variables as Predictors of Mortality in a Cohort of 179,383 Persons.” *American Journal of Epidemiology*. Johns Hopkins Bloomberg School of Public Health. Vol. 159, No. 11: pp. 1047-1056. 2004.]

Urquhart et al. (1991) conducted a case-control study to examine whether the observed excess of childhood leukemia and non-Hodgkin’s lymphoma in the area around the Dounreay nuclear installation was associated with established risk factors, factors related to the plant, or parental occupation in the nuclear industry (including antenatal abdominal x-ray examinations, drugs taken and viral infections during pregnancy, father's occupation, father's employment at Dounreay and radiation dose, distance of usual residence from the path of microwave beams, pre-conceptual exposure to nonionizing radiation in the father, and other lifestyle factors). Subjects in the study included 14 cases of leukemia and non-Hodgkin's lymphoma in children under 15 years of age diagnosed between 1970 and 1986 and 55 control subjects matched for sex, date of birth, and area of residence within Caithness at time of birth. The study showed no raised relative risks for prenatal exposure to x-rays, social class of parents, father's employment at Dounreay before conception or diagnosis, father's dose of ionizing radiation before conception, or child's residence within 50 m of the path of microwave transmission beams. Results also proved negative for all lifestyle factors except an apparent association with use of beaches within 25 km of Dounreay. This result was based on small numbers and might be an artifact of multiple testing and influenced by recall bias. [Urquhart, J. D., *et al.* "Case-Control Study of Leukaemia and Non-Hodgkin's Lymphoma in Children in Caithness Near the Dounreay Nuclear Installation." *BMJ*. Vol. 302: pp. 687-692. 1991]

Viel and Richardson (1990) reported preliminary results on mortality from childhood leukemia observed around the nuclear waste reprocessing plant at La Hague, France, that began operation in 1966. Mortality data for the periods 1968–1978 and 1979–1986 were provided by the Institute National de la Santé et de la Recherche Medicale, which records all the medical causes of deaths in France centrally. Three age groups were examined: 0–4 years, 5–14 years, and 15–24 years. All electoral wards that had half or more of their areas within a specified radius of the nuclear plant were studied. Radii of 10 km, 20 km, and 35 km were chosen before the analyses; 10 wards were included in the study. Expected numbers of leukemia cases were estimated by applying the age-specific rates for department de la Manche for 1968–1978 and 1979–1986 to the 1975 and 1982 census populations of the predefined areas. Results were analyzed by two-tailed tests based on a Poisson distribution. Only one death occurred in the area closest to the nuclear installation between 1968 and 1986. Only one standardized mortality ratio (SMR) was significantly different from one: the ratio for the age group 5–14 living 10 to 20 km from the plant during 1968–1978 showed a decreased risk (observed number of deaths = 0, expected = 3.935). The SMR for all the age groups, periods, and areas was 89% (observed deaths = 21, expected = 23.6) and was not significant (95% confidence interval 0.55–1.36). No significant trend between the two periods was found. The authors suggest that a registry of all cases of leukemia and their exact locations needs to be established. [Viel, J. F. and S. T. Richardson. "Childhood Leukaemia Around the La Hague Nuclear Waste Reprocessing Plant." *BMJ*. Vol. 300: pp. 580-581. 1990]

Viel et al. (1993) examined the incidence of leukemia in young people (less than 25 years of age) living within a 35 km radius of the French nuclear waste reprocessing plant operating in La Hague, Normandy. The study included the period 1978–1990, since patient files before this time were impossible to trace. The study area included 10 electoral wards (all with at least half of their area in a 35 km radius of the nuclear plant); the usual places of residence of the La Hague workforce were included in the study area. During the study period, 23 per persons aged 0 to 24 years living in any of the cantons were diagnosed with leukemia (incidence rate of

