Web Appendix for:

Risk of leukemia mortality from exposure to ionizing radiation in U.S. nuclear workers: a pooled case-control study.

Robert D. Daniels[1*], Stephen Bertke[1], Kathleen M. Waters[1] and Mary K. Schubauer-Berigan[1]

[1]National Institute for Occupational Safety and Health (NIOSH); Division of Surveillance, Hazard Evaluations, and Field Studies (DSHEFS); Industrywide Studies Branch (IWSB); 4676 Columbia Parkway, Cincinnati, OH 45226

[*]Corresponding author; NIOSH, DSHEFS, IWSB, 4676 Columbia Parkway, Mailstop R-13, Cincinnati, OH 45226

Table 1. Characteristics of the base cohort assembled for case-control selection

			Main sites					
		All	Hanford	INL	LANL/Zia	PNS	SRS	ORNL
Subjects	N	105,245	23,177	33,473	12,296	9,657	12,585	14,057
Sex	male	85,726	16,672	27,802	10,343	9,619	10,868	10,422
	female	19,158	6,503	5,667	1,688	38	1,627	3,635
	unknown	361	2	4	265	0	90	0
Race	White	85,041	21,666	28,619	6,953	9,607	5,284	1,2912
	other	4,214	1,491	1,027	168	22	599	906
	unknown	15,991	20	3,827	5,175	28	6,702	239
Birth year	median	1936	1938	1942	1937	1926	1928	1937
	range	1884-1974	1887-1962	1884-1974	1885-1964	1889-1960	1892-1958	1891-1960
Employment	median hire year	1965	1967	1974	1967	1959	1953	1965
	median emp years	8.4	6.3	7.3	9.9	23.8	11.5	4.0
	period of eligibility		1951-1978	1949-1999	1951-1978[†]	1952-1977	1951-1974	1951-1978
Deaths								
	deceased	30,266	5,684	7,332	3,041	4,995	5,932	3,282
	cancer deaths	8,721	1,705	2,050	794	1,503	1,681	988
	leukemia deaths	369	58	90	46	48	78	49
	missing UCOD	423	55	176	37	39	67	49
Dose (mSv)[‡]								
cumulative	average	17.8	16.9	13.8	8.2	24.2	29.8	8.8
annual avg.	all years	1.8	1.8	1.7	0.9	3.5	2.5	0.8
	<1960	2.4	2.2	3.4	3.7	5.5	1.5	2.9
	1960-<1980	2.6	2.8	3.0	0.9	4.1	3.5	0.9
	≥1980	0.6	0.6	0.6	0.4	1.4	0.7	0.2

[*]Abbreviations: HAN (Hanford site); INL (Idaho National Laboratory); LANL (Los Alamos National Laboratory incl. Zia Company); ORNL (Oak Ridge National Laboratory); PNS (Portsmouth Naval Shipyard); SRS (Savannah River Site); UCOD (underlying cause of death).
[†]A small number of workers who were first employed after 1978 were included if they otherwise met the cohort criteria.
[‡] All doses reported in equivalent dose (mSv) to the whole-body from low-LET penetrating radiation based on site dosimetry records.

Table 2. Leukemia case distribution

	Chronic	Acute	Other	Unknown	Total
Lymphoid	74	18	1	9	102
Myeloid	52	139	0	1	192
Monocytic	0	11	0	1	12
Other	0	1	4	0	5
Unknown	1	35	1	21	58
Total:	127	201	9	32	369

Chronic Lymphocytic (CLL)

Indeterminate

Table 3. Characteristics of cases and controls

Variable		Cases	Controls	Total
Cases and controls	N	369	1476	1845
Sex (%)	Male	333 (90.2)	1,283 (86.9)	1,616 (87.6)
	Female	36 (9.8)	193 (13.11)	229 (12.40)
Race/ethnicity (%)	White non-Hispanic	301 (81.6)	1249 (84.6)	1,550 (84.1)
	Hispanic	12 (3.3)	19 (1.3)	31 (1.7)
	Other	13 (3.5)	31 (2.1)	44 (2.4)
	Unknown	43 (11.7)	177 (12.0)	220 (11.9)
Birth year (%)	≤ 1919	110 (29.8)	565 (38.3)	666 (36.1)
	1920-≤1927	124 (33.6)	437 (29.6)	572 (31.0)
	>1927	135 (36.6)	474 (32.1)	607 (32.9)
Hire year (%)	≤ 1952	117 (31.7)	549 (37.2)	668 (36.1)
	1953-≤ 1959	131 (35.5)	441 (29.9)	573 (31.0)
	>1959	121 (32.8)	486 (32.9)	609 (32.9)
Facility (%)	HAN	55 (14.9)	349 (23.6)	385 (20.9)
	INL	91 (24.7)	371 (25.1)	287 (15.6)
	LANL	48 (13.0)	116 (7.9)	212 (11.5)
	ORNL	49 (13.3)	165 (11.2)	678 (36.8)
	PNS	48 (13.0)	243 (16.5)	87 (4.7)
	SRS	78 (21.1)	232 (15.7)	196 (10.6)

