RADIATION RESEARCH **148**, 64–80 (1997)
0033-7587/97 $5.00
©1997 by Radiation Research Society.
All rights of reproduction in any form reserved.

A Mortality Study of Employees of the Nuclear Industry in Oak Ridge, Tennessee

E. L. Frome,* D. L. Cragle,† J. P. Watkins,† S. Wing,‡ C. M. Shy,‡ W. G. Tankersley† and C. M. West†

*Mathematical Sciences Section, Oak Ridge National Laboratory, P. O. Box 2008, Oak Ridge, Tennessee 37831-6367; †Center for Epidemiologic Research, Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee 37831-0117; and ‡Department of Epidemiology, University of North Carolina, Chapel Hill, North Carolina 27599-7400

Frome, E. L., Cragle, D. L., Watkins, J. P., Wing, S., Shy, C. M., Tankersley, W. G. and West, C. M. A Mortality Study of Employees of the Nuclear Industry in Oak Ridge, Tennessee. *Radiat. Res.* 148, 64–80 (1997).

An analysis was conducted of 27,982 deaths among 106,020 persons employed at four Federal nuclear plants in Oak Ridge, Tennessee, between 1943 and 1985. The main objectives were to extend the evaluation of the health effects of employment in the nuclear industry in Oak Ridge to include most workers who were omitted from earlier studies, to compare the mortality experience of workers among the facilities, to address methodological problems that occur when individuals employed at more than one facility are included in the analysis, and to conduct dose–response analyses for those individuals with potential exposure to external radiation. All-cause mortality and all-cancer mortality were in close agreement with national rates. The only notable excesses occurred for white males for lung cancer [standardized mortality ratio (SMR) = 1.18, 1,849 deaths] and nonmalignant respiratory disease (SMR = 1.12, 1,568 deaths). A more detailed analysis revealed substantial differences in death rates among workers at the Oak Ridge plants. Evaluation of internally adjusted log SMRs using Poisson regression showed that workers employed only at Tennessee Eastman Corporation or K-25 and at multiple facilities had higher death rates than similar workers employed only at X-10 or Y-12, and that the differences were primarily due to non-cancer causes. Analysis of selected cancer causes for white males indicated large differences among the workers at the different facilities for lung cancer, leukemia and other lymphatic cancer. Dose–response analyses for external penetrating radiation were limited to a subcohort of 28,347 white males employed at X-10 or Y-12. Their collective recorded dose equivalent was 376 Sv. There was a strong "healthy worker effect" in this subcohort—all-cause SMR = 0.80 (4,786 deaths) and all-cancer SMR = 0.87 (1,134 deaths). Variables included in the analyses were age, birth cohort, a measure of socioeconomic status, length of employment, internal radiation exposure potential and facility. For external radiation dose with a 10-year lag, the excess relative risk was 0.31 per Sv (95% CI = –0.16, 1.01) for all causes and 1.45 per Sv (95% CI = 0.15, 3.48) for all cancer. The estimated excess relative risk for leukemia was negative but imprecisely determined. A preliminary dose adjustment procedure was developed to compensate for missing dose but not other dosimetry errors. Results of the analyses using the adjusted doses suggest that the effect of missing dose is an upward bias in dose–response coefficients and test statistics. © 1997 by Radiation Research Society

INTRODUCTION

This report is the second phase of a study of the mortality of most workers employed at Federal nuclear plants in Oak Ridge, Tennessee, between 1943 and 1985. In the first phase the analysis was limited to white males who were employed only during the World War II era, when radiation monitoring programs were in the developmental stages (*1*). Workers were assigned a relative radiation exposure index based on job and department codes and were designated as "probably exposed" or "probably non-exposed." Additional factors considered in the analyses were socioeconomic status, place of employment, length of employment, birth year and period of follow-up. *The facility of employment is an important exposure-related variable since the type of radiation exposure was different at each plant.* Previous dose–response studies have been limited to subgroups of white males and have excluded individuals who were employed at more than one facility after 1947 (*2–4*). Results of a mortality study for white males employed only at X-10 with follow-up through 1984 have also been reported in combination with populations of workers employed at other Department of Energy (DOE)[1] facilities (*5*).

[1]Abbreviations used: AG, age group factor in main-effects model; *B*, birth cohort factor in main-effects model; CI, confidence interval; CEDR, Comprehensive Epidemiologic Data Resource; *df*, degrees of freedom; *D*, external radiation dose; DOE, Department of Energy; *EM*, eligible for monitoring and monitored; *EN*, eligible for monitoring and not monitored; ERR, excess relative risk; *F*, facility factor in main-effects model; GLIM, generalized linear interactive modeling; *IG*, internal radiation exposure group factor in main-effects model; K-25, Oak Ridge facility (also known as Oak Ridge Gaseous Diffusion Plant); *L*, length of employment factor main-effects model; L%, logarithmic percent; MULT, Oak Ridge workers employed at more than one facility; *NE*, not eligible for monitoring; *S*, factor that is surrogate for SES in main-effects model; SAS, Statistical Analysis System; SE, standard error;

(*Continued on next page*)

The main objectives of this second phase are to extend the evaluation of the health effects of employment in the nuclear industry in Oak Ridge to include Oak Ridge workers who were omitted from earlier studies, to compare the mortality experience of workers among the facilities, to carry out dose–response analyses for those individuals who were potentially exposed to external radiation, and to address methodological problems that occur when individuals employed at more than one facility are included in the analyses. These difficulties are due to the fact that the nature and extent of the radiation hazards and monitoring programs were different at each facility and varied over time. Three types of analyses were done for this report. First, cause-specific mortality for the Oak Ridge cohort was compared with the U.S. population by race and gender groups. Second, Poisson regression methods were used to evaluate the joint influence of several risk factors on cause-specific mortality, with special emphasis on facility as a surrogate for radiation exposure. Observed and expected deaths were cross-classified by levels of facility of employment, duration of employment, socioeconomic status and period of follow-up, and a main-effects model was used to describe the joint effects of the four risk factors. The third type of analysis evaluated the potential adverse health effects of low-level occupational exposure to ionizing radiation. These analyses were limited to white males ever employed at the X-10 or Y-12 facility. A uniform approach to assessment of radiation exposure (based on ordered exposure categories for internal and external radiation for each facility) was used, and cause-specific mortality patterns were evaluated for potential association with radiation exposure. Length of employment, socioeconomic status, birth year and age were considered as covariates. During the course of this study, it was determined that external radiation doses at X-10 and Y-12 were underestimated for some individuals—before 1957 at X-10 and before 1961 at Y-12, when not all workers were monitored. A preliminary procedure for computing adjusted doses was developed (*2, 3, 6*) and used to evaluate the bias that may result in dose–response coefficients as the result of this dose underestimation.

MATERIALS AND METHODS

Definition and Description of Cohort and Study Factors

On December 18, 1941, 11 days after the Japanese attack on Pearl Harbor, the decision was made to focus atomic energy research on the development of a weapon for the war. The Army was assigned the responsibility for this design and construction project of unprecedented size. The headquarters for the project was established in New York and named the Manhattan Engineer District. In September 1942 an isolated area in eastern Tennessee was selected as the site for the development of the full-scale production facilities for uranium separation and for the construction of an experimental nuclear pile that would be used to produce plutonium for research in the war effort. An air-cooled experimental pile, a chemical separation plant and supporting laboratories were constructed by the DuPont Co. at the X-10 site. This facility was officially named the Clinton Laboratories—later renamed Oak Ridge National Laboratory (ORNL)—and will be referred to in this report as the X-10 facility. By the summer of 1944 the primary goal of the war effort was achieved and the laboratory was transformed into the first well-rounded institution for nuclear research. A history of ORNL is available via the World-Wide Web (WWW)—see *The History of ORNL* at URL http://www.ornl.gov/swords/swords.html.

The major portion of the war effort in Oak Ridge was devoted to obtaining enriched uranium. Part of this work was done at the Y-12 site using an electromagnetic separation process. The Tennessee Eastman Corporation operated the facilities at the Y-12 site from June 1943 to May 1947 and is referred to as the TEC facility. In May of 1947 work at the Y-12 site changed from uranium enrichment to nuclear materials fabrication, and Union Carbide Corporation became the operating contractor. There was also a significant change in the work force, with only 6.7% of the workers staying on to work in the new operations. In this report Y-12 facility refers to the plant at the Y-12 site that began operation in May 1947 and continued until the end of this study.

The main purpose of the facility at the K-25 site was to produce enriched uranium via the gaseous diffusion process. In support of the enrichment process, the K-25 facility (later named the Oak Ridge Gaseous Diffusion Plant) also operated a plant that produced barrier material, ran a feed mill operation and conducted laboratory research.

A more detailed description of these facilities and the potential for occupational exposure to hazardous material is given by Watkins *et al.* (*2, 3*). A total of 118,588 workers are known to have been employed at one of the four nuclear facilities in Oak Ridge between 1943 and 1985. The study cohort consists of 106,020 workers who were employed for at least 30 days and whose records did not have any critical errors (e.g. gender, race, date of birth or employment dates were unknown).

Facility. Workers were initially categorized according to their facility of first employment—X-10, TEC, Y-12 or K-25. An individual who worked at more than one Oak Ridge facility was assigned to a fifth category, MULT, at the time of first entry into the second facility. In the dose–response analysis of white males ever employed at X-10 or Y-12 (X-10/Y-12), an individual could also enter follow-up as a multiple-facility worker if his entry into X-10 or Y-12 was preceded by employment at K-25 or TEC. Entry dates were adjusted to the appropriate lag (2, 10 or 20 years).

External radiation exposure. The nature and extent of the radiation hazard differed considerably among facilities and over time. A detailed description of the monitoring programs for external and internal radiation at each facility and results summarizing the exposure characteristics by race and gender are given by Watkins *et al.* (*2, 3*). Annual external dose estimates were obtained for each monitored worker at each Oak Ridge facility. Evaluation of these results (*2, 3*) showed that over 93% of the total recorded external dose was received by the 28,770 white males who had ever been employed at the X-10 or Y-12 sites, and that about 30% of these workers were employed at more than one Oak Ridge facility. Results from the facility comparison analyses (see Results) show that most of the workers at K-25 and TEC had higher death rates than those at X-10 and Y-12, so inclusion of K-25 and TEC workers would potentially lead to overestimation of baseline mortality rates and underestimation of radiation effects. For these reasons the dose–response analyses for external radiation were restricted to white males ever employed at X-10 or Y-12. The other race and gender groups at these facilities were not included since they would contribute little to the assessment of effects of low-level radiation and would unduly complicate the dose–response analyses.

(*Continued*)
SES, socioeconomic status; SMR, standardized mortality ratio; TEC, Oak Ridge facility consisting of workers employed at the Y-12 site when the plant was operated by Tennessee Eastman Corporation; X-10, Oak Ridge facility also known as Oak Ridge National Laboratory (ORNL); *XG*, external radiation exposure group factor in main-effects model; X-10/Y-12, subcohort of white males employed at X-10 or Y-12 between 1943 and 1984; Y-12, Oak Ridge facility at Y-12 site after May 1947.

To provide a preliminary evaluation of the potential effect of "missing dose" on radiation dose–response estimates, the doses for X-10 workers prior to 1957 and for Y-12 workers prior to 1961 were adjusted. The adjustment procedure increased dose estimates for some person-years under assumptions about the minimum detectable dose and the monitoring policies that were followed at X-10 and Y-12. Other sources of systematic and random measurement error are not addressed by this procedure. A detailed discussion of how these crude adjustments were made and summary results are provided by Watkins *et al.* (*2, 3, 6*).

Internal radiation exposure. There were considerable differences in the potential for internal radiation exposure and the monitoring policies that were followed at each facility. For this reason internal radiation exposure was represented as a factor (which is referred to as *IG*) with three levels: level 1: *eligible* for monitoring but *not monitored* (*EN*); level 2: *eligible* for monitoring and *monitored* (*EM*); and level 3: *not eligible* for monitoring (*NE*).

The precise definition of this variable was dependent on the facility and changed over time—see Watkins *et al.* for additional details (*2, 3*). Exposure analysis files that contained yearly values for external dose and the internal exposure indicator variable for each individual at each Oak Ridge facility were created (see Appendix). In the dose–response analyses radiation exposure is a time-dependent variable, and cumulative dose (with a lag) was used to form dose groups for external radiation. For internal exposure an individual was assigned to the appropriate category based on the sequential yearly values for the internal exposure indicator variable.