2.99 per 100,000, which is close to the expected rate). Thirteen were deceased at the time of the study. The only significant excess of leukemia incidence was observed for the 0 to 4 years age group in the area within the 20 to 35 km radius (standardized incidence ratio: 3.2, 95% confidence interval: 1.0–7.4). The authors recommended that a case-control study be undertaken to assess the part played by occupational radiation exposure in leukemia incidence for this area. [Viel, J.-F., *et al.* "Childhood Leukemia Incidence in the Vicinity of La Hague Nuclear-Waste Reprocessing Facility (France)." *Cancer Causes and Control*. Vol. 4: pp. 341-343. 1993]

Wakeford (2002) responded by letter to the Cartwright et al. (2001) paper with factual corrections to the Cartwright data concerning the reporting of cancer cases in Seascale. Corrections included one date and two places of birth, one date of diagnosis, and omission of one case. Wakeford takes issue with Cartwright et al. (2001) failing to acknowledge that Seascale could have played no part regarding a case in which a child was diagnosed while living elsewhere than Seascale but later moved to Seascale with the child's family and died there. Wakeford also suggests that Cartwright et al. (2001) made use of unspecified sources of information other than the certificates for deaths registered in the Whitehaven Registration District, as they claimed, and by doing so introduced the potential for information bias in the mortality rates reported. [Wakeford, R. "Childhood Cancer in Seascale." *Journal of Public Health Medicine*. Vol. 24, No. 4: pp. 343-344. 2002]

White-Koning et al. (2004) studied childhood leukemia incidence rates around 19 French nuclear power plants and 10 other nuclear facilities of various types, comparing observed rates in areas surrounding the sites to expected rates based on National Registry data. The authors reported that for the period between 1990 and 1998 the number of diagnosed (O) childhood leukemia cases was lower than expected (E) among children under 15 years at time of diagnosis around the 29 nuclear sites (standardized incidence ratio (SIR) = O/E = 0.92; 95% confidence interval = 0.85–0.99). The SIR was lower, but not significantly lower, than expected for each of four areas (0–5 km, 5–10 km, 10–15 km, 15–20 km) defined around the sites. There was no evidence of a trend in SIR with distance from the sites for all children or for any of the three age groups (0–4, 5–9, 10–14 years) in the study. Results were similar for a pooled analysis of only the 19 nuclear power sites. [White-Koning, M. L., *et al.* "Incidence of Childhood Leukaemia in the Vicinity of Nuclear Sites in France, 1990-1998." British Journal of Cancer. Vol. 91: pp. 916-922. 2004]

Yasui and Whitton (1999) considered the potential for bias and problems with statistical inferences associated with the use of age-stratum-specific reference rates in indirect standardization. The authors described a simple remedy, and its limitations, using linear splines to replace the step functions with a continuous function of age. [Yasui, Y. and J. Whitton. "Problems in Using Age-Stratum-Specific Reference Rates for Indirect Standardization." *Journal of Clinical Epidemiology*. Vol. 52, No. 5: pp. 393-398. 1999]

Yasui and Whitton (1999) considered the potential for bias and problems with statistical inferences associated with the use of age-stratum-specific reference rates in indirect standardization. The authors described a simple remedy, which is using linear splines to replace the step functions with a continuous function of age. The importance of using consistent linear splines rather than interpolated linear splines was highlighted. Potential problems that can be avoided by using splines are more likely to occur when risks change appreciably by age. [Yasui, Y and Whitton, J. Problems in Using Age-Stratum-Specific Reference Rates for Indirect Standardization." *Journal of Clinical Epidemiology.* Elsevier Science, Inc. Vol. 52, No. 5: pp. 393-398. 1999.]

Appendix B: Selection of Control Counties

<u>Specific Issues Concerning Selection of Control Counties</u>

1. Restriction of Control Counties to the Same State as the Study County

For the reasons listed below, control counties should be in the same state as their study county with the exception of control counties in the original study that were in a neighboring state.