[*]Abbreviations: HAN (Hanford site); INL (Idaho National Laboratory); LANL (Los Alamos National Laboratory incl. Zia Company); ORNL (Oak Ridge National Laboratory); PNS (Portsmouth Naval Shipyard); SRS (Savannah River Site);

Table 4. Summary of exposure information for cases and controls (two-year lag)

Variable	Statistic	Cases	Controls	Total
Subjects	n	369	1,476	1,845
Gamma (mGy)	mean	24.4	22.9	23.4
	median	3.3	2.8	2.9
	maximum	626.3	566.3	626.3
	exposed (%)	367 (99.5)	1,458 (98.8)	1,825 (98.9)
Tritium (mGy)	mean	0.2	0.2	0.2
	median	0.0	0.0	0.0
	maximum	28.3	85.1	85.1
	exposed (%)	66 (17.9)	227 (15.4)	293 (15.9)
WRX (mGy)	mean	2.6	3.3	3.2
	median	0.0	0.0	0.0
	maximum	15.4	28.6	28.6
	exposed (%)	175 (47.4)	728 (49.3)	903 (48.9)
Low-LET	Mean	27.3	26.3	26.5
(sum of Gamma,	Median	5.8	7.5	7.2
Tritium, and WRX)	maximum	633.8	574.0	633.8
	Exposed (%)	367 (99.5)	1,464 (99.2)	1,831 (99.2)
Neutron (mGy)	mean	0.4	0.0	0.0
	median	0.1	0.0	0.0
	maximum	4.9	6.9	6.9
	exposed (%)	52 (14.1)	185 (12.5)	237 (12.8)
Plutonium (mGy)	mean	2.0	0.1	0.1
	median	0.0	0.0	0.0
	maximum	49.1	20.9	49.1
	exposed (%)	31 (8.4)	99 (6.7)	130 (7.0)
Benzene scores	mean	0.8	2.1	1.8
	median	0.0	0.0	0.0
	maximum	61.0	283.9	283.9
	exposed (%)	69 (18.7)	291 (19.7)	360 (19.5)

*Ionizing radiation "dose" is defined as absorbed dose to red bone marrow.

Table 5. Univariate analysis of covariates

Variable[*]	Description	Cases (n=369)	Controls (n=1,476)	Total (n=1,845)	Hazard Ratio (95% CI)
Sex (%)	Male	333 (90.2)	1,283 (86.9)	1,616 (87.6)	1.0
	Female	36 (9.8)	193 (13.1)	229 (12.4)	0.72 (0.49, 1.04)
Race (%)	White non-Hispanic	344 (93.2)	1,426 (96.6)	1,770 (95.9)	1.0
	Other	25 (6.8)	50 (3.4)	75 (4.1)	2.13 (1.27, 3.52)
Birth year (%)	Birth year <1920	110 (29.8)	565 (38.3)	675 (36.6)	1.0
	Birth year 1920-1927	124 (33.6)	437 (29.6)	561 (30.4)	1.53 (1.14, 2.07)
	Birth year >1927	135 (36.6)	474 (32.1)	609 (33.0)	1.68 (1.20, 2.37)
Hire year (%)	Hire year <1953	117 (31.7)	549 (37.2)	666 (36.1	1.0
	Hire year 1953-1959	131 (35.5)	441 (29.9)	572 (31.0)	1.43 (1.07, 1.91)
	Hire year > 1959	121 (32.8)	486 (32.9)	607 (32.9)	1.20 (0.88, 1.62)
SES (%)	Professional	81 (22.0)	304 (20.6)	385 (20.9)	1.0
	Intermediate	50 (13.6)	237 (16.1)	287 (15.6)	0.79 (0.53, 1.17)
	Skilled non-manual	36 (9.8)	176 (11.9)	212 (11.5)	0.76 (0.49, 1.17)
	Skilled manual	140 (37.9)	538 (36.5)	678 (36.8)	0.98 (0.72, 1.34)
	Partly skilled	21 (5.7)	66 (4.5)	87 (4.7)	1.20 (0.68, 2.05)
	Unskilled	41 (11.1)	155 (10.5)	196 (10.6)	1.00 (0.65, 1.50)
Low-LET[†] dose distribution (%)	0-<1.0 mGy	95 (25.8)	353 (23.9)	448 (24.3)	1.0
	1-<10 mGy	123 (33.3)	503 (34.1)	626 (33.9)	0.90 (0.65, 1.23)
	10-<50 mGy	101 (27.4)	434 (29.4)	535 (29.0)	0.85 (0.61, 1.18)
	50-<100 mGy	24 (6.5)	77 (5.2)	101 (5.5)	1.14 (0.67, 1.88)
	≥100 mGy	26 (7.1)	109 (7.4)	135 (7.3)	0.87 (0.52, 1.42)
Max plutonium[†] urine bioassay results (%)	unmonitored	254 (68.8)	1,037 (70.3)	1,291 (70.0)	1.0
	0-<1.7 mBq·d^{-1}	86 (23.3)	340 (23.0)	426 (23.1)	1.04 0.78, 1.38)
	1.7-<17 mBq·d^{-1}	23 (6.2)	81 (5.5)	104 (5.6)	1.17 (0.70, 1.89)
	≥17 mBq·d^{-1}	6 (1.6)	18 (1.2)	24 (1.3)	1.36 (0.49, 3.26)
Benzene[†] (%)	Unexposed (score=0)	300 (81.3)	1,185 (80.3)	1,485 (80.5)	1.0
	Low 0-<median exposed	37 (10.3)	143 (9.7)	180 (9.8)	1.02 (0.69, 1.48)
	High > median exposed	32 (8.7)	148 (10.0)	180 (9.8)	0.85 (0.55, 1.26)