Socioeconomic status (*SES*). Each individual was categorized as either a non-monthly paid worker or a monthly paid worker based on the variable *Paycode* in the demographic analysis file (*2, 3, 7*). This variable is used as a surrogate for SES in the regression analyses with non-monthly workers as the referent category so that estimated coefficients represent relative risks for monthly workers.

Length of employment. Length of employment was calculated as the length of time between first hire and last termination at one of the Oak Ridge facilities. In all analyses, length of employment was categorized into two levels: level 1, 1 year or greater; or level 2, less than 1 year. The reference level used is 1 year or greater, so that estimated coefficients represent relative risks for "short-term" workers relative to "long-term" workers.

Birth year. Workers were divided into five categories according to year of birth: before 1900, 1900–1909, 1910–1919, 1920–1929 and 1930 or after.

Age. Age at risk is divided into 15 groups (15–, 20–, ..., 80–, 85+) starting at 15–19 and continuing through 85+. Age was alternately treated as a factor (*AG*) and as a continuous variate $A = (\text{age} - 52.5)/100$, where age is the interval midpoint.

Vital status. Vital status was ascertained primarily through the Social Security Administration. All cohort members with unknown vital status were allowed to contribute person-years up to the date at which they became "unknown." Underlying cause of death and non-underlying cancer causes were coded to the *Eighth Revision of the International Classification of Diseases, Adapted for Use in the United States* (ICDA-8)—see Watkins *et al.* (*2, 3*) for further details.

Data Reduction

The six analysis files described by Watkins *et al.* (*2, 3, 6*) contain demographic, vital status and annual exposure history data for each cohort member. Regression analyses are based on an analytical data structure that consists of a table of observed deaths, expected deaths (based on U.S. rates) and person-years at risk for each combination of levels of four or more risk factors for each cause of death. The facility comparison analysis focuses on the cause-specific mortality at the Oak Ridge facilities and includes length of employment, SES and calendar year. The resulting analytical data structure is a four-dimensional table of observed and expected deaths for each cause of death. The most complex analytical data structure is required for the dose–response analyses of the white males at X-10/Y-12. Each cause of death requires a seven-dimensional table of observed deaths, expected deaths and person-years at risk. The factors that define the table are socioeconomic status (denoted by *S* with 2 levels), length of employment (denoted by *L* with 2 levels), birth cohort (denoted by *B* with 5 levels), age at risk (denoted by *AG* with 15 levels), facility (denoted by *F* with 3 levels), internal exposure (denoted by *IG* with 3 levels) and external exposure (denoted by *XG* with 10 levels). The 10 external-dose categories were defined to be equally spaced on a logarithmic scale using cut points at 5, 10, 20, 40, 80, 160, 320 and 640 mSv. In the case of the last four (time-dependent) covariates, workers contribute person-years to all levels that they attain. An entry criterion of at least 365 days of follow-up was used for all analyses. Each observation in the analytical data structure consists of the index value of each of the stratifying factors, the observed deaths, the expected deaths, the person-years and the lagged average cumulative dose (see the Appendix).

Statistical Methods

Traditional SMR analysis. In this "external" analysis the mortality of Oak Ridge workers was compared with that of the general population of the U.S. using standardized mortality ratios (SMRs). SMRs were computed for race and gender groups for each cause-of-death category for which rates are provided by Monson (*8*). The statistical strength of the deviation of observed deaths from those expected based on U.S. rates is indicated using the Freeman-Tukey residual (*9*). Under the null hypothesis the Freeman-Tukey residuals are approximately normally distributed with mean zero and variance one.

Grouped data Poisson regression. The second and third approaches used Poisson regression methods (*10–13*) to describe the joint effect of several risk factors on cause-specific mortality. The general form of the regression function is

$$E(y_{ijk}) = n_{ijk}\lambda_{ijk} = n_{ijk}\lambda^0_{ijk}R(Z_j, X_k), \tag{1}$$

where λ_{ijk} represents the unknown mortality rate, y_{ijk} is the number of deaths, and n_{ijk} denotes the person-years at risk in the *ijk*th cell of an analytical data structure. The *i* subscript refers to age, the *j* subscript indicates the dimensions of the analytical data structure that correspond to factors of secondary interest (e.g. birth cohort, SES), and the *k* subscript indicates exposure-related covariates that are of primary interest, i.e. facility, internal exposure and external exposure. We use the "external/internal" model (see chapter 4 of ref. *13*) in which the baseline rates (λ^0_{ijk}) are proportional to known external standard rates (λ^*_i), and the y_{ijk} are treated as observed values of Poisson variates with expectation given by Eq. (1). For a given cell in the analytical data structure, the value of (λ^*_i) will also depend on birth cohort. This approach has two advantages. First, it is not necessary to provide a parametric description of the age component of the baseline rates, and second, the "intercept" terms (when all explanatory variables are at their reference level) provide estimates of the SMRs for the internal control group.

Facility comparison analysis. Mortality differences between workforces at these facilities reflect a combination of occupational and other factors. A preliminary analysis of death rates due to all causes with three explanatory variables (birth cohort, age at risk and facility) is presented by Frome *et al.* (*4*) to demonstrate the relationship between the two approaches that are used to "adjust" for age at risk. Results presented here are based on Eq. (1) with a multiplicative main-effects model using external age–cause-specific death rates (from U.S. vital statistics) to compute expected deaths. The resulting analytical data structure contains y_{jk}, the observed deaths, μ^*_{jk}, the expected deaths, and the level of each of the factors (which is equivalent to a covariate vector) SES, calendar period, length of employment and facility. The multiplicative main-effects model is expressed on a logarithmic scale as

$$\log(y_{jk}/\mu^*_{jk}) = F + S + L + t. \tag{2}$$

For convenience in describing results, the convention (see chapter 22 of ref. *14*) of dropping Greek letters (which represent the unknown parameters) and listing the explanatory variables that define the relative risk

function is used. This corresponds to standard GLIM notation (*15*) for a log-linear model in which F is the facility factor (5 levels), S is the socioeconomic status proxy *Paycode* (2 levels), L is the length of employment factor (2 levels), and t = (calendar year – 1965)/100, which represents a calendar period trend in the log of the SMR. The indicator variables for the factors F, S and L are coded so that the coefficients for the facilities represent the log of the SMR for each facility at the reference level of S and L when $t = 0$ (i.e. in 1965, which is the midpoint of follow-up). The coefficient for t describes the change in the log SMR over follow-up. The results of fitting the main-effects model for selected causes of death for white males are presented in tabular form.

Dose–response analysis. These analyses were based on Eq. (1) for white males with a multiplicative main-effects model for the variables A, B, S, L, IG and F. The effect of dose is represented with an exponential relative risk function or an additive excess relative risk (ERR) function. The main-effects model with exponential relative risk can be expressed as

$$\log(r_{ijk}) = A + B + S + L + IG + F + D, \qquad (3)$$

where $r_{ijk} = y_{ijk}/n_{ijk}\lambda^*_{ijk}$ and D is external dose in sieverts. In Eq. (3), B, S, L, IG and F are factors and A and D are continuous variates. Score test statistics (*16*) for external dose are presented for selected cause-of-death categories using all 10 dose groups. Additional summary results—parameter estimates, standard errors and likelihood ratio test statistics—are given for each cause-of-death category with the highest dose group deleted. The score test for the variable D in Eq. (3) is identical (*17*) to that obtained for the D variable in Eq. (4) below, and can be compared to the standard normal distribution to evaluate the strength of the dose–response relationship. These analyses were then repeated using adjusted doses. The score test and low-dose exponential relative risk are use as a screening procedure to identify cause-of-death categories that may show a strong association with dose. More detailed results are presented for several cause-of-death categories using a main-effects model with the additive ERR function to describe the dose–response relationship for external radiation; e.g.,

$$r_{ijk} = \exp(A + B + S + L + IG + F)(1 + D). \qquad (4)$$

The main-effects model provides an overall descriptive summary of the effects of each stratification variable on cause-specific mortality. Thus inclusion of these potential confounding variables (A, B, S, L) and exposure variables (F and IG) provides a broader context in which to evaluate the relative importance of the estimated effect of external radiation. A saturated model for the confounding variables AG, B, S and L was also considered and was found to have little effect on the dose parameter estimate. Detailed results are given for all cancer in the Appendix of Frome *et al.* (*4*). The score statistic for a linear dose term for the main-effects model and the saturated model (i.e. stratified analysis) were calculated routinely, and no important difference for any cause-of-death categories was found.

Most summary statistics (estimates and SEs) for relative risk parameters are expressed in log percent (L%) units; i.e., they are given in logarithmic units multiplied by 100—see ref. (*18*), Chapter 22 of ref. (*14*) and the Appendix of ref. (*4*). For the ERR estimates, likelihood-based confidence intervals are given—see refs. (*19, 20*). A detailed analysis for all-cancer mortality that uses the Akaike Information Criteria to contrast the effectiveness of several exponential and ERR models is presented by Frome *et al.* (*4*).

RESULTS

Traditional SMR Analysis

The results of the SMR analysis by race and gender groups for selected cause-of-death categories are given in Table I. For white males the all-cause SMR is 1.00 and the all-cancer SMR is 0.98. Death rates are elevated in the Oak Ridge cohort for lung cancer, diseases of the respiratory system and all external causes (note that large positive/negative values of the Freeman-Tukey residual indicate that observed deaths are higher/lower than expected after accounting for the number of deaths involved). Death rates are lower than those for U.S. white males for cancer of the buccal cavity, digestive system, bladder and thyroid. Death rates are also lower than expected for white males in Oak Ridge for diseases of the blood, nervous system, circulatory system, digestive system and genitourinary system. For non-white males the all-cause SMR is 0.96. The only elevated cancer SMR with a relatively large Freeman-Tukey residual is cancer of the large intestine. Death rates for diseases of the circulatory system and digestive system and liver cancer are lower than those for U.S. non-white males.

Facility Comparison Analyses

Table II presents results for white males for selected causes of death. Additional results for the other race/gender groups and a detailed description of the data reduction procedure are given by Frome *et al.* (*4*).[2] The observed deaths (Table II) are slightly less than those given in Table I since only individuals with at least 1 year of follow-up were included in these analyses. From Table II it is clear that monthly workers have much lower death rates than non-monthly workers. The all-cause death rates are lower by 41.5 L%; this corresponds to a relative risk of exp(–0.415) = 0.66 for monthly compared to non-monthly workers. The facility effects given in Table II are estimates of the SMRs (in L% units) for each facility at the middle of follow-up (1965–1969) for non-monthly long-term workers, and provide a direct comparison with the external referent population. These estimates are internally "adjusted" for SES, length of employment and calendar time, and for attained age through the use of the external rates. For example, for all-cause mortality for white males employed only at TEC, the facility effect is –5.9L%, and the estimated SMR is exp (–0.059) = 0.94. An estimate of the log relative risk with one facility as the referent facility is obtained as the difference between two estimates of the facility effect. Using the facility-effect estimates for all-cause mortality for white males (see Table II) with X-10 as the referent group, we obtain:

	X-10	TEC	Y-12	K-25	MULT
Effect difference (L%)	0.0	20.9	9.7	25.8	20.8
Relative risk	1.0	1.23	1.10	1.29	1.23

This *internal comparison* shows that white males employed only at TEC or K-25 and multiple-facility workers have higher death rates than similar workers employed only at X-10 or Y-12. The large value of the likelihood ratio test statistic in Table II—101.0, 4

[2]At URL: http://www.epm.ornl.gov/~frome/see Oak Ridge Mortality Study.