- Analysis will be stratified by white/nonwhite. Although percent white is a factor in the similarity index (SI), the makeup of the nonwhite group may tend to differ from state to state but be similar within a state, particularly in the same region of a state. A finer stratification on race is not possible because of limitations in the national data for earlier years.
- Because of state health-care policies and extent of medical coverage for persons without insurance, the stage of cancer at diagnosis and quality of medical care for individuals with cancer may differ considerably from state to state.
- The quality of the mortality data reported on the death certificate and of the coding of the causes of death according the International Classification of Diseases (ICD) may lack consistency among states as opposed to within states (Cragle and Fetcher 1992; Terry 2001).
- Restricting control counties to the same state as the study county helps to control for other factors which may influence cancer occurrence and reporting. These factors include diet, smoking, other potential cancer risk factors, and local medical community customs for certifying deaths.

2. Exclusion of Adjacent Counties from Potential Control Counties

Counties adjacent to any NRC or DOE site will not be control counties for any study county. Adaptation to this restriction will be needed because certain small states (e.g., Connecticut) have no potential control counties available when all counties adjacent to a study county are excluded. Since Connecticut has so few counties, it is proposed that the original study counties for this state be used.

Because adjacent counties were not excluded from being control counties in the original study, adopting this exclusion will lower the percent of original study counties that are retained in the current study. Nonetheless, this exclusion appears to be scientifically valid for the following reasons:

- Disallowing adjacent counties will indirectly adjust for possible downwind or downstream effluents. Of concern is the selection of control counties that are in the aerial or water streams flowing from the site. Because of unpredictable changes in wind patterns, it is not feasible to determine accurately which counties are downwind of a study county. In addition, there is community concern about tritium-contaminated groundwater around specific NRC sites. Eliminating all adjacent counties from the pool of potential control counties should indirectly exclude counties with possible downwind or downstream exposure as well as counties with tritium-contaminated groundwater.

- Disallowing adjacent counties will also adjust indirectly for reactor workers whose residences may be near their workplaces. Because the spatial analysis, which will be conducted on completion of the county level analysis, will compare cancer risk in concentric rings around a site, adjacent counties will comprise a large portion of the comparison areas. Selecting nonadjacent control counties for the county analysis will provide complementary assessment of whether nuclear reactors are associated with increased cancer mortality. This point is not quite as strong as it appears since subcounty analyses will be carried out only for 1990 and later and only for sites in states from which address data can be obtained.

3. Accounting for Nonreactor Industrial Pollution

The effect on the relative risk (RR) of pollutants from nonnuclear industries must be accounted for and mitigated. Some study counties may contain polluting industries in addition to the nuclear reactors, and some potential control counties may contain polluting industries. Pollutants from these industries could increase cancer rates in study counties from sources other than nuclear reactors, inflating the RR. Alternatively, when these industries are in control counties, the pollutants could reduce the RR for study counties. This issue will be addressed as follows:

- Having three control counties for each study county should diminish the effect on the RR unless more than one of the control counties contains such industries.
- Considering the addition of two factors to the SI should help ensure that study and control counties are more alike with respect to additional industrial pollutants. The first factor rates industrial pollutants in counties based on the Environmental Protection Agency's (EPA's) 2000 Risk Screening Environmental Indicators database. The second factor measures the county percent of employment in manufacturing.
- An appendix to document attention to this issue will be included with the final report listing, for all study and control counties, any polluting industries, along with the starting date, and, if appropriate, closing date of the facility.

<u>Development of the Matching Algorithm to Select Control Counties</u>

For sites included in the original study, a series of preliminary tests is being carried out to examine the percent of original control counties that would be re-selected and what patterns might occur in situations where original control counties would not be re-selected. Each successive test builds on the previous test in order to refine the algorithm as follows:

- Test 1: For each site, the SI was created for each potential control county by using a set of variables defined by Boice et al. (2003a). One of these variables is household income. In Boice's paper, it is unclear whether mean or median income was used since the text states mean income but Table 1 presents median income. For this test and subsequent tests, median income was used. Potential control counties were restricted to the same state as the study county, with the exception of out-of-state control counties that were used in the original study.
- Test 2: The SI from Test 1 was combined with the distance from the reactor site's coordinates to each county's population-weighted centroid. The population-weighted centroids were calculated from the nighttime LandScan USA population distribution model. The nighttime grid was used to represent residential locations. For accurate straight-line distances, the distance calculation was automated to reproject the data centered around each reactor before calculating. Ordered pairs of SI and distance were graphed, and the Euclidean distances were ranked, with these ranks being used to determine similarity to the study county. The distance function replaced the state boundary restriction, allowing counties from any state to be potential matches.
- Test 3: Test 3 was the same as Test 1, with the addition of the distance as defined in Test 2 being ranked and included as a component in the SI. Also, any county adjacent to a study county or DOE site county was excluded from control county consideration. A sample state map with county boundaries based on Test 3 results can be seen in Figure 1. This map allows visual examination for patterns when the control counties from the original study were not among the best choices according to SI values.
- Test 4: test 4 was the same as Test 3 except the distance component of the SI was counted twice when summing the ranks for each county.
- Test 5: Test 5 was the same as Test 4 with the addition to the SI calculation of a factor for percent of workforce in manufacturing and a factor for ranking potential exposure to industrial pollutants other than radiation. Percent manufacturing values were obtained from the 2000 census, and values for the industrial pollution factor were obtained from the EPA 2000 Risk-Screening Environmental Indicators. (http://www.epa.gov/oppt/rsei/)
- Test 6: A principle components analysis based on correlations was conducted and the results were combined with the distance rankings.

Final Selection Criteria for Control Counties

After all six tests were completed, the Test 5 SI was selected based on the criteria of including the variables that are important as outlined above and providing the highest percent of control counties corresponding to the original study. Following the example of Aylin et al. (1999)the three counties chosen to match each study county will be from the first quintile of the SI ranking. When an original control county is among counties in the first quintile, it will be selected as a control county for this study. When all three of the original control counties are not included in the first quintile, the counties with the lowest SI will be chosen until three control counties have been selected.

Table: Comparison of Select Tests for Choosing Control Counties

	State	TotalCtrls	Test1	Test2	Test3	Test4	Test5	T5NoExcl	Test6	T6NoExcl
Browns Ferry	AL	6	3	3	2	3	3	5	3	4
Farley	Al	6	3	3	2	4	4	5	4	4
Arkansas	Ar	3	2	2	2	2	2	2	1	1
Humboldt Bay	CA	3	3	1	1	1	1	3	1	2
Rancho Seco	CA	9	7	5	5	4	3	9	4	8
San Onofre	CA	6	4	4	4	4	3	5	2	3
Ft St Vrain	CO	9	3	4	3	4	3	6	3	5
Haddam Neck	CT	3	3	0	0	0	0	3	0	2
Millstone	CT	3	2	0	0	0	0	2	0	1
Crystal River	FL	3	3	2	2	2	2	3	2	3
St Lucie	FL	3	0	0	0	0	0	0	0	1
Turkey Point	FL	3	3	3	3	3	3	3	3	3
Hatch	GA	6	4	3	3	3	2	4	2	2
Duane Arnold	IA	6	2	4	1	3	3	5	3	5
Ft Calhoun	IA	6	5	1	1	1	1	5	0	4
Dresden	IL	6	6	5	5	5	5	5	3	5
Quad Cities	IL	6	2	1	2	4	4	4	1	2
Zion	IL	6	6	3	3	3	3	6	3	6
Pilgrim	MA	3	2	0	0	0	0	1	0	1
Yankee Rowe	MA	6	3	2	2	2	1	3	0	4
Calvert Cliffs	MD	3	0	0	0	1	0	0	0	0
Maine Yankee	ME	6	2	1	1	1	1	2	1	2
Big Rock Point	MI	6	4	2	2	2	2	5	2	4
Cook	MI	3	3	2	2	2	2	3	2	3
Fermi	MI	3	1	3	2	2	1	2	2	2
Palisades	MI	3	3	2	2	2	2	3	2	3
Monticello	MN	6	6	4	4	4	4	6	4	6
Prairie Island	MN	6	4	3	3	3	3	5	1	2
Cooper Station	MO	9	4	2	2	3	2	5	1	4
Brunswick	NC	3	1	1	1	1	1	2	0	1
Mcguire	NC	9	7	6	6	6	6	7	4	7
Hallam	NE	6	6	6	6	6	4	5	6	6
Oyster Creek	NJ	3	2	2	2	2	1	1	2	6
Salem	NJ	6	4	3	2	3	1	3	1	4
Ginna	NY	3	2	1	1	0	0	3	0	2
Indian Point	NY	6	4	3	2	3	2	6	3	6
Nine Mile Point	NY	3	1	1	1	1	0	2	1	1
Davis-Besse	OH	3	2	1	1	2	2	3	0	1
Trojan	OR	6	2	1	1	2	1	3	1	1
Beaver Valley	PA	6	6	5	5	5	5	6	4	5
Peach Bottom	PA	6	2	2	2	1	1	2	1	1
Three Mile Island	PA	9	2	1	2	1	1	2	2	3
Oconee	SC	6	3	1	1	1	0	4	0	4
Robinson	SC	6	1	2	1	2	0	1	0	1
Pathfinder	SD	6	4	4	4	4	4	5	2	3
Sequoyah	TN	3	2	1	1	1	1	2	1	2
North Anna	VA	9	6	5	5	5	4	8	4	6
Surry	VA	6	1	1	1	1	1	3	1	0
Vermont Yankee	MA	9	5	4	5	5	2	5	4	7
Kewaunee	WI	6	3	2	2	2	2	4	2	4
La Crosse	WI	3	2	2	1	2	2	3	0	1
Point Beach	WI	3	2	1	1	1	1	2	1	2
TOTAL		273	163	121	113	125	102	192	90	166
Percent of original study counties			**60**	**44**	**41**	**46**	**37**	**70**	**33**	**61**

