EPIDEMIOLOGY 168

Fall 1983

Examination I

October 6, 1983

Instructions:

1. Please do not write your name on this examination. Instead, please show:

   The third letter of your last name ____

   The last four digits of your social security number ________.

2. PLEASE:

   Write all answers and intermediate results in this booklet.

   Write LEGIBLY.

   Indicate clearly if you change your mind about an answer.

3. Read instructions for each question carefully. Some are true-false, some ask you to choose the <u>best</u> answer, some require that you give <u>support</u> for your answer.

4. Pace yourself so that you have time to attempt every question.

5. This examination is <u>closed</u> book. However, you may use:

   - a calculator
   - a dictionary (including foreign language and/or medical dictionary--a medical dictionary has been provided for your use).

6. When you have finished the examination, please sign your name on the signout sheet, under the pledge:

   "I have neither given nor received help from others in completing this examination."

7. Good luck. We hope you enjoy the examination and that you find it a valuable educational experience. Exams will be returned in Monday's lab.

10/4/83

The questions on this examination relate to the article "Childhood leukemias associated with fallout from nuclear testing", by Joseph L. Lyon, Melville R. Klauber, John W. Gardner, and King S. Udall (N Engl J Med 1979;300:397-402). A two-page excerpt consisting of the Introduction, Methods, Tables 1-4, and Figure 3 is attached at the end of the examination booklet.

(4 pts) 1. Which of the following statements best characterizes existing knowledge (according to the excerpt) about the effects of radiation on cancer risk? [Choose one best answer]

____ A. Radiation is known to be hazardous to health, but it is not established whether or not it can cause cancer.

____ B. It is known that acute high-level radiation exposure increases cancer risk, but the carcinogenic effects of low-level radiation have not been studied.

____ C. Studies of the association between radioactive fallout and cancer risk have yielded conflicting results.

____ D. Low-level radioactive fallout is a well-known carcinogenic exposure; the only issue is whether the U.S. Government should be held legally liable for cancers arising from nuclear tests between 1951-1958.

(5 pts) 2. Give a succinct (one-sentence) statement of the primary study question:

____

____

____

____

(4 pts) 3. Give one (1) reason why the authors chose to study childhood, rather than adult, cancer?

____

____

10/4/83

(8 pts) 4. Give two (2) reasons why the authors focused specifically on leukemia.

a. ____

____

b. ____

____

(3 pts) 5. The study population for this investigation is best characterized as a [Choose one answer]:

____ A. dynamic population

____ B. fixed cohort

(8 pts) 6. What are two (2) ways in which childhood leukemias developing in Utah might have been missed by the authors' study?

a. ____

b. ____

(7 pts) 7. Identify a deficiency in the information available to the investigators concerning time and location of nuclear fallout.

a. ____

____

b. Would the deficiency identified above have move likely caused a true association between fallout and leukemia to be: [Choose one of the following]

____ A. understated

____ B. overstated.

10/4/83

(6 pts) 8. Using the authors' classification system, how many person-years would a child born on January 1, 1941 (and growing up in Utah without cancer) have contributed to:

a. the low-exposure cohort? ______________

b. the high-exposure cohort? ______________

(4 pts) 9. Based on the data in Table 2, calculate the mortality rate for leukemia deaths in the <u>total state</u> for the <u>high-exposure cohort</u>: [Show your work]

(4 pts) 10. Give one (1) reason for preferring mortality rates based on person-years (e.g., as in Table 2) to cumulative mortality (e.g., percent died) for this study?

____

____

(4 pts) 11. Which of the following measures does the rate calculated in Question 9 most closely resemble? [Choose <u>one best</u> answer]:

____ A. Incidence density

____ B. Cumulative incidence

____ C. Prevalence

____ D. Attributable risk proportion

(4 pts) 12. Why does the rate calculated in Question 9 differ from the rate in Table 3 for the high-exposure cohort in Utah?

____

____

(6 pts) 13. Which of the following statements about the data in Table 3 is(are) TRUE and which is(are) FALSE? [Indicate TRUE or FALSE for <u>each</u> statement.]