TABLE I
Summary Statistics for Mortality among Oak Ridge Workers 1942–1984 by Race and Gender for Selected Causes of Death

	Males						Females					
	White			Non-white			White			Non-white		
Cause of death (ICDA-8)[a]	SMR[b]	(Obs)	FTR[c]	SMR	(Obs)	FTR	SMR	(Obs)	FTR	SMR	(Obs)	FTR
All causes	1.00	(22,724)	–0.7	0.96	(1,121)	–1.4	0.89	(3,595)	–7.5	0.76	(542)	–6.8
All cancer	0.98	(4,679)	–1.1	0.98	(202)	–0.3	0.86	(1,124)	–5.1	0.78	(109)	–2.8
Buccal cavity (140–149)	0.79	(117)	–2.6	1.13	(9)	0.4	1.44	(26)	1.7	2.36	(5)	1.6
Digestive (150–159)	0.79	(1,041)	–8.0	0.98	(64)	–0.2	0.71	(202)	–5.4	0.64	(24)	–2.4
Esophagus (150)	0.82	(93)	–2.0	0.94	(12)	–0.1	1.23	(13)	0.8	0.60	(2)	–0.6
Stomach (151)	0.73	(176)	–4.5	0.72	(12)	–1.2	0.75	(26)	–1.6	0.58	(4)	–1.1
Large intestine (153)	0.81	(347)	–4.2	1.73	(23)	2.3	0.71	(89)	–3.4	0.73	(9)	–1.0
Rectum (154)	0.55	(78)	–6.1	0.91	(4)	–0.1	0.39	(11)	–3.8	0.90	(3)	–0.0
Liver (155–156)	0.78	(78)	–2.3	0.16	(1)	–2.7	0.53	(14)	–2.7	1.49	(5)	0.9
Pancreas (157)	0.95	(241)	–0.9	1.01	(11)	0.1	0.88	(46)	–0.9	0.14	(1)	–2.9
Respiratory (160–163)	1.16	(1,919)	6.4	0.97	(65)	–0.2	1.01	(181)	0.1	0.92	(13)	–0.2
Larynx (161)	0.88	(62)	–1.1	1.34	(5)	0.7	1.69	(7)	1.3	1.64	(1)	0.6
Lung (162–163)	1.18	(1,849)	7.0	0.94	(59)	–0.4	1.00	(172)	–0.0	0.92	(12)	–0.2
Bone (170)	1.19	(25)	0.9	1.15	(1)	0.3	0.89	(4)	–0.1	0.00	(0)	–0.8
Skin (172–173)	0.95	(80)	–0.4	1.70	(2)	0.8	1.17	(22)	0.8	1.28	(1)	0.4
Breast (174)	—	(—)	—	—	(—)	—	0.86	(263)	–2.6	0.55	(14)	–2.5
All genital organs (180–184)	—	(—)	—	—	(—)	—	0.87	(186)	–2.0	0.70	(23)	–2.0
Cervis uteri (180)	—	(—)	—	—	(—)	—	1.10	(70)	0.8	0.88	(13)	–0.4
Corpus uteri (181–182)	—	(—)	—	—	(—)	—	0.68	(27)	–2.3	0.66	(5)	–0.9
All uterus (180–182)	—	(—)	—	—	(—)	—	0.95	(106)	–0.5	0.80	(20)	–1.0
Other genital (183–184)	—	(—)	—	—	(—)	—	0.79	(80)	–2.2	0.38	(3)	–2.0
Prostate (185)	1.01	(319)	0.1	0.94	(20)	–0.2	—	(—)	—	—	(—)	—
Testes (186–187)	0.72	(18)	–1.4	0.00	(0)	–1.2	—	(—)	—	—	(—)	—
Bladder (188)	0.76	(105)	–3.0	0.98	(4)	0.1	0.76	(9)	–0.8	0.43	(1)	–1.0
Kidney (189)	0.92	(109)	–0.9	0.31	(1)	–1.3	0.95	(18)	–2.2	2.69	(4)	1.6
Eye (190)	0.99	(4)	0.1	0.00	(0)	–0.1	1.80	(2)	0.8	0.00	(0)	–0.0
Brain (191–192)	1.09	(151)	1.0	0.37	(1)	–1.0	0.80	(30)	–1.2	0.66	(1)	–0.2
Thyroid (193)	0.33	(3)	–2.4	0.00	(0)	–0.5	0.52	(2)	–0.9	0.00	(0)	–0.7
Lymphosarcoma and RCS (200)	0.91	(82)	–0.8	0.93	(2)	0.0	1.15	(25)	0.7	0.00	(0)	–1.4
Hodgkin's disease (201)	0.77	(40)	–1.7	0.62	(1)	–0.3	0.41	(5)	–2.3	1.43	(1)	0.5
Leukemia, aleukemia (204–207)	0.98	(180)	–0.2	1.11	(6)	0.3	0.82	(34)	–1.2	0.57	(2)	–0.7
Other lymphatic (202–203, 208)	0.84	(105)	–1.8	1.28	(7)	0.7	1.26	(41)	1.4	1.33	(5)	0.7
All lymphatic (200–209)	0.93	(420)	–1.6	1.10	(16)	0.4	1.00	(109)	0.1	0.87	(8)	–0.3
Benign neoplasms (210)	0.94	(60)	–0.5	2.01	(6)	1.5	0.87	(21)	–0.6	0.39	(2)	–1.5
Disease of blood (280–289)	0.52	(29)	–4.1	1.19	(5)	0.4	0.63	(10)	–1.5	0.69	(2)	–0.4
Nervous system (320–329)	0.70	(148)	–4.7	0.66	(8)	–1.2	0.37	(22)	–5.9	0.74	(5)	–0.6
Circulatory system (390–458)	0.95	(11,076)	–5.6	0.88	(438)	–2.8	0.84	(1,323)	–6.7	0.70	(235)	–6.1
Respiratory system (460–519)	1.12	(1,568)	4.2	0.81	(54)	–1.6	1.00	(193)	0.0	0.57	(16)	–2.5
Digestive system (520–577)	0.80	(865)	–6.9	0.73	(40)	–2.1	0.85	(178)	–2.2	0.52	(16)	–3.0
Genitourinary system (580–629)	0.83	(270)	–3.2	0.78	(26)	–1.3	0.64	(46)	–3.3	0.63	(17)	–2.1
External causes (800–998)	1.05	(2,140)	2.3	1.02	(171)	0.3	1.02	(281)	0.3	0.95	(34)	–0.2

[a]*Eighth Revision of the International Classification of Diseases, Adapted for Use in the United States.*
[b]Standardized mortality ratios = observed deaths/expected deaths. The expected deaths were computed using age–calendar year-specific rates for the U.S. population.
[c]Freeman-Tukey residuals = $\sqrt{\text{Obs}} + \sqrt{\text{Obs} + 1} - \sqrt{4 + \text{Exp} + 1}$ are approximately normally distributed with mean zero and variance one.

degrees of freedom (*df*)—indicates that the facility differences are not due to small numbers of deaths, i.e. unstable rates. Evaluation of the corresponding estimates for white females [see Frome *et al.* (*4*)] reveals a similar pattern.

Table II also shows the results of the main-effects analyses for selected cancer causes. Differences in death rate among the facilities are large enough and based on a sufficient number of deaths to yield large likelihood ratio test statistics for lung cancer (21.6, 4 *df*), leukemia (10.7, 4 *df*) and other lymphatic tissues (12.3, 4 *df*). The estimates of facility effect indicate that lung cancer is low at X-10 (–34.8L%), and that rates for other lymphatic tissue are low for X-10 (–92.8L%) and highest for Y-12 (71.9L%). The

TABLE II
Parameter Estimates for the Main-Effects Model[a] for Mortality from Selected Cancer Causes of Death among White Males (N = 67,197) Who Worked in Oak Ridge between 1943 and 1984

Cause of death (ICDA-8)	Observed number	Facilities[a] SMR	X-10	TEC	Y-12	K-25	MULT	LRT[b]	SES[c] (monthly)	Length of employment (<1 year)	Period trend[d] (percentage per year)
All causes	22,590	1.00	−26.8	−5.9	−17.1	−1.0	−6.0	101.0	−41.5 (2.9)[c]	19.2 (1.4)	0.49 (0.07)
Non-cancer (omit 140–209)	17,917	1.00	−29.2	−5.2	−20.5	0.0	−6.7	106.0	−42.5 (3.3)	20.0 (1.6)	0.48 (0.08)
Circulatory system (390–458)	11,043	0.95	−26.5	−7.5	−18.5	−1.8	−14.6	50.9	−34.4 (4.1)	9.9 (2.0)	0.59 (0.10)
Respiratory system (460–519)	1,565	1.12	−43.0	1.6	−29.4	6.6	6.3	24.4	−78.6 (13.6)	26.1 (5.3)	0.97 (0.28)
All external causes (800–998)	2,073	1.06	−33.7	−3.1	−24.1	−3.5	−1.9	18.5	−55.6 (9.8)	42.2 (4.6)	0.26 (0.21)
All cancer	4,673	0.99	−18.9	−8.80	−6.0	−5.2	−4.2	6.5	−38.1 (6.2)	16.3 (3.1)	0.58 (0.16)
Mouth and pharynx (140–149)	117	0.80	−32.7	−29.7	−161.2	−28.4	−3.3	6.9	—	31.7 (19.4)	0.50 (0.99)
Digestive (150–159)	1,038	0.79	−17.8	−33.6	31.7	−20.2	−36.4	5.2	−20.5 (12.1)	9.8 (6.5)	0.55 (0.32)
Esophagus (150)	93	0.83	−6.2	−30.9	−53.3	−3.3	−40.4	2.4	−97.9 (53.2)	26.6 (21.6)	−0.91 (1.08)
Stomach (151)	176	0.74	5.9	−23.9	−52.3	−22.0	−29.3	2.0	−88.2 (37.7)	−5.3 (15.9)	−0.22 (0.72)
Large intestine (153)	344	0.80	−14.5	−38.0	−40.5	−19.1	−34.7	3.1	−0.7 (19.0)	2.3 (11.4)	1.01 (0.60)
Rectum (154)	78	0.55	−88.0	−74.0	−23.0	−50.8	−89.8	2.6	20.6 (40.4)	12.4 (23.7)	−0.96 (1.12)
Liver (155–156)	78	0.78	−108.6	−59.2	−39.0	−51.2	−58.0	1.8	63.2 (36.4)	47.4 (24.0)	1.46 (1.14)
Pancreas (157)	241	0.95	8.0	−21.4	−2.0	−14.5	−22.9	1.9	−51.6 (27.3)	22.2 (13.6)	0.92 (0.73)
Larynx (161)	62	0.88	−4.5	−82.7	6.3	−0.4	−52.4	8.6	−207.1 (99.6)	59.6 (27.0)	−0.18 (1.35)
Lung (162–163)	1,848	1.19	−34.8	10.5	15.4	9.4	13.1	21.6	−62.3 (11.1)	21.7 (4.9)	0.85 (0.28)
Bone (170)	25	1.22	−80.5	−4.5	—	45.6	3.0	5.3	7.6 (77.8)	11.3 (41.4)	−2.51 (1.94)
Skin (172–173)	80	0.96	−3.7	−0.3	−31.6	−18.6	22.0	2.1	−18.8 (39.0)	−35.0 (25.6)	2.80 (1.29)
Prostate (185)	319	1.01	0.8	−8.8	1.0	−10.1	16.9	2.6	−21.5 (22.7)	17.1 (11.8)	−0.08 (0.67)
Testes (186–187)	18	0.75	−10.3	22.0	—	3.9	105.0	5.4	−74.8 (110.2)	−32.1 (49.0)	−0.46 (2.20)
Bladder (188)	105	0.76	−108.0	−9.0	−56.7	−47.0	−8.9	6.6	−21.5 (44.0)	9.9 (20.6)	−0.07 (1.05)
Kidney (189)	109	0.92	−41.7	−23.0	17.8	−21.3	−20.0	1.8	34.5 (31.3)	7.6 (20.6)	1.07 (1.08)
Brain, CNS (191–192)	51	1.10	15.4	−16.3	55.8	13.3	4.2	6.1	−43.9 (32.7)	20.2 (17.3)	−1.61 (0.79)
All lymphatic (200–209)	418	0.93	9.7	4.2	−4.2	−3.6	0.6	0.8	4.4 (16.9)	−19.3 (10.6)	−0.52 (0.50)
Lympho/reticulosarcoma (200)	82	0.92	−23.7	−14.8	50.3	20.1	−12.9	3.5	43.4 (33.6)	−35.0 (24.4)	1.15 (1.27)
Hodgkin's disease (201)	39	0.77	−13.4	−5.5	−32.9	−28.9	−57.1	1.0	34.6 (51.1)	−22.2 (34.6)	0.04 (1.59)
Leukemia (204–207)	180	0.99	61.7	4.8	−64.5	0.7	13.3	10.7	−39.7 (27.9)	−10.1 (15.9)	−0.46 (0.74)
Other lymphatic (202, 203, 208)	105	0.84	−92.8	8.2	71.9	−15.4	7.9	12.3	23.0 (34.3)	−27.0 (22.2)	−1.48 (1.16)

[a]The "facility" factor is used as the reference category so that the first five-parameter estimates (columns 4–8) are the natural logarithms of the SMRs in logarithmic percent (L%) units at the reference level of SES and length of employment at the midpoint (1965) of period of follow-up.