Note: After Test 1 additional counties were excluded in subsequent tests except for T5NoExcl and T6NoExcl.

Appendix C: Cause of Death Categories Used in the Analysis and Code Groups of the International Classification of Diseases (ICD)

	Calendar Years			
	1950–1967	1968–1978	1979–1998	1999–Present
ICD Revision	6th, 7th	8th	9th	10th
DIAGNOSTIC GROUPS				
Leukemia and aleukemia	204	204–207	204–208	C91–C95
Hodgkin's disease	201	201	201	C81
Other lymphoma	200, 202, 205	200, 202	200, 202	C82–C85
Multiple myeloma	203	203	203	C88, C90
All Malignant Neoplasms Except Leukemia	140–203 205	140–203	140–203	C00–C90, C96, C97
Digestive Organs	150–159	150–159, 197.8	150–159	C15–C26, C48
Stomach	151	151	151	C16
Colon and rectum	153, 154	153, 154	153, 154	C18–C21
Liver (primary)	155, 156	155, 197.8	155	C22
Trachea, bronchus and lung	162, 163	162	162	C33, C34
Breast (female)	170	174	174	C50
Thyroid	194	193	193	C73
Bones and joints	196	170	170	C40, C41
Bladder	181, excluding 181.7	188	188	C67
Brain and other central nervous system	193	191, 192.1–192.3, 225.0, 225.2-225.4, 238.1	191, 192.1–192.3, 225.0, 225.2-225.4, 237.5, 237.6	C71, C70.0, C70.1, C72.0, D33.0–D33.2, D32.0, D32.1, D33.4, D43.0–D43.2, D43.4, D42
Benign, In Situ, and Unspecified Neoplasms*	---	210–239	210–239	D00–D48

*Benign and unspecified neoplasms (codes 210–239) were not available in the 6th or 7th revisions of the ICD and appeared in the 8th revision only starting in 1970. In situ neoplasms first appeared in the 9th revision (codes 235–239).

(continued)

Sources:

Centers for Disease Control and Prevention, National Center for Health Statistics. "A Guide to State Implementation of ICD-10 for Mortality." July 16, 1998. <http://www.cdc.gov/nchs/about/major/dvs/icd10des.htm> (12 March 2009).