[*]Abbreviations: LET (linear energy transfer); SES (socioeconomic status).
[†]Exposure categories (low-LET, plutonium, and benzene) are under a 2-year lag.

<u>Alternate lag assumptions:</u> All models were examined under alternate exposure lag assumptions of 0-, 2-, 5-, 7-, and 10 years. CLL models also included exposure lags of 15-, 20, 25, and 30 years. The preferred exposure lag period was determined based on the lowest model deviance after adjustment for relevant cofactors.

Table 6. The effects of exposure lag on the excess relative risk of leukemia mortality from radiation dose

| Outcome: | Non-CLL (n=264) | | | AML (n=150) | | | CML (n=52) | | | CLL (n=74) | | |
| Adjust for: | race, sex, and hire date | | | birth date | | | race, sex, and hire date | | | race, sex, and birth date | | |
Lag (years)	ERR per 100 mGy	P-value	-2LL	ERR per 100 mGy	P-value	-2LL	ERR per 100 mGy	P-value	-2LL	ERR per 100 mGy	P-value	-2LL
0	0.08	0.568	840.95	0.22	0.320	474.93	0.26	0.429	158.15	-0.038	0.770	227.47
2	0.09	0.522	840.87	0.23	0.312	474.89	0.28	0.404	158.07	-0.038	0.770	227.47
5	0.09	0.529	840.88	0.23	0.322	474.94	0.29	0.398	158.05	-0.038	0.772	227.48
7	0.08	0.575	840.96	0.20	0.367	475.10	0.28	0.403	158.07	-0.037	0.783	227.48
10	0.06	0.697	841.13	0.16	0.471	475.40	0.24	0.458	158.22	-0.036	0.789	227.49
15										-0.026	0.850	225.16
20					Restricted to CLL models					-0.024	0.868	225.17
25										-0.029	0.841	225.16
30										-0.020	0.915	225.19

[*]Abbreviations: AML (acute myeloid leukemia); CML (chronic myeloid leukemia); CLL (chronic lymphocytic leukemia); ERR (excess relative risk); LL (log likelihood).

Time since exposure: Models were constructed following division of cumulative exposure (*d*) into time windows, in years, before the attained age of the case in the risk-set. A linear excess relative risk (ERR) model was used to examine risk in windows individually (Table 7). Simultaneous solutions to windows were obtained using log-linear models and results are reported as relative risk (RR) at 100 mGy [RR = exp(*d*)] (Table 8). Simultaneous solutions were attempted in ERR models but did not converge due to strong negative effects in the first window. Leukemia risks were assessed in windows of 0-<5, 5-<10, 10-<15, and 15+ years. Given its suspected long latency, CLL risk was further assessed in time periods of 15-<20, 20-<25, 25-<30 and 30+ years (ERR model only).