[b]Likelihood ratio test statistic is χ^2 (with 4 *df*) for the null hypothesis of no difference in the facility effects adjusted for SES, length of employment and period trend (values that exceed 9.49 are significant at 0.05 level).

[c]The reference category for SES is the non-monthly (compared to monthly) workers, and the reference level for length of employment is greater than 1 year. The parameter estimates for SES and length of employment are log relative risks in L% units. These estimates can be compared with the null value zero using the SES given in parentheses, or converted into estimates of relative risk.

[d]The period trend describes the change in the SMR (percentage per year) over the 40 years of follow-up.

leukemia estimate is lowest at Y-12 (−64.5L%) and is high for X-10 (61.7L%).

Dose–Response Analyses

Selected results for main-effects model using ERR. The marginal distribution (dose group by facility) of person years, observed and expected cancer deaths, and average dose is given in Table AI. The parameter estimates for the ERR main-effects model (see Eq. 4) with external rates and using unadjusted doses with a 10-year lag (2 years for leukemia) are given in Tables III and IV. *The referent group is non-monthly workers employed at least 1 year at the X-10 facility who were eligible but not monitored for internal radiation exposure and had zero external occupational dose.* The parameter estimates for the factor B (Tables III and IV) are estimates of the log SMR for the referent group for each birth cohort for each cause of death. The large negative values for all causes of death (Table III) indicate a strong "healthy worker" selection effect for the X-10 facility, and that the effect is strongest among workers born after 1930 [SMR = exp(−0.63) = 0.53]. Review of the estimates of birth cohort effect shows a similar pattern for diseases of the circulatory system and external causes of death. For all cancer causes, lower rates were observed primarily for those born after 1920 (see Table III). By contrast, the estimates of birth cohort effect for selected cancer causes in Table IV show a much different pattern. The estimates of birth cohort effect for those born before 1930 are large and

TABLE III
Parameter Estimates for Selected Causes of Death for the X-10/Y-12 Subcohort (N = 28,347) Using Main-Effects ERR Model with External Rates and Unadjusted Cumulative Dose with 10-Year Lag

	Term	All causes		All cancer		Circulatory system		External causes	
		Est	SE	Est	SE	Est	SE	Est	SE
A^a	(age – 52.5)/100	0.35	0.17	–0.27	0.38	–0.1	0.26	0.83	0.51
B^b	<1900	–28.8	6.2	–9.2	13.4	–19.5	8.7	–56.4	25.2
	1900–1909	–17.0	4.8	–4.3	10.4	–9.3	6.9	–20.2	16.1
	1910–1919	–20.9	4.5	–10.1	9.4	–20.2	6.5	–27.8	14.1
	1920–1929	–30.2	5.0	–25.0	10.3	–31.8	7.5	–18.9	14.5
	1930+	–63.1	7.8	–66.2	17.9	–71.3	14.4	–47.3	17.3
S^c	Non-monthly	0	—	0	—	0	—	0	—
	Monthly compared to non-monthly	–42.6	4.1	–41.4	8.3	–37.6	5.8	–55.5	12.82
L^c	At least 1 year	0	—	0	—	0	—	0	—
	Less than 1 year	9.9	4.3	11.3	9.1	1.3	6.3	24.9	12.3
$IG^{c,d}$	*EN*	0	—	0	—	0	—	0	—
	EM	–2.4	3.7	4.3	7.5	–5.3	5.3	–1.5	12.5
	NE	7.3	4.1	2.9	8.7	7.9	5.8	34.5	13.0
F^c	X-10	0	—	0	—	0	—	0	—
	Y-12 compared to X-10	12.4	4.2	15.3	8.7	10.8	6.2	12.2	12.3
	Multiple compared to X-10	8.4	3.8	5.9	7.8	3.1	5.4	8.5	12.4
D^e	Dose	0.31	—	1.45	—	0^f	—	0^f	—
	95% CI[g]	(0.16, 1.01)	—	(0.15, 3.48)	—	(<0, 0.86)	—	(<0, 1.99)	—

[a]This term describes (and adjusts for) any systematic age-related difference in the external rates (U.S. white males) and the study cohort in percentage per year units—see Eq. (3) and the Appendix of ref. (*4*) for further discussion.

[b]The estimates for each birth cohort are SMRs (in L% units) for the reference level of each of the other terms in the model, e.g., for the 1910–1919 cohort the estimated all-cause SMR = exp(–0.208) = 0.81. The reference group is nonmonthly workers employed at least 1 year at X-10 and who were eligible but not monitored for internal radiation exposure.

[c]For *S*, *L*, *IG* and *F*, the estimates are of relative risks in L% units; i.e., for all cancer the relative risk for monthly compared to non-monthly workers is exp(–0.414) = 0.66.

[d]Internal radiation; *EN*, eligible and not monitored; *EM*, eligible and monitored; *NE*, not eligible for monitoring.

[e]Dose response for the ERR per Sv (see Eq. 4) which is equivalent to percentage per 10 mSv (rem).

[f]Likelihood maximized at value that would lead to negative relative risk estimate.

[g]Likelihood ratio-based confidence interval for ERR.

positive for cancer of the prostate and leukemia, indicating that for the internal referent group these death rates are higher that those for U.S. white males.

The estimates of the effect of SES (see *S* in Tables III and IV) are large and negative, indicating that death rates are substantially lower for monthly workers than for non-monthly workers. For example, for all cancer the relative risk for monthly compared to non-monthly workers is exp(–0.419) = 0.66 with 95% CI of 0.56, 0.78. The SES effect is most pronounced for lung cancer, where the relative risk for monthly workers is 0.43 with 95% CI of 0.31, 0.59.

The log relative risk for all-cause mortality for short-term workers is 9.9L%, mostly due to higher rates for external causes. Differences in mortality rates among the three levels of the internal radiation risk group (*IG*) were unstable and in varying directions (see Tables III and IV). Likelihood ratio test statistics (not shown in the table) for the null hypothesis of no difference among the levels of this factor were all below the 95th percentile of the χ^2 distribution with 2 *df*.

There are differences in the death rates in the facility groups in the X-10/Y-12 subcohort. All-cause death rates for those employed only at Y-12 are 12.4L% higher than for those employed only at X-10, and those for multiple-facility workers are higher by 8.4L% (see Tables III and IV). These differences appear to be due primarily to higher lung cancer rates for the Y-12 workers (log relative risk = 46L%) and multiple-facility workers (log relative risk = 33L%). A notable exception occurs for leukemia, where the rates are substantially lower for the Y-12 (–121.4L%) and multiple-facility (–64.0L%) workers than for X-10 workers.

The last lines in Tables III and IV provide an estimate of and 95% CI for the ERR per Sv. The average lifetime dose for the X-10/Y-12 subcohort is about 10 mSv, so this coefficient can be used to compute the relative risk of the "average" worker in the subcohort of Oak Ridge workers with potential for exposure to external penetrating radiation. This estimate can be compared with the other estimates of the log relative risk parameters for each cause of death. Using all cancer as an example, the log relative risk for the average worker is about $100 \times \log(1 + 0.0145) = 1.44$L%. By contrast, the effect of being a non-monthly worker is 41.4L%, suggesting that SES factors are far more influential than external radiation exposure in determining cancer risk

TABLE IV
Parameter Estimates for Selected Cancer Causes of Death for the X-10/Y-12 Subcohort (N = 28,347) Using Main-Effects ERR Model with External Rates and Unadjusted Cumulative Dose with 10-Year Lag (2-Year Lag for Leukemia)

	Term	Digestive		Lung		Prostate		Leukemia	
		Est	SE	Est	SE	Est	SE	Est	SE
A^a	(age – 52.5)/100	2.50	0.83	–1.17	0.69	–1.78	1.68	–2.55	1.5
B^b	<1900	–64.7	27.7	–11.6	25.3	71.9	50.3	68.9	59.7
	1900–1909	–30.5	21.6	–6.9	18.2	27.5	45.0	85.3	44.8
	1910–1919	–17.7	19.3	–5.5	16.1	8.9	41.7	47.6	43.1
	1920–1929	–26.9	21.9	–36.4	17.4	54.6	43.2	39.2	45.7
	1930+	–34.8	41.4	–104.5	34.9	—	—	–105.1	82.4
S^c	Non-monthly	0	—	0	—	0	—	0	—
	Monthly compared to non-monthly	–21.7	16.2	–84.0	16.1	–18.2	30.3	–9.3	33.4
L^c	At least 1 year	0	—	0	—	0	—	0	—
	Less than 1 year	–9.6	18.9	19.7	15.5	37.1	34.1	8.4	39.9
$IG^{c,d}$	*EN*	0	—	0	—	0	—	0	—
	EM	–14.3	15.8	11.2	11.9	–15.3	29.1	20.0	36.2
	NE	–5.7	17.6	0.5	15.4	–42.0	32.1	3.3	39.2
F^c	X-10	0	—	0	—	0	—	0	—
	Y-12 compared to X-10	–14.2	18.4	46.0	14.6	–5.3	36.0	–113.9	48.2
	Multiple compared to X-10	–23.0	15.8	33.4	13.5	20.7	28.9	–64.4	35.0
D^e	Dose (10 mSv)	1.42	—	1.68	—	2.06	—	0[f]	—
	95% CI[g]	(<0, 6.79)	—	(0.03, 4.94)	—	(<0, 24.6)	—	(<0, 6.5)	—

[a]This term describes (and adjusts for) any systematic age-related difference in the external rates (U.S. white males) and the study cohort in percentage per year units—see Eq. (3) and the Appendix of ref. (*4*) for the discussion.

[b]The estimates for each birth cohort are SMRs (in L% units) for the reference level of each of the other terms in the model; e.g., for the 1910–1919 cohort the estimated lung cancer SMR = exp(–0.055) = 0.95. The reference group is non-monthly workers employed at least 1 year at X-10 and who were eligible but not monitored for internal radiation exposure.

[c]For *S*, *L*, *IG* and *F*, the estimates are of relative risks in L% units; i.e., for lung cancer the relative risk for monthly compared to non-monthly workers is exp(–0.84) = 0.43.

[d]Internal radiation: *EN*, eligible and not monitored; *EM*, eligible and monitored; *NE*, not eligible for monitoring.

[e]Dose response for the ERR per Sv (see Eq. 4) which is equivalent to percentage per 10 mSv (rem).

[f]Likelihood maximized at value that would lead to negative relative risk estimate.

[g]Likelihood ratio-based confidence interval for ERR.

in this group of workers. The estimated dose–response relationships are represented graphically in Figs. 1 and 2.

Results of the screening procedure for selected causes of death. Table V gives the unadjusted SMR (in percentage and L%), the value of the score test statistic based on all of the data, and the estimated dose–response coefficient based on the main-effects model with exponential relative risk using the "low-dose" data. In this low-dose analysis all cells in the analytical data structure in the highest (640 mSv+) dose group were omitted so that once an individual's cumulative dose exceeded 640 mSv he was censored. This choice was based on the results of the regression diagnostics and the fact that a radiation worker would be very unlikely to receive a cumulative lifetime dose above 640 mSv—see Figs. 4 and AII in Frome *et al.* (*4*). There are 41 cells with 220 person-years (total person-years is 603,365) and 3 cancer deaths in the highest dose group (Table AI). The regression diagnostics in the Appendix of ref. (*4*) (which are based on Eq. 3 using all data) suggest that these few cells with cumulative dose values that exceed 640 mSv have a large influence on the estimate of the dose–response coefficient for the exponential relative risk model. For the X-10/Y-12 subcohort about 0.1% of the workers exceeded 640 mSv. (It may be more appropriate to think of this as a low to medium dose analysis.)