TRUE FALSE

____ ____ a. The rates in the first row represent weighted averages of the rates in the second and third rows.

____ ____ b. The low-fallout counties have uniformly higher leukemia mortality than the high-fallout counties.

(4 pts) 14. In Table 4, the expected numbers of deaths used in calculating the SMRs were obtained by: [Choose <u>one best</u> answer]

____ A. applying US year and age-specific leukemia mortality rates to the person-years of risk in the high-exposure cohort;

____ B. applying low-exposure cohort age specific rates to the person-years at risk in the high exposure cohort;

____ C. applying age specific high-exposure cohort rates to the 1960 US white population

____ D. applying low-exposure cohort rates to the estimated 1975 Utah population.

(6 pts) 15. Which of the following statements concerning Table 4 is(are) TRUE and which is(are) FALSE? [Indicate TRUE or FALSE for each statement]

TRUE FALSE

____ ____ a. Though the SMR was estimated to be only 1.28, the data for the low-fallout counties are statistically compatible with a true SMR at least as large as that observed in the high-fallout counties.

____ ____ b. The fact that the SMR for the high-fallout counties (2.44) is statistically significant (P<.05) whereas that for the low-fallout counties (1.28) is not primarily reflects the differences in number of person-years (i.e., sample size) for the two regions.

(4 pts) 16. Comparison of the SMR's in Table 4 is: [Choose one best answer]

____ A. Valid because the same standard population has been used.

____ B. Technically invalid because the weightings are different.

____ C. Technically invalid because the age-specific mortality rates used to compute expected deaths should have been those of Utah rather than a subpopulation.

____ D. Valid because they are age-adjusted by the direct method.

(6 pts) 17. The high fallout counties were all rural in nature and the low fallout counties were heavily urban. Can the excess leukemia rates in high fallout counties be attributed to rural-urban differences in leukemia mortality rates? [Support your answer in one sentence.]

____

____

____

____

(9 pts) 18. Does this study present convincing evidence that exposure to low-level radioactive fallout increases leukemia risk in children under 15 years old? Support your answer in a brief statement making reference to Bradford Hill's criteria for causal inference? [Answer in 3-4 sentences; refer to three (3) relevant criteria of Bradford Hill.]

(4 pts) 19. If you were called as an expert witness to a commission assessing claims for alleged US Government liability for leukemia deaths to children in Utah, which of the following measures would be most appropriate: [Choose one measure from the following list for part a. and another measure for part b.]

FREE GIFT

CI	Cumulative incidence
SMR	Standardized mortality ratio
EF	Etiologic fraction (population attributable risk)
EF_1	Etiologic fraction in the exposed (attributable proportion)
IDD	Incidence density difference

EF_1 a. for evaluating a claim by the parents of a child who had died from leukemia in a high-fallout county during 1951-1958?

EF b. for evaluating a claim by the Utah state health department on behalf of all Utah families with a child dying from leukemia during 1951-1958?

10/4/83

CHILDHOOD LEUKEMIAS ASSOCIATED WITH FALLOUT FROM NUCLEAR TESTING

Joseph L. Lyon, M.D., M.P.H., Melville R. Klauber, Ph.D., John W. Gardner, M.D., and King S. Udall, M.D.

THE carcinogenic effects of ionizing radiation are well established,[1] but the invention of the atomic bomb produced a new source of exposure to ionizing radiation by the creation of long-lived radioactive isotopes. Although survivors of the Hiroshima and Nagasaki bombings have experienced excess mortality from leukemia and other cancers,[2-5] their exposure was primarily to acute high-level radiation, rather than radioactive fallout.[6] In only one report has fallout at sites remote from the nuclear blast been implicated as causing human cancer. This exposure occurred after a United States thermonuclear test in 1954. An excess of thyroid cancer, probably due to ingestion of ^{131}I produced by the blast, was found in a small group of exposed Marshallese natives.[7] Other studies relating human cancers to radioactive fallout have thus far been negative.[8-10]

Between January, 1951, and the end of October, 1958, at least 97 above-ground atomic devices were detonated in the Nevada desert at a site located approximately 160 km west of the Utah–Nevada border (the Nevada Test Site).[11] Fallout from at least 26 tests (amounting to over half the total kiloton yield) was carried by winds into Utah. Because of continuing concern about the carcinogenic effects of low-level radiation,[12,13] and the known exposure of a substantial portion of the Utah population to radioactive fallout, we examined cancer risk in Utah related to this exposure.