Table 7. Analysis of radiation and excess leukemia risk by exposure windows in years before the attained age of the case

Outcome: Adjust for:	Non-CLL (n=264) race, sex, and hire date			AML (n=150) birth date			CML (n=52) race, sex, and hire date			CLL (n=74) race, sex, and birth date		
Exposure Window (years)	ERR per 100 mGy	P-value	-2LL	ERR per 100 mGy	P-value	-2LL	ERR per 100 mGy	P-value	-2LL	ERR per 100 mGy	P-value	-2LL
0-<5	-0.26	0.786	841.20	0.46	0.800	475.85	-9.75	0.458	158.22	-1.10	0.850	227.52
5-<10	1.97	0.120	838.86	7.81	0.024	470.85	1.82	0.494	158.30	NC	NC	NC
10-<15	1.30	0.280	840.11	4.73	0.072	472.69	4.38	0.248	157.44	-2.61	0.133	225.30
15+ (15-<20 CLL)	0.04	0.280	840.11	0.11	0.605	475.65	0.20	0.523	158.36	-0.71	0.710	225.06
20-<25										0.19	0.851	225.16
25-<30				Restricted to CLL models						-0.39	0.545	224.83
30+										-0.02	0.915	225.19

[*]Abbreviations: AML (acute myeloid leukemia); CML (chronic myeloid leukemia); CLL (chronic lymphocytic leukemia); ERR (excess relative risk); LL (log likelihood); NC (not-calculable)

Table 8. Analysis of radiation and excess leukemia risk in exposure windows in years before the attained age of the case under a log-linear model

| Outcome: | Non-CLL (n=264) | | AML (n=150) | | CML (n=52) | | CLL (n=74) | |
| Adjust for: | race, sex, and hire date | | birth date | | race, sex, and hire date | | race, sex, and birth date | |
Exposure Window (years)	RR at 100 mGy	p-value	RR at 100 mGy	p-value	RR at 100 mGy	p-value	RR at 100 mGy	p-value
0-<5	0.12	0.171	0.09	0.192	0.00	0.272	1.09	0.987
5-<10	10.9	0.047	40.0	0.038	4.90	0.514	2.92	0.786
10-<15	0.80	0.777	1.12	0.904	1.58	0.792	0.01	0.143
15+	1.02	0.906	1.05	0.802	1.17	0.564	1.04	0.837

[*]Abbreviations: AML (acute myeloid leukemia); CML (chronic myeloid leukemia); CLL (chronic lymphocytic leukemia); LL (log likelihood); RR (relative risk);

High-dose worker effects: Models of non-CLL leukemia under the preferred exposure lag were determined using risk sets restricted to subjects who have lagged cumulative low-LET doses <100 mGy. The removal of cases exceeding 100 mGy also meant the removal of matched controls, regardless of cumulative dose. Similarly, the model of the best fit exposure window was restricted to persons in the lower 99% of the dose distribution (i.e., 1% trimming)

Table 9. Summary of final linear modeling results for low-LET radiation and leukemia mortality

Outcome	No. Cases[‡]	Adjusted for:	Best fit exposure lag ERR per 100 mGy			Best fit exposure window ERR per 100 mGy		
			Lag (years)	Full Model	Excl. >100 mGy	Window (years)	Full model	1% trim
All Leukemia	369	sex, race, hire year	5	0.02 (-0.13, 0.29)	0.42 (-0.23, 1.4)	5-10	1.1 (-0.47, 4.6)	2.9 (<-0.34, 9.4)
Non-CLL Leukemia[†]	264	sex, race, hire year	2	0.09 (-0.14, 0.51)	0.65 (-0.17, 1.9)	5-10	2.0 (-0.32, 6.8)	3.2 (-1.1, 11.0)
AML	150	birth cohort	2	0.23 (-0.14, 0.96)	0.60 (-0.36, 2.3)	5-10	7.8 (0.51, 27.0)	11.0 (0.017, 38.0)
CML	52	sex, race, hire year	5	0.29 (<0, 1.8)	1.4 (-0.48, 6.2)	10-15	4.4 (<0, 24.0)	10 (<0, 40.3)
CLL	74	sex, race, birth cohort	25	-0.03 (-0.15, 0.51)	0.43 (-0.13, 1.9)	25-30	-0.20 (NC, NC)	-0.125 (NC, NC)

[*]Abbreviations: AML (acute myeloid leukemia); CML (chronic myeloid leukemia); CLL (chronic lymphocytic leukemia); ERR (excess relative risk); NC (not calculable).
[†]Excluding leukemias of CLL and CLL-indeterminate subtypes
[‡]Number of cases in full models (i.e., there are fewer cases in restricted risk sets for trimmed models)