The effect of the high-dose group is to decrease the trend estimate when the exponential model is used, since most of the 41 cells have no events and high leverage values. For all cancer causes the estimate obtained using the exponential relative risk model and all the data is lower than that obtained when cells for the highest dose group are omitted. The low-dose estimate (1.59 per Sv) is three times larger than the estimate using all the data (0.49 per Sv). Figure 1A shows the relative risk estimates for all cancer for each dose group (10-year lag). These estimates were obtained using the 10-level factor *XG* in the main-effects model and are therefore "adjusted" for factors *B*, *S*, *L*, *IG*, *F* and age through use of the external rates—see Appendix of ref. (*4*). Figure 1A shows that the exponential dose response is reasonable in the low-dose region, but that it does not provide a good description of the relationship between risk and dose over the range of doses in this study. Note that while the relative risk for the highest dose group is lower than that predicted from the exponential

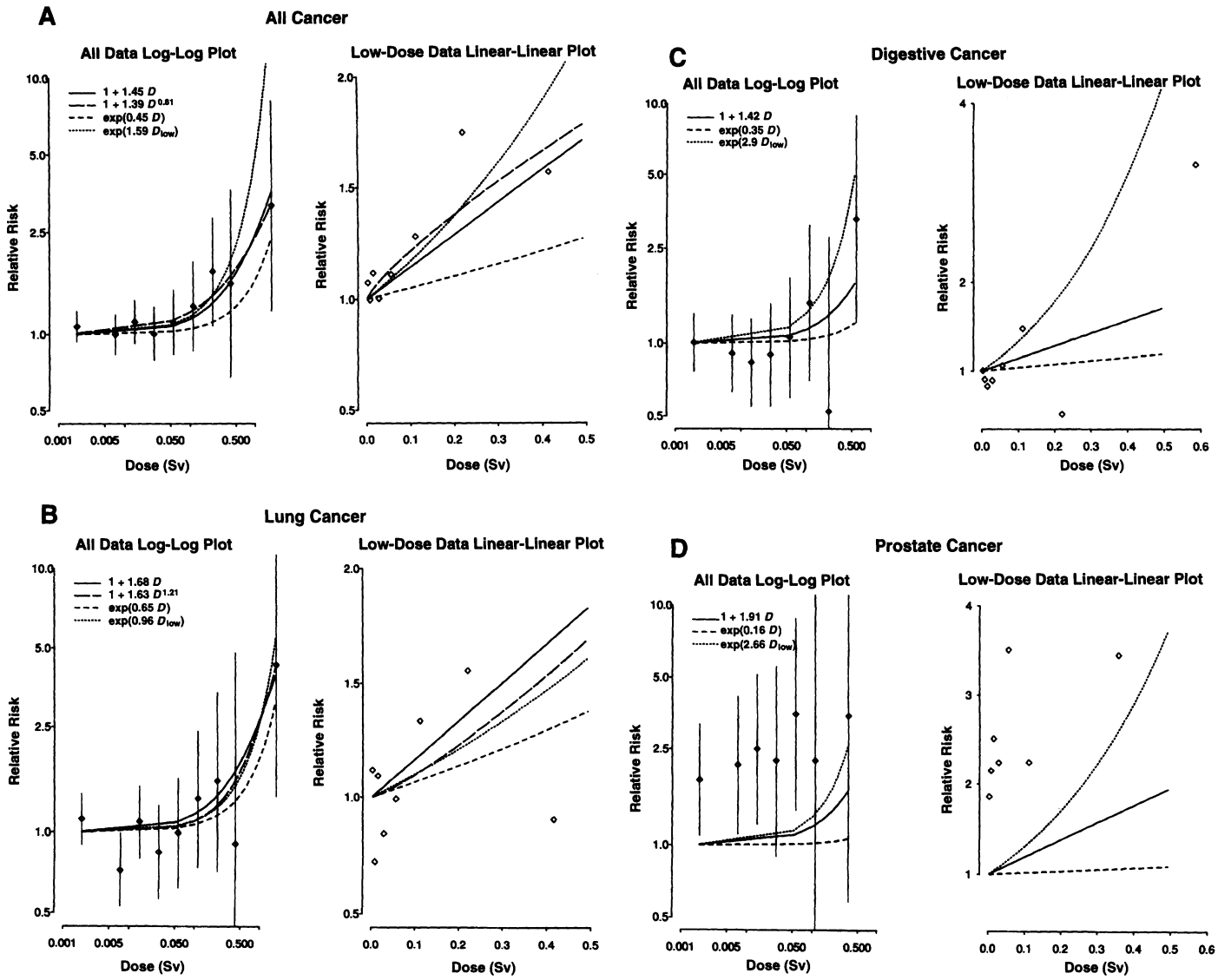

FIG. 1. Fitted dose–response functions for all cancer (panel A) and selected sites (panels B–D). Point estimates (◇) and 90% CIs (vertical lines) are shown for each dose group. D_{low} indicates that the high-dose group was not used in the fitting.

model fitted over the lower doses, it is roughly in line with the linear ERR model.

In Table V, the score test values in column 6 were based on all the data, and the likelihood ratio test values in column 9 were obtained with the cells in the highest dose category excluded. When all the data are used, the results for all cancer and lung cancer show the strongest association between external dose and deaths attributed to these causes (see column 6 of Table V). When the high-dose data are excluded, there is a decrease in strength of the association for all cancer, and a large decrease occurs for lung cancer (see column 9 of Table V). The opposite pattern is observed for emphysema and cancer of the digestive system. Estimates of the relative risk by dose group and those derived from the exponential relative risk and ERR models are shown graphically for lung cancer in Fig. 1B and for cancer of the digestive system in Fig. 1C. For cancer of the digestive system, there were no deaths in the highest dose group, so the relative risk was estimated for the last two groups combined. The dose values used for the graphical displays in Figs. 1 and 2 were the person-year weighted average of the doses associated with each stratum in the analytical data structure (see the Appendix) for a given dose category. For prostate cancer there were no deaths in the highest two dose categories, so the relative risk at the highest dose value in Fig. 1D is a combined estimate for the three highest dose groups. The dose–response coefficient for prostate cancer is positive, but the score test and likelihood ratio test do not show a strong association with dose (see Table V). Figure 1D shows that the risk is increased for workers with external doses greater than zero (recall that the internal referent group is based on cumulative lifetime occupational dose with a 10-year lag). An *ad hoc* analysis yields a relative risk estimate of 70.4L% (SE = 29.8) for

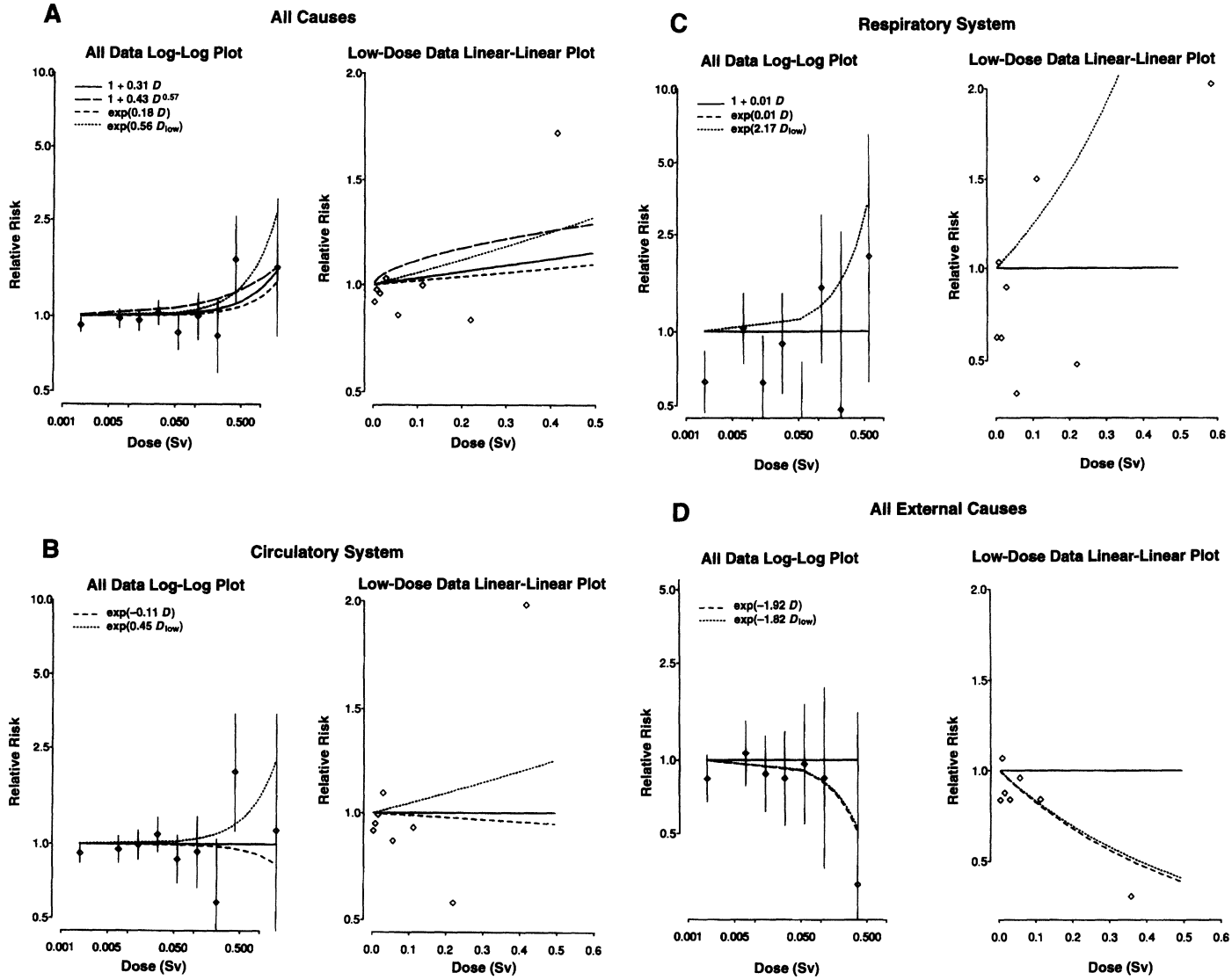

FIG. 2. Fitted dose–response functions for all causes (panel A) and selected causes (panels B–D). Point estimates (◇) and 90% CIs (vertical lines) are shown for each dose group. D_{low} indicates that the high-dose group was not used in the fitting.

those with any external radiation exposure compared to those with zero dose. This *ad hoc* result was obtained using the main-effects model with an indicator variable for external radiation exposure. The unadjusted SMR for the 10-year lag zero-dose group is –19.8L% (SE = 21.8), and for those with dose greater than zero the unadjusted SMR is 16.4L% (SE = 13.4).

Figure 2A shows relative risk as a function of dose for all-cause mortality. Figures 2B–2D show similar results for diseases of the circulatory system, non-malignant respiratory disease and all external causes of death. Dose–response coefficients, score test statistics and likelihood ratio test statistics are given in Table V.

Dose response using adjusted doses. To evaluate the effect of the dose adjustment procedure at each facility on the ERR dose–response coefficients, analyses were done using 2-, 10- and 20-year lag intervals for all cancer causes. The impact of facility differences on the dose adjustment procedures is of interest because external radiation monitoring differed in coverage and other respects at X-10 and Y-12 before 1961. Most dose adjustment at Y-12 resulted from the replacement of missing values for unmonitored workers with one of three assumed values, whereas at X-10 most workers were monitored for external radiation after 1947 and individual yearly doses for each worker were adjusted using the preliminary *ad hoc* procedure (*2*, *3*). The cumulative adjusted dose assignments for the 20-year lag are based almost entirely on annual doses obtained during the period when the adjustments were made.