Methods

We chose to study cancers only in children under 15 years of age, because of their increased sensitivity to radiation carcinogenesis reported in other studies[6] and because of the lack of a suitable low-exposure comparison population over the age of 15 years among present Utah residents. Leukemias were studied as a separate category from other childhood neoplasms because of their high incidence in children, their known association with radiation exposure and their relatively short latency period after exposure.[14]

The available maps of fallout patterns related to each of the announced nuclear tests at the Nevada Test Site were obtained from the United States Defense Nuclear Agency and the Energy Research and Development Administration (now the Department of Energy). Table 1 shows the number of above-ground nuclear tests each year, with their combined kiloton yield, and the number of tests for which fallout maps were available. This listing includes only announced nuclear tests, and other tests may still be classified. Testing stopped after October, 1958, and was not resumed until September, 1961. Nuclear testing has continued at the Nevada Test Site since 1961, but has been conducted underground, including 10 cratering experiments. Eighteen of the underground tests have been announced as having vented into the atmosphere.[11] Available information from these 28 tests is also included in the lower part of Table 1.[11]

The above maps identified 26 nuclear tests during the 1951-1958 period that probably deposited radioactive fallout in the state of Utah. These are included in the upper right-hand portion of Table 1. We studied the fallout patterns from the maps of these 26 tests and identified 17 southern and eastern counties of Utah as "high-fallout counties." These counties are all rural in nature and contain about 10 per cent of the state population; racial composition is almost uniformly white. The remaining counties (90 per cent of the state population) are heavily urban and were defined as a low-exposure area.

All death certificates for all childhood neoplasms occurring in Utah residents from 1944 to 1975 were obtained from the State Registrar of Vital Statistics. All deaths for children under 15 years of age were identified, and those with cause of death attributed to cancer were abstracted. Cancers were divided into two categories: leukemias and all other childhood neoplasms. There were 357 (48 per cent) deaths from leukemias, and 386 (52 per cent) deaths from other cancers in this age group during this period.

The high-exposure cohort was defined as Utah residents under the age of 15 during 1951 through 1958. From 1944 to 1950 all children in the State under the age of 15 were included in the low-exposure cohort. Those born after 1958 were included in the low-exposure cohort. For example, a child born in 1945 would be included in the low-exposure cohort until the age of six (1951), and then moved to the high-exposure cohort until he reached the age of 15. Each cancer death was then assigned to the high-exposure or the low-exposure cohort.

Populations for the two cohorts were obtained by interpolation of the Utah populations from the 1940, 1950, 1960 and 1970 United States Census Reports and from an estimated 1975 population received from the Utah State Bureau of Vital Statistics. The annual populations for each year of age were summed according to the definitions of the high-exposure and low-exposure cohorts.

Age-specific mortality rates were calculated for the merged low-exposure periods (1944-1950 and 1959-1975) for each single year up to the age of 14 and then applied to the high-exposure cohort to derive the expected number of deaths. The observed deaths were divided by the expected to produce a standardized mortality ratio

We tested the differences between the high-exposure and low-exposure cohorts, using the Mantel–Haenszel summary chi-square method and summary odds ratios controlling for age in three five-year strata.[16] Approximate confidence intervals for the standardized mortality ratios were calculated with the method described by Miettinen.[17]

For each of the three cohorts, age and sex rates adjusted to the United States 1960 white population were calculated by the direct method, and their Standard Deviations were computed.[18] United States white leukemia mortality rates were obtained from United States Vital Statistics for the central years of each of the three periods (1948, 1955 and 1970) and adjusted for age and sex to the United States 1960 white population.

Four summary mortality rates for Utah, adjusted for age and sex, were computed by direct method (United States 1960 population as standard) for the period 1944-1975. These summary rates cover the intervals 1944-1950, 1951-1958, 1959-1967 and 1968-1975. These intervals were chosen to reflect the pre-fallout period as one interval, the fallout period as the second, the nine years after fallout as the third, and the final period after 1968 when leukemia mortality declined nationally as the fourth. United States white leukemia mortality rates for children up to 14 years of age were obtained for the central year of each of the above periods (1948, 1955, 1963 and 1972) and adjusted by the direct method to the 1960 United States white population.