Centers for Disease Control and Prevention, National Center for Health Statistics. "A Guide to Implementation of ICD-10 for Mortality Part II: Applying Comparability Ratios." December 4, 2000. <http://www.cdc.gov/nchs/about/major/dvs/icd10des.htm> (12 March 2009).

Appendix D: Statistical Results Example

Please note: Figures and numbers in the tables will be supplied by October 20. Changes in format of results presented in this appendix are possible as pilot study analyses are carried out and more information becomes available. A pilot study is being conducted for the two nuclear power plants in the state of Alabama.

These sites are Browns Ferry and Farley. Browns Ferry is a three-unit boiling water reactor (BWR) site. Unit 1 came online in 1973, unit 2 in 1974, and unit 3 in 1976. All three units were placed on “administrative” hold in 1985 for TVA to address operational and management issues. In 1991, unit 2 resumed commercial operation and unit 3 restarted in 1995. Unit 1 was restarted in 2007. Farley is a two-unit pressurized water reactor (PWR) site which started operation 1977.

Analysis is based on five-year time periods, the first of which ends in the year a site became operational. Time periods for Browns Ferry are these: t_0=1969-73, t_1=1974-78, t_3=1979-83, t_4=1984-88, t_5=1989-93, t_6=1994-98, t_7=1999-2003, t_7=2004-2006. For Farley the time periods are as follows: t_0=1973-77, t_1=1978-82, t_3=1983-87, t_4=1988-92, t_5=1993-97, t_6=1998-2002, t_7=2003-2006. Since the restricted county mortality data for 1989 onward has just been received from NCHS, the example results show only the first four time periods for Browns Ferry and three for Farley.

The Browns Ferry and Farley sites each have two study counties. The three matching control counties for each study county were selected based on the SI of Test 5 and the criteria detailed in Appendix B. Table 1 contains the names of the study and control counties and indicates with blue font those control counties that correspond to the original study controls.

Table D1: Study Counties and Corresponding Control Counties Based on Test 5 for AL Sites

Site	Study County	Control County 1	Control County 2	Control County 3
Browns Ferry	Lawrence, AL[a]	Lamar, AL	Pontotoc, MS	Chilton, Al
	Limestone, AL[b]	Alcorn, MS	Blount, AL	St. Clair, AL
Farley	Houston, AL[c]	Lee, AL	Calhoun, Al	Coffee, AL
	Early, GA[d]	Brooks, GA	Crisp, GA	Sumter, GA

[a] Original control counties were Lamar, AL, Pontotoc, MS, and Maury, TN
[b] Original control counties were Alcorn, MS, Colbert, AL, and Giles, TN
[c] Original control counties were Lee, AL, Elmore, AL, and Houston, GA
[d] Original control counties were Brooks, GA, Crisp, GA, and Sumter, GA

Study results will be presented electronically, moving from the overview to the most detailed. The main page for each of the 81 sites will have links to each of the cancer outcome that are analyzed. Clicking on the link to a particular cancer cause will pull up the first-level page, which will contain a graph showing the relative risks over time, trend test results, RRs with 95% confidence intervals by time period and a link to the second-level page. The second-level page will present the observed deaths, expected deaths, and SMRs for study and control counties by time period, along with a link to the third-level page. For individuals interested in great detail, the third-level page will give the observed deaths and expected deaths for each separate study county and control county for each time period. The sample results given below show what might be seen at the various level links for one cause of death – namely, all cancers except leukemia. Note that when study or control counties contain no deaths in one or more time periods for the given cancer, the trend test will not be available.