The first row of section (a) in Table VI shows the estimated ERR per Sv for each lag using the unadjusted doses. The second line gives the value of the likelihood ratio test statistic comparing the estimated ERR to the assumption of zero slope. Lines three, four and five show the estimated ERRs for each facility separately, and the final line is the likelihood ratio test statistic for facility dif-

TABLE V
White Males Ever Employed at X-10 or Y-12 Plant between 1943 and 1984 (N = 28,347): Dose–Response Estimates for Multiplicative Relative Risk for Selected Causes of Death Based on Main-Effects Model Using Unadjusted Doses with 10-Year Lag (2-Year Lag for Leukemia)

	SMR[a]					Low-dose β[c,d]		
	Obs	Percentage	L%	SE	Score[b]	Est	SE	LRT[d]
All causes	4,786	79.84	–22.52	1.45	1.10	0.56	0.50	1.19
All cancer causes (140–209)	1,134	87.31	–13.57	2.97	2.46	1.59	0.83	3.23
Digestive (150–159)	258	76.10	–27.32	6.22	.53	2.90	1.46	3.12
Lung (162–163)	424	94.40	–5.76	4.83	2.91	0.97	1.39	0.43
Skin (172–173)	29	109.60	9.16	18.52	–0.42	–7.33	10.44	0.71
Prostate (185)	77	105.33	5.19	11.26	0.13	2.67	2.98	0.62
Kidney (189)	35	104.81	4.70	16.86	0.13	2.61	4.22	0.30
Brain (191–192)	46	108.50	8.16	14.73	–0.62	–15.97	14.15	2.13
Leukemia (204–207)	50	99.51	–0.49	14.12	–0.65	–3.93	6.83	0.42
Other lymphatic (202–203, 208)	34	92.16	–8.16	17.12	0.47	5.67	3.50	1.62
All lymphatic (200–209)	123	95.72	–4.38	8.96	0.08	1.71	2.48	0.42
Non-cancer causes	3,652	77.77	–25.14	1.65	–0.22	0.06	0.63	0.01
Circulatory system (390–458)	2,281	78.03	–24.81	2.09	–0.30	0.45	0.74	0.35
Arteriosclerotic disease (410–413)	1,658	78.85	–23.76	2.45	0.09	0.81	0.83	0.87
Cerebrovascular disease (430–438)	292	88.53	–12.18	5.85	–0.35	0.25	2.26	0.01
Respiratory (460–519)	275	78.41	–24.33	5.98	0.01	2.17	1.73	1.30
Emphysema (492)	73	95.97	–4.11	11.64	1.25	6.91	1.86	7.93
Digestive (420–577)	165	54.80	–60.15	7.78	–0.21	0.35	2.78	0.02
Ill-defined (790–799)	185	264.64	97.32	7.35	1.59	–2.77	3.06	0.98
All external causes (800–998)	485	75.40	–28.24	4.51	–0.69	–1.82	2.41	0.65
All accidents (800–949)	298	70.25	–35.31	5.79	–0.86	–6.27	4.66	2.54
Motor vehicle (810–827)	147	72.37	–32.33	8.24	–0.90	–19.53	11.38	5.23
Suicide (950–959)	146	93.81	–6.39	8.25	0.03	1.53	2.64	0.30

[a]Marginal SMRs for the X-10/Y-12 subcohort.
[b]Score test statistic using all data.
[c]Relative risk is represented as exp(βD), where D is cumulative dose in Sv, so β represents the change in the log relative risk per sievert (which is equivalent to L% per 10 mSv). Data in the highest dose group (greater than 640 mSv) were excluded.
[d]Likelihood ratio test statistic for null hypothesis β (values that exceed 3.84 are significant at 0.05 level).

ferences in slope compared to the assumption of a common slope. Section (b) gives the same results for adjusted doses. The estimated ERRs for all X-10 and Y-12 workers combined based on unadjusted doses are approximately 50% larger than those based on adjusted doses, and the largest ERR and likelihood ratio test values are observed for the 10-year lag.

The lower lines of each section of Table VI show that the change in ERR with increasing lag differs between X-10 workers and the other groups. Estimated ERRs at X-10 increase with increasing lag for both unadjusted and adjusted doses, while estimates for Y-12 and multiple-facility workers are positive for 2- and 10-year lags but negative for the 20-year lag, the period when the majority of Y-12 workers were not monitored for external radiation and adjusted annual doses for Y-12 workers took on one of three assigned values. The likelihood ratio test statistic for facility differences in ERR increases with increasing lag. The difference between ERRs based on adjusted and unadjusted doses is proportionately larger for Y-12 than for X-10 workers. Unadjusted values for multiple-facility workers are closest to zero and change the least with adjustment assumptions.

Further results—see Table IX of Frome *et al.* (*4*)—show the effect of using the adjusted doses on the score test values and the dose–response coefficients and likelihood ratio test statistics (for the low-dose data) for each cause-of-death category that was presented in Table V. The results suggest that the effect of missing dose is an overestimation of the strength of the dose–response association, and an upward bias in the dose–response coefficients.

Alternative representations of dose–response relationship. The results in Table V and Fig. 1 show that the restriction of results to the low-dose region has a stronger effect on β (using the exponential relative risk model) than does dose adjustment. The graphical results in Fig. 1A and regression diagnostics—see the Appendix of Frome *et al.* (*4*)—further indicate that the main-effects model with cumulative dose represented as a linear term in the exponent (see Eq. 3) does not provide an adequate description of the dose–response relationship over the entire range of doses. This dose–response model was used in some previous studies of the X-10-only subcohort of Oak Ridge workers (*21*, *22*). The results presented in Tables III and IV are based on the ERR (see Eq. 4), which has been used widely

TABLE VI
Estimates[a] of Linear Excess Relative Risk (per Sv) (and Likelihood Ratio Test Statistics) for All Cancer Causes by Facility and Lag Interval Using Unadjusted and Adjusted Cumulative Doses for the X-10/Y-12 Subcohort (N = 28,347)

Facility	Lag interval (years) 2	10	20
(a) Results using unadjusted doses			
Combined	0.79	1.45	1.27
LRT[b]	(2.42)	(5.30)	(1.05)
X-10	1.87	3.59	6.27
Y-12	1.23	1.75	–0.33
Multiple	0.16	0.36	–0.24
LRT[c]	(1.41)	(3.32)	(7.87)
(b) Results using adjusted doses			
Combined	0.48	0.93	0.84
LRT[b]	(1.53)	(3.65)	(0.62)
X-10	1.43	2.80	4.68
Y-12	0.72	0.91	–0.17
Multiple	0.00	0.21	–0.17
LRT[c]	(1.62)	(2.89)	(7.81)

[a]Using main-effects model with external rates for baseline risk.
[b]Likelihood ratio test for slope equal to zero has χ^2 distribution with 1 *df*.
[c]Likelihood ratio test for common slope, has χ^2 distribution with 2 *df*.

in radiation epidemiology (*5*, *23*, *24*). These two regression functions cannot be compared directly using likelihood ratio tests but can be compared indirectly using the values of the deviance and *df* for each model. Results of a more extensive analysis of all-cancer mortality that further explain and clarify the differences between the ERR and exponential relative risk functions are given in Table XI of ref. (*4*). These results further support the conclusion that the linear ERR model is a reasonable representation of the relationship of the relative risk to dose over the entire dose range. Figure 1 also presents the results of fitting the exponential and linear ERR function to lung, digestive and prostate cancer. Figure 2 presents similar results for all-cause mortality, diseases of the circulatory system, non-malignant respiratory disease and all external causes.

DISCUSSION

This study presents results of the combined analysis of all workers employed for at least 30 days at one or more of the four nuclear industry facilities in Oak Ridge, Tennessee. Numerical and graphical summaries based on Poisson regression methods that effectively describe the joint influence of several risk factors on cause-specific mortality were presented. The primary focus of this report was on the statistical aspects of this multiple-facility analysis. A detailed account of the nature and extent of the radiation hazards and monitoring programs is presented in companion reports (*2*, *3*).

All-cause mortality rates for male Oak Ridge workers over the entire follow-up period were similar to national rates (Table I; SMR = 1.00 and 0.96 for white and non-white males, respectively). This is unusual in occupational studies; workers in large industries typically show a "healthy worker effect" [see chapter 4 of ref. (*25*)]. One possible explanation is the large proportion of male workers who were hired at young ages during the war years—all-cause SMR = 1.11 (*1*)—and who worked for only a short time. These may have been transient workers not eligible for the draft due to poor health, and/or they may have been subjected to more hazardous working conditions because of the war effort. Notable excesses in mortality occurred only for white males for lung cancer and non-malignant respiratory disease, and notable deficits occurred for diseases of the digestive system (both malignant and non-malignant) and diseases of the circulatory system. For both white and non-white females, the SMRs based on U.S. rates are generally lower than one. This apparent negative bias may be due to underascertainment of vital status. It is known that females are more difficult to follow through some national data sources. If, however, failure to determine vital status is not differentially related to one or more risk factors of interest, then internal comparisons of disease rates are appropriate. This assumption is implicit in our presentation of results for the facility comparison analyses in Table III of Frome *et al.* (*4*).

A more detailed analysis based on facility, SES, length of employment and period trend revealed substantial differences in the death rates among workers at the four Oak Ridge sites for white males (see Table II). Estimates of the internally adjusted log SMRs (facility effect estimates) show that the TEC, K-25 and multiple-facility workers have higher death rates than similar workers employed only at X-10 or Y-12. The likelihood ratio test statistics indicate that the differences among the facilities are due primarily to non-cancer causes of death. However, further analysis of selected cancer causes (see likelihood ratio test statistics in Table II) shows that there are large differences among the four facilities for lung cancer, leukemia and other lymphatic cancer. Monthly paid workers had substantially lower mortality than weekly or hourly workers; this is in agreement with other studies showing socioeconomic differentials in mortality. For white males, paycode differentials in mortality were greatest for respiratory diseases in general and emphysema in particular. These observations are consistent with studies showing socioeconomic differentials in smoking. Excess mortality was also observed for workers employed for less than 1 year, and among white males the relative risk was greatest for external causes of death. Over calendar time SMRs tended to increase. For white males, all-cause SMRs increased at an average rate of 0.49L% per year, with values of 0.58L% for all cancer, 0.59L% for diseases of the circulatory system and 0.97L% for respiratory diseases. The magnitude of changes in SMRs with calendar time and differences in trends for causes of death of interest, including can-

cer and smoking-related diseases, suggests the importance of continued follow-up of these populations.

All dose–response analyses were restricted to the subcohort of white males employed at X-10 or Y-12 (see Materials and Methods). In previous studies with follow-up through 1984, the dose–response analyses were based on white males (N = 8,318, with 346 cancer deaths) employed only at X-10 (*21*, *22*). The addition of Y-12 and multiple-facility workers increased the cohort size to 28,347, with 1,038 cancer deaths. The methods used in this study differ in several ways from those in our previous analysis of the X-10 only group. First, there were 10 dose groups equally spaced on a logarithmic scale (instead of 8 equally spaced on a linear scale with a width of 20 mSv). Second, we used the person-year weighted average dose in each cell of the analytical data structure. In the previous analysis the median value of all of the person-years in all of the cells in the highest (greater than 120 mSv) dose category was used as the value of D for all cells in the highest dose group, and the interval midpoint was used for all of the other cells. Third, external rates and a multiplicative main-effects model were used to describe the baseline rates, and internal radiation monitoring status and facility factors were included in the model. In the previous dose–response analyses, external rates were not used, and the baseline rates were described with a parametric model—see the Appendix of ref. (*4*) for further discussion. Fourth, in previous dose–response analyses, deaths where cancer was a "contributing cause" were included. Only underlying causes of death were used in the current study. Fifth, all of the previous dose–response analyses were limited to the exponential relative risk model.

For all-cancer mortality with a 10-year lag, the estimated ERR for the X-10/Y-12 subcohort was 1.45 per Sv with a likelihood ratio-based 95% CI = (0.15, 3.48)—see Table III and Fig. 1A. Results were also presented for all cancers for 2- and 20-year lags by facility group. The results based on unadjusted doses for the X-10-only subcohort (see Table VI) are consistent with results in earlier studies, which showed a positive dose–response relationship for all cancers (*21*, *22*). The dissimilarity of dose–response associations between X-10, Y-12 and multiple-facility workers increases with the lag assumption, as indicated by both the slope estimate and the likelihood ratio test. A similar pattern is observed for adjusted doses. Results for the 20-year lag are based on doses received before 1965, the period when radiation monitoring was substantially more complete at X-10 than at Y-12—see Watkins *et al.* (*2*, *3*).