Results

Table 1. Announced Above-Ground Nuclear Tests at the Nevada Test Site.*

YR	TOTAL TESTS		TESTS WITH MAPPED FALLOUT†				TESTS WITH FALLOUT IN UTAH‡			
	NO.	KILOTON YIELD	NO.	%	KILOTON YIELD	%	NO.	%	KILOTON YIELD	%
1951	12	112	2	17	2	2	1	8	1	1
1952	8	104	4	50	52	50	2	25	23	22
1953	11	252	9	82	21	85	5	46	130	52
1955	14	167	12	86	161	96	7	50	144	86
1956	1	(?)	0							
1957	25	343	17	68	322	94	9	36	233	65
1958	26	38	9	35	2	5	2	8	<1	<1
Totals	97	>1,016	53	55	560	55	26	27	521	51
1962	6	>101§	6	100	>101	100	2	33	>100	
1963	1	<20	0							
1964	3	<20	0							
1965	4	<80	0							
1966	3	<60	0							
1967	3	20–200	0							
1968	4	<60	0							
1969	1	20–200	0							
1970	2	<30	0				1‖	50	10	
1971	1	<20	0							
Totals	28	<851¶	6	21	>101		3	11	>110	

*As of June 30, 1976 (includes underground tests announced as having vented).

†All available fallout maps were included; percentages are of total tests.

‡Tests with fallout maps showing exposure in Utah; percentages are of total tests.

§There were 3 tests with "low" yield (<20 kilotons each) not included.

¶Most tests were listed as "low" (<20 kilotons) yield, making an accurate total kiloton yield impossible to determine.

‖Baneberry event.[11]

Table 3. Leukemia Mortality Rates per 100,000 Population of Both Sexes, Adjusted for Age and Sex,* According to High-Exposure and Low-Exposure Cohorts for Utah and Counties with High and Low Fallout.

AREA	LOW-EXPOSURE COHORT, 1944–50	HIGH-EXPOSURE COHORT, 1951–58	LOW-EXPOSURE COHORT, 1959–75
Utah	3.45 (2.50±4.40)†	4.23 (3.60±4.87)	3.11 (2.54±3.69)
High-fallout counties	2.10 (0.54±3.66)	4.39 (2.81±5.98)	1.96 (0.73±3.19)
Low-fallout counties	3.84 (2.70±4.97)	4.21 (3.51±4.90)	3.28 (2.64±3.92)

*Adjustment was by the direct method to U.S. 1960 white population. See Table 4 for statistical significance.

†± 2 SD of the rate.

Table 3A. Mortality Rates from Other Childhood Cancers per 100,000 Population of Both Sexes, Adjusted for Age and Sex,* According to High-Exposure and Low-Exposure Cohorts for Utah and Counties with High and Low Fallout.

AREA	LOW-EXPOSURE COHORT, 1944–50	HIGH-EXPOSURE COHORT, 1951–58	LOW-EXPOSURE COHORT, 1959–75
Utah	4.95 (3.80±6.11)†	4.29 (3.66±4.92)	3.08 (2.51±3.66)
High-fallout counties	6.36 (3.64±9.08)	3.07 (1.70±4.43)	3.05 (1.45±4.66)
Low-fallout counties	4.52 (3.27±5.78)	4.33 (3.64±5.01)	3.09 (2.47±3.71)

*Adjustment was by the direct method to U.S. 1960 white population. See Table 4 for statistical significance.

†±2 SD of the rate.

Table 2. Observed Deaths from Leukemia and Other Cancers and Person-Years in the High-Exposure and Low-Exposure Cohorts of Both Sexes According to Counties with High and Low Fallout.