Analysis Results for Browns Ferry, AL Site for All Cancers except Leukemia

Level 1 Link

Figure 1: RRs and Trend over Time for Browns Ferry, AL
All Cancers except Leukemia
Start Year - 1973

RRs with 95% Confidence Intervals by Time Period – Browns Ferry, AL
All Cancers except Leukemia
Start Year - 1973

Time Period	**t_0**	**t_1**	**t_2**	**t_3**
RR				
Lower Bound				
Upper Bound				

Level 2 Link

SMRs for Combined Study and Control Counties by Time Period – Browns Ferry, AL
All Cancers except Leukemia
Start Year - 1973

Site	Time Period	County Type	Observed Deaths	Expected Deaths	SMR
Browns Ferry	t_0	Study			
	t_0	Control			
Browns Ferry	t_1	Study			
	t_1	Control			
Browns Ferry	t_2	Study			
	t_2	Control			
Browns Ferry	t_3	Study			
	t_3	Control			

Level 3 Link

Observed and Expected Deaths by Each County and Time Period – Browns Ferry, AL
All Cancers except Leukemia
Start Year - 1973

Site	Time Period	County	County Type	Observed Deaths	Expected Deaths
Browns Ferry Study County 1	t_0	Lawrence	Study		
	t_0	Lamar	Control		
	t_0	Pontotoc	Control		
	t_0	Chilton	Control		
	t_1	Lawrence	Study		
	t_1	Lamar	Control		
	t_1	Pontotoc	Control		
	t_1	Chilton	Control		
	t_2	Lawrence	Study		
	t_2	Lamar	Control		
	t_2	Pontotoc	Control		

(continues)

Site	Time Period	County	County Type	Observed Deaths	Expected Deaths
	t_2	Chilton	Control		
	t_3	Lawrence	Study		
	t_3	Lamar	Control		
	t_3	Pontotoc	Control		
	t_3	Chilton	Control		
Browns Ferry Study County 2	t_0	Limestone	Study		
	t_0	Alcorn	Control		
	t_0	Blount	Control		
	t_0	St. Clair	Control		
	t_1	Limestone	Study		
	t_1	Alcorn	Control		
	t_1	Blount	Control		
	t_1	St. Clair	Control		
	t_2	Limestone	Study		
	t_2	Alcorn	Control		
	t_2	Blount	Control		
	t_2	St. Clair	Control		
	t_3	Limestone	Study		
	t_3	Alcorn	Control		
	t_3	Blount	Control		
	t_3	St. Clair	Control		

Analysis Results for Farley, AL Site for All Cancers except Leukemia

Level 1 Link

Figure 1: RRs over Time for Farley, AL
All Cancers except Leukemia
Start Year - 1977

RRs with 95% Confidence Intervals by Time Period – Farley, AL
All Cancers except Leukemia
Start Year – 1977

Time Period	t_0	t_1	t_2
RR			
Lower Bound			
Upper Bound			

Level 2 Link

SMRs for Combined Study and Control Counties by Time Period – Farley, AL
All Cancers except Leukemia
Start Year - 1973

Time Period	County Type	Observed Deaths	Expected Deaths	SMR
t_0	Study			
t_0	Control			
t_1	Study			
t_1	Control			
t_2	Study			
t_2	Control			

Level 3 Link

RRs with 95% Confidence Intervals Time Period – Farley, AL
All Cancers except Leukemia
Start Year – 1973

Site	Time Period	County	County Type	Observed Deaths	Expected Deaths
Farley Study County 1	t_0	Houston	Study		
	t_0	Lee	Control		
	t_0	Calhoun	Control		
	t_0	Coffee	Control		
	t_1	Houston	Study		
	t_1	Lee	Control		
	t_1	Calhoun	Control		
	t_1	Coffee	Control		
	t_2	Houston	Study		
	t_2	Lee	Control		
	t_2	Calhoun	Control		
	t_2	Coffee	Control		
Farley Study County 2	t_0	Early	Study		
	t_0	Brooks	Control		
	t_0	Crisp	Control		
	t_0	Sumter	Control		
	t_1	Early	Study		
	t_1	Brooks	Control		
	t_1	Crisp	Control		
	t_1	Sumter	Control		
	t_2	Early	Study		
	t_2	Brooks	Control		
	t_2	Crisp	Control		
	t_2	Sumter	Control		