Most dose–response analyses were based on unadjusted doses with a 10-year lag. There was no evidence for an association between leukemia deaths (using a 2-year lag) and external radiation dose. Except for those born after 1930, leukemia mortality rates at X-10 were higher than those for U.S. white males and higher than those for similar Y-12 and multiple-facility workers (see Table IV). Prostate cancer rates were elevated relative to the U.S. rates and were about two times higher in workers with any amount of recorded external doses relative to those who received no occupational dose (see Fig. 1D). There was, however, no evidence for a smoothly increasing dose response for prostate cancer. Two studies of UK workers have reported statistical associations between radiation dose and mortality from cancer of the prostate (*26*, *27*). Cardis and colleagues (*24*), however, note that more recent studies indicate that the association with external dose was largely a result of correlation between external radiation and radionuclide contamination.

The only specific cancer for which there was evidence for a positive association with external radiation was lung cancer (see Tables IV and V and Fig. 1B). There were two lung cancers in the highest dose group, and exclusion of high-dose data results in a likelihood ratio test statistic of 0.43 for the multiplicative dose–response model. The estimate of the lung cancer ERR per Sv is 1.68 with a likelihood ratio-based 95% CI of 0.03, 4.94. Results in Table IV show that there was a strong SES effect, that baseline rates were higher for Y-12 and multiple-facility workers, and that the relative risk for workers monitored for internal exposure was slightly elevated. Information on cigarette smoking for this cohort is not available for analysis, and residual confounding by cigarette smoking patterns cannot be ruled out. Such confounding could bias dose–response estimates in either direction. There was no evidence for an association between diseases of the circulatory system or non-malignant respiratory disease and external radiation (see Table V and Figs. 2B and 2C). Note, however, that the largest likelihood ratio test statistic in Table V occurred for emphysema for the low-dose data (there were two deaths in the 320–640-mSv dose group with 0.16 expected based on U.S. rates).

Another important issue that has not been considered previously for this cohort is the "missing dose" that may have occurred as the result of recording a zero for below-detectable doses, especially for frequent (weekly) film badge readings at X-10. The results presented here are based on a preliminary dose adjustment procedure that was derived from a small sample of hard-copy X-10 personnel dose records (*2*, *3*, *6*). The sample was needed because daily and weekly radiation monitoring data prior to 1957 are not available in electronic form. *Future studies that include X-10 workers should use all available dosimetry data to deal with the uncertainty* (*systematic bias and random measurement error*) *in these data* (*28–32*). Our preliminary dose adjustment method does not consider other sources of systematic (e.g. neutron exposures) and random measurement error, nor did we consider the effect of measurement error on other covariates (internal exposures, SES) used in the analyses. Results based on adjusted doses are consistent with earlier studies, but suggest that the effect of missing dose was to introduce an upward bias in the dose–response coefficient and the score test statistics. Differences in measurement of external radiation at X-10 and Y-12 are relevant to the results reported in Table VI, which show consistently increasing dose coefficients for longer lags only at X-10.

The lag-20 coefficients are based entirely on exposure measurements made before 1965. For most of those years, less than one-quarter of Y-12 workers routinely wore external dosimeters, while the proportion for white male X-10 workers after 1946 was much higher (*30*). If there were an association between radiation exposures and cancer mortality during this period, it would be difficult to detect if few workers were monitored. In addition, recorded external exposures were higher at X-10 than at Y-12 during this period, resulting in a less skewed dose distribution upon which to base the dose–response estimates.

The factor *IG* was included as a crude indicator of occupational hazard associated with internal radiation monitoring status in all dose–response analyses. The results for this factor are never impressive and no doubt mix selection factors (including facility selection) with any effect of heterogeneous exposures. It is likely that these estimates are affected by measurement error since the accuracy and completeness of internal exposure data vary considerably by facility and over time—see Watkins *et al.* (*2*, *3*). The *EM* coefficient for lung cancer is positive and may reflect the contribution of Y-12 workers to this category (*33*). The coefficient for circulatory diseases is negative, suggesting that the positive *EM* coefficient for lung cancer is not merely a smoking-related phenomenon. The *NE* group has a large coefficient for external causes, which has been interpreted in other places as an SES effect. This is noteworthy because it is adjusted for paycode, facility and cohort.

In all dose–response analyses the potential biases associated with time-related factors and time-dependent exposures were dealt with through the use of an internal control group based on birth cohort, age at risk and length of employment. Different approaches to dealing with time-dependent variables are possible—see e.g. refs. (*13*, *25*)—and alternative approaches to dealing with these and other variables in mortality studies of nuclear industry workers have been presented (*5*, *27*, *34–39*).

In the most recent combined analyses of the data for workers in several countries exposed to low-level external radiation, Cardis *et al.* (*24*, *40*) present an excellent discussion of the importance of and difficulties encountered in studies of occupational effects of external radiation. The subgroup of workers from Oak Ridge who are in these combined studies are referred to as the ORNL subpopulation and correspond to X-10-only workers in this report. Their estimates of ERR per Sv for the ORNL subpopulation for all cancer excluding leukemia is 1.66 with a 90% CI of 0.04, 4.4 and for leukemia excluding CLL is –1.06 with a 90% CI of <0, 4.8—see Table V in ref. (*24*). Their results are consistent with the results presented here for the larger X-10/Y-12 subcohort of Oak Ridge workers. Cardis *et al.* [Table IV of ref. (*24*)] give estimates of ERR per Sv for all cancer for their combined data of –0.02 with a 90% CI of –0.34, 0.35; for leukemia the estimate is 1.55 with a 90% CI of –0.21, 4.7.

A recent high-dose study by Pierce *et al.* (*41*) presented risk estimates based on mortality in the atomic bomb survivors through 1990 (see Table AI of ref. *41*). Their excess relative risk estimates for all cancers (0.37 per Sv with a 90% CI of 0.31, 0.44) and lung cancer (0.42 per Sv with a 90% CI of 0.24, 0.63) are compatible with those derived here. Failure of this study to detect a significant dose response for leukemia may be due to a lack of power, confounding or measurement error. Another possibility is the presence of an unidentified toxic chemical that is present only at X-10 (e.g. some type of solvent) that is independent of, or negatively correlated with, external dose, and causes leukemia. This would also be a possible explanation of the increase in leukemia risk at X-10 relative to U.S. rates and other Oak Ridge facilities. The combined risk estimates derived from the present study are generally comparable to the positive dose–response estimates in Pierce *et al.* (*41*) for those categories where there were larger numbers of deaths. However, this study also suggests that there are differences in dose response between worker cohorts in the same location followed over about the same period, and that these differences are associated with measurement issues. Specifically, dose–response associations are stronger for X-10 workers, the population with more complete external radiation monitoring. Differences in dose response between X-10 and other workers are larger under longer latency assumptions that depend more on exposure classification based on radiation data from that historical period when monitoring differences between populations were greatest. This observation suggests that investigations of external radiation effects in combined-facility studies should be sensitive to differences in other exposures and in radiation measurement characteristics between the cohorts.

APPENDIX

The analysis files (which are SAS data sets) at the top of Fig. A1 were the starting point for all results in this report. These four analysis files and two additional files that contain adjusted doses for X-10 and Y-12 are available through CEDR (*7*) at URL http://cedr.lbl.gov/CEDRhomepage.html. A detailed description of the data collection and validation procedures, as well as tabular and graphical summaries of the resulting database, are presented in companion reports—see Watkins *et al.* (*2*, *3*, *6*). The facility comparison results presented in Table II were obtained using data derived from the demographic analysis file. The dose–response results were restricted to white males employed at either X-10 or Y-12 and use the yearly external and internal radiation exposure data contained in the three additional analysis files shown at the top of Fig. A1. Several steps were required to generate the analytical data structure, which contains a seven-dimensional table for each cause of death. Each of the 4,230 cells contains the index values for each of the factors, the person-years, the average dose, the observed deaths and the expected deaths for each cause-of-death category. The analytical data structure used to obtain the results in Tables III–V is also available through CEDR.

The marginal distribution of person-years by facility and dose group for X-10/Y-12 workers (white males) with a 10-year lag is given in Table AI. Line 3 of Table AI shows the marginal average dose, i.e. the person-year weighted average of all the average doses from each cell in the full table. In most dose groups the marginal average dose was slightly less than the midpoint of the interval used to define the category. The dose distribution for Y-12 workers differed considerably from that of the other two groups. The person-years in the X-10-only

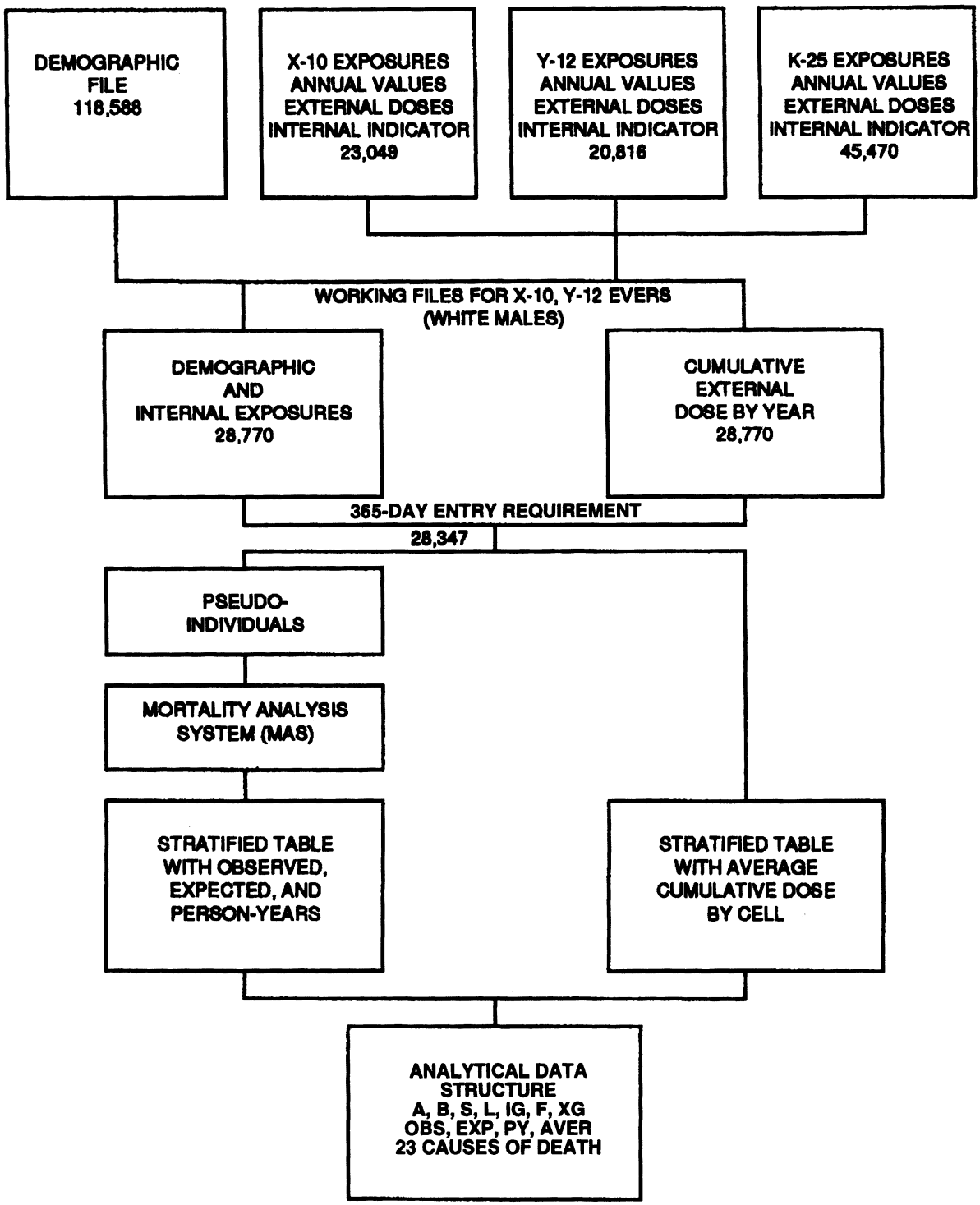

FIG. A1. Procedure used to generate the analytical data structure.

category is greater than reported in previous studies (*21*, *22*) since individuals who were initially employed at X-10 and then at another Oak Ridge facility contributed person-years to the appropriate dose groups in the X-10-only category until 10 years (the lag) after the date at which each became a multiple-facility worker. Table AI also shows the marginal distribution of observed and expected deaths (using U.S. rates) by facility and dose groups for all cancer deaths, and the marginal total for each dose group. These unadjusted SMRs indicate that mortality rates for all cancer causes are less than those for U.S. white males. To adjust for this selection effect, Eq. (3) with $D = 0$ was used. The adjusted SMRs are given in Table AI.