AREA	LOW-EXPOSURE COHORT, 1944–1950			HIGH-EXPOSURE COHORT, 1951–1958			LOW-EXPOSURE COHORT, 1959–1975		
	LEUKEMIA DEATHS	DEATHS FROM OTHER CANCERS	PERSON-YR	LEUKEMIA DEATHS	DEATHS FROM OTHER CANCERS	PERSON-YR	LEUKEMIA DEATHS	DEATHS FROM OTHER CANCERS	PERSON-YR
Total state	51	71	1,426,174	184	194*	4,623,432	122	121	3,604,416
High-fallout counties	7	21	330,177	32	21	724,531	10	15	451,408
Low-fallout counties	44	50	1,095,997	152	165	3,898,901	112	106	3,153,008

*Includes 8 cases with county of residence unknown.

Table 4. Standardized Leukemia Mortality Ratios (SMR) for the High-Exposure Cohort as Compared to the Low-Exposure Cohort for Utah and High-Fallout and Low-Fallout Counties.

AREA	SEX	OBSERVED DEATHS*	EXPECTED DEATHS†	SMR‡	CONFIDENCE INTERVAL§ LOW	UPPER
Utah	M	89	57.8	1.54¶	1.00	2.37
	F	95	74.1	1.28	0.93	1.76
Totals		184	131.9	1.40‖	1.08	1.82
High-fallout counties	M	16	5.6	2.88	0.96	8.60
	F	16	7.5	2.12	0.63	7.11
Totals		32	13.1	2.44¶	1.18	5.03
Low-fallout counties	M	73	52.2	1.40	0.84	2.35
	F	79	66.7	1.19	0.87	1.63
Totals		152	118.9	1.28	0.97	1.69

*Observed deaths were those occurring in the high-exposure cohort.

†Expected deaths were generated by application of age-specific mortality rates to person-yr at risk in the high-exposure cohort.

‡Tested by the Mantel-Haenszel procedure controlled for age & sex.

§Approximate confidence intervals after Miettinen.[17]

¶P<0.05.

‖P<0.01.

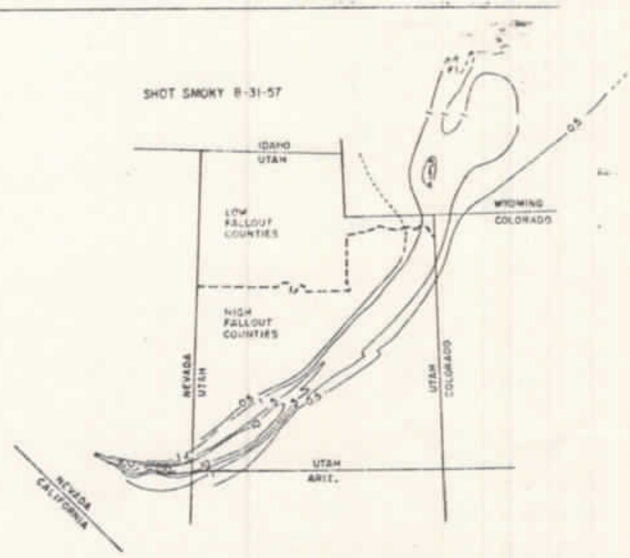

Figure 3. Fallout-Exposure Map (44 Kiloton Test, "Shot Smoky," August 31, 1957).

The contour lines indicate residual surface intensities in milli-Roentgens per hour at 12 hours after a test.

Examination I: Answer Guide

(4 pts) 1. C. Studies of the association between radioactive fallout and cancer risk have yielded conflicting results.

(5 pts) 2. Key elements in study question:
i. Low-level radiation or radioactive fallout;
ii. Cancer or leukemia risk or rates.
Examples:
"Does low-level ionizing radiation increase cancer risk?"
"Did radioactive fallout from nuclear testing increase cancer (childhood) (leukemia) rates (in Utah)?"

(4 pts) 3. Increased sensitivity to radiation carcinogenesis. Lack of a suitable low-exposure comparison with adults.

(8 pts) 4. Known association with radiation exposure; short latency period after exposure; relatively high incidence in children.

(3 pts) 5. A. dynamic population

(8 pts) 6. remission/cure, outmigration of cases, misdiagnosis or miscoding of death certificate, death from other cause with leukemia not mentioned on death certificate.

(7 pts) 7. a. Classified tests, incomplete data on reported tests, poor quality of fallout maps, venting of underground tests, incorrect information supplied by government.

b. All of the above would have more likely caused a true association between fallout and leukemia to be: A. understated.

(6 pts) 8. Person-years contributed by a child born on January 1, 1941 to:

a. the low-exposure cohort? 7 years.

b. the high-exposure cohort? 5 years.
[2 points for 6 years].

10/10/83

(4 pts) 9. 184 / 4,623,432 = 0.0000397 deaths/py
= 3.97 deaths per 100,000 py

[No points off for arithmetic error; 1 point off if units not correctly specified; 1 point off if total death rate rather than leukemia; 2 points off if misunderstanding of concept (e.g., divided by 7 years].

(4 pts) 10. Varying length of follow-up for different subjects; dynamic population, not fixed cohort;
[3 points for extended risk period for disease; this is debatable given the restriction to below age 15 and is not as compelling as the other reasons.]

(4 pts) 11. A. Incidence density.

(4 pts) 12. The rate in Table 3 is adjusted for age and sex.

(6 pts) 13. a. TRUE. A rates in the first row represent weighted averages of the rates in the second and third rows.

b. FALSE. The low-fallout counties [do not] have uniformly higher leukemia mortality than the high-fallout counties.

(4 pts) 14. B. applying low-exposure cohort age specific rates to the person-years at risk in the high exposure cohort.

(6 pts) 15. a. FALSE. The confidence interval for the SMR for the low-fallout counties is (0.97,1.69), giving the range of true SMR's that are statistically compatible with the observed data. 2.44 (the SMR observed in the high-fallout counties) is not within this range.

b. FALSE. The difference in statistical significance is clearly due to the fact that the association (as indexed by the SMR) is stronger in the low-fallout counties; the smaller P-value in the high-fallout counties could not be due to a larger number of person-years, since 90% of the population live in the low-fallout counties.

(4 pts) 16. B. Technically invalid because the weightings are different.

10/10/83

(6 pts) 17. Possible answers for full credit:

"No: within high-fallout (rural) counties, leukemia increased for the high-exposure cohort;"

"No: in both low-exposure cohorts, leukemia rates for the rural (high-fallout) counties were lower than for the urban (low-fallout) counties; in the high-exposure cohort, the leukemia rate was higher in the rural counties."

Point allocations for part credit:

Some relevant information specific to the study, but not based on the data = 3 points;

Some relevant information concerning the general issue of confounding but not specific to this study = 2 points;

Irrelevant answer (e.g., "rates were adjusted"), regardless of "yes" or "no", = 0 points.

(9 pts) 18. Relevant Bradford-Hill criteria [1 point for each of three mentioned, plus 1-2 more points if illustrated or supported; the position argued, i.e., "convincing" or "not convincing" was not a factor]:

Strength: SMR of 2.44 is quite strong considering that aggregate data are involved and measurement of exposure was problematic; (or could say that 2.44 is quite suggestive of etiologic relationship but is not convincing).

Consistency: not clearly present, because there is not a consistent body of studies to compare to;

Specificity: with regard to leukemia (no increase in mortality from other childhood cancers), with regard to counties of exposure (rates were elevated most for the high-fallout counties), with regard to exposure cohort (leukemia mortality rates rose and fell with exposure cohort).

Temporality: pretty good - exposure generally could be regarded as occurring sufficiently in advance of mortality.

Biological gradient (dose-response): some basis for this considering change from 1944-1950 low-exposure cohort to 1951-1958 high-exposure cohort with respect to low-fallout counties (low-dose) and high-fallout counties (high-dose)

[continued]

Plausibility: leukemia has known association with radiation.

Experiment: decline in leukemia after cessation of atmospheric testing.

Analogy: ?

(4 pts) 19. a. EF_1 for claim on behalf of an <u>exposed</u> child dying from leukemia.

b. EF for claim on behalf of all children (exposed and unexposed) dying from leukemia.

Summary of scores (N=40)

Quartiles: 74, 83.5, 88.5 (minimum 60, maximum 97).

Grade distribution: H (8), P+ (9), P (13), P- (7), L (3).

10/10/83