A detailed outline of the steps in the data analysis process is given in the Appendix of an ORNL report (*4*) available via the WWW at URL http://www.epm.ornl.gov/~frome/. The 10-year lag all-cancer data, a GLIM program to compute Table AI and an AMFIT (*20*) program that uses these data to fit the ERR model are also provided.

TABLE AI
Summary Results for White Males Ever Employed at X-10 or Y-12 by Dose Group Using 10-Year Lag

		Dose category (mSv)										
Interval		0	01–5	5–10	10–20	20–40	40–80	80–160	160–320	320–640	640+	
Midpoint		0	2.5	7.5	15	30	60	120	240	480	—	
Average		0	1.9	7.2	14.2	27.8	55.2	110.8	219.6	414.8	1773.8	
Facility		Person years										Total
X-10		140,426	57,666	17,220	18,288	12,255	6,258	3,271	1,681	571	89	257,726
Y-12		125,574	35,718	12,504	8,661	4,699	1,233	239	17	0	39	188,684
MULT		89,456	31,798	13,420	9,199	6,046	3,997	1,888	872	188	91	156,955
Total		355,457	125,182	43,144	36,148	23,000	11,488	5,398	2,570	759	220	603,365
		Observed and expected[a] deaths for all cancer causes										
X-10	Obs	110	100	42	54	30	22	14	10	3	1	386
	Exp	153.56	138.44	53.53	65.98	42.58	24.17	11.16	6.08	2.47	0.32	498.3
Y-12	Obs	153	69	42	30	14	4	0	0	0	1	313
	Exp	149.79	72.97	45.46	28.09	16.23	5.19	0.79	0.01	0.00	0.14	318.7
MULT	Obs	173	117	54	39	24	17	6	3	1	1	435
	Exp	200.30	116.08	66.93	41.89	26.30	18.37	7.54	3.11	0.73	0.58	481.8
Total	Obs	436	286	138	123	68	43	20	13	4	3	1,134
	Exp	503.65	327.49	165.92	135.96	85.11	47.73	19.48	9.21	3.20	1.04	1,299
SMR		86.6	87.3	83.2	90.5	79.9	90.1	102.7	141.2	125.1	287.6	87.3
		Adjusted[b] expected deaths for all cancer causes										
X-10		115.72	105.71	41.78	52.05	33.13	20.37	9.52	5.31	2.14	0.29	
Y-12		148.35	69.43	44.91	27.97	16.18	5.23	0.79	0.01	0.00	0.15	
MULT		182.39	104.00	59.99	37.82	23.60	16.35	6.75	2.85	0.68	0.59	
Total		446.47	279.12	146.69	117.83	72.90	41.96	17.06	8.17	2.82	1.03	
SMR		97.7	102.5	94.1	104.4	93.3	102.5	117.3	159.1	141.8	290.3	

[a]Expected deaths based on U.S. white male rates.
[b]Adjusted for all factors (except external dose) in main-effects model (see Table III).

ACKNOWLEDGMENTS

The research was conducted by Oak Ridge Institute for Science and Education (ORISE) with the collaboration of the School of Public Health, University of North Carolina at Chapel Hill, and the Computer Science and Mathematics Division of ORNL under Contract DE-AC05-76OR00033 with the U.S. Department of Energy, Office of Energy Research. Additional funding and oversight have been provided by the National Institute for Occupational Safety and Health. The authors thank the staff of ORISE's Center for Epidemiologic Research and Lockheed-Martin Energy Systems for their help in data collection, and Marjorie Harris, Richard L. Neubert and Stelmo Poteet for assistance in manuscript preparation. Part of the data used were collected under a previous contract from the U.S. Atomic Energy Commission and later from the U.S. Energy Research and Development Administration (E11-1-3428). The authors acknowledge the vital statistics offices of the individual states as the source of death record data and appreciate the offices' technical support of this research. The authors are solely responsible for the data analysis and the interpretation of the results. The work has been authored by a contractor of the U.S. Government. Accordingly, the U.S. Government retains a nonexclusive, royalty-free license to publish or reproduce the published form of this work, or to allow others to do so for U.S. Government purposes.

Received: March 13, 1995; accepted: February 5, 1997

REFERENCES

1. E. L. Frome, D. L. Cragle and R. W. McLain, Poisson regression analysis of the mortality among a cohort of World War II nuclear industry workers. *Radiat. Res.* **123**, 138–152 (1990).
2. J. P. Watkins, J. L. Reagan, D. L. Cragle, E. L. Frome, C. M. West, D. Crawford-Brown and W. G. Tankersley, *Collection, Validation, and Description of Data for the Oak Ridge Nuclear Facilities Mortality Study*. Technical Report J42, Oak Ridge Institute for Science and Education, Oak Ridge, TN, 1993.
3. J. P. Watkins, J. L. Reagan, D. L. Cragle, E. L. Frome, C. M. West, D. Crawford-Brown and W. G. Tankersley, Collection, validation, and treatment of data for a mortality study of nuclear industry workers. *Appl. Occup. Environ. Hyg.* **12**, 195–205 (1997).
4. E. L. Frome, D. L. Cragle, J. P. Watkins, S. Wing, C. Shy, W. M. Tankersley and C. M. West, *A Mortality Study of Employees of the Nuclear Industry in Oak Ridge, Tennessee*. Technical Report 6785, Oak Ridge National Laboratory, Oak Ridge, TN, 1997.
5. E. S. Gilbert, D. L. Cragle and L. D. Wiggs, Updated analyses of combined mortality data for workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats weapons plant. *Radiat. Res.* **136**, 408–421 (1993).
6. J. P. Watkins, D. L. Cragle, E. L. Frome, C. M. West, D. J. Crawford-Brown and W. G. Tankersley, *Adjusting External Doses from the ORNL and Y-12 Facilities for the Oak Ridge Nuclear Facilities Mortality Study*. Technical Report G-34, Oak Ridge Institute for Science and Education, Oak Ridge, TN, 1994.
7. CEDR: Comprehensive Epidemiologic Data Resource. U.S. Department of Energy, Office of Environment Safety and Health, Washington, DC, May 1995. URL http://cedr.lbl.gov/CEDRhomepage.html.
8. R. R. Monson, Analysis of relative survival and proportional mortality. *Comput. Biomed. Res.* **9**, 325–332 (1974).
9. E. L. Crow, Freeman-Tukey test. In *Encyclopedia of Statistical Sciences* (S. Kotz and N. L. Johnson, Eds.), Vol. 3, pp. 210–211. Wiley, New York, 1983.

10. E. L. Frome, M. K. Kutner and J. J. Beauchamp, Regression analysis of Poisson distributed data. *J. Am. Stat. Assoc.* **68**, 935–940 (1972).

11. E. L. Frome and D. R. Hudson, A general statistical data structure for epidemiologic studies of DOE workers. In *Proceedings of the 1980 DOE Statistical Symposium* (T. Truet, D. Margolis and R. W. Mensing, Eds.), pp. 206–218. Report No. CONF801045, Oak Ridge National Laboratory, Oak Ridge, TN, 1981.

12. E. L. Frome, The analysis of rates using Poisson regression models. *Biometrics* **39**, 665–674 (1983).

13. N. E. Breslow and N. E. Day, *Statistical Methods in Cancer Research, Volume II: The Design and Analysis of Cohort Studies*. Scientific Publication 82, International Agency for Research on Cancer, Lyon, 1987.

14. D. Clayton and M. Hills, *Statistical Models in Epidemiology*. Oxford University Press, Oxford, 1993.

15. B. Francis, M. Green and C. Payne, *GLIM 4, the Statistical System for Generalized Linear Interactive Modelling*, Release 4. Royal Statistical Society, Oxford University Press, Oxford, 1993.

16. C. R. Rao, *Linear Statistical Inference and Its Application*. Wiley, New York, 1975.

17. C-F. Chen, Robustness aspects of score tests for generalized linear and partially linear regression models. *Technometrics* **27**, 277–283 (1985).

18. L. Törnquvist, P. Vartia and Y. O. Vartia, How should relative changes be measured? *Am. Stat.* **39**, 43–46 (1985).

19. M. Aitkin, D. Anderson, B. Francis and J. Hinde, *Statistical Modelling in GLIM*. Clarendon Press, Oxford, 1989.

20. D. L. Preston, J. H. Lubin, D. A. Pierce and M. E. McConney, *EPICURE Users's Guide*. Hirosoft International Corporation, Seattle, WA, 1993.

21. S. Wing, C. M. Shy, J. L. Wood, S. Wolf, D. L. Cragle and E. L. Frome, Mortality among workers at Oak Ridge National Laboratory: Evidence of radiation effects in follow-up through 1984. *J. Am. Med. Assoc.* **265**, 397–402 (1991).

22. S. Wing, C. M. Shy, J. L. Wood, S. Wolf, D. L. Cragle, W. Tankersley and E. L. Frome, Job factors, radiation, and cancer mortality at Oak Ridge National Laboratory: Follow-up through 1994. *Am. J. Ind. Med.* **23**, 265–279 (1993); erratum *Am. J. Ind. Med.* **23**, 673 (1993).

23. National Research Council, Committee on the Biological Effects of Ionizing Radiation, *Health Effects of Exposure to Low Levels of Ionizing Radiation (BEIR V)*. National Academy Press, Washington, DC, 1990.

24. E. Cardis, E. S. Gilbert, L. Carpenter, G. Howe, I. Kato, B. K. Armstrong, V. Beral, G. Cowper, A. Douglas, J. Fix, S. A. Fry, J. Kaldor, C. Lave, L. Salmon, P. G. Smith, G. L. Voelz and L. D. Wiggs, Effects of low doses and low dose rates of external ionizing radiation: Cancer mortality among nuclear industry workers in three countries. *Radiat. Res.* **142**, 117–132 (1995).

25. H. Checkoway, N. E. Pearce and D. Crawford-Brown, *Research Methods in Occupational Epidemiology*. Oxford University Press, Oxford, 1989.

26. V. Beral, H. Inskip, L. Fraser, M. Booth, D. Coleman and G. Rose, Mortality of employees of the United Kingdom Atomic Energy Authority, 1946–1979. *Br. Med. J.* **291**, 440–447 (1985).

27. V. Beral, P. Fraser, L. Carpenter, M. Booth, A. Brown and G. Rose, Mortality of employees of the Atomic Weapons Establishment, 1951–1982. *Br. Med. J.* **297**, 757–770 (1988).

28. G. D. Kerr, Missing dose from mortality studies of radiation effects among workers at Oak Ridge National Laboratory. *Health Phys.* **66**, 206–208 (1994).

29. T. J. Mitchell, G. Ostrouchov, E. L. Frome and G. D. Kerr, A method for estimating occupational dose to individuals, using weekly dosimetry data. *Radiat. Res.* **147**, 195–207 (1997).

30. S. Wing, C. M. West, J. L. Wood and W. Tankersley, Recording of external radiation exposures at Oak Ridge National Laboratory: Implications for epidemiologic studies. *J. Exposure Anal. Environ. Epidemiol.* **4**, 83–93 (1994).

31. J. W. Smith and H. Inskip, Estimation of below threshold doses following the measurement of a sample of old films. *J. Soc. Radiol. Prot.* **5**, 159–164 (1985).

32. E. S. Gilbert, J. J. Fix and W. V. Baumgartner, An approach to evaluating bias and uncertainty in estimates of external dose obtained from personal dosimeters. *Health Phys.* **70**, 336–345 (1996).

33. D. Loomis and S. Wolf, Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennessee, 1947–1990. *Am. J. Ind. Med.* **29**, 131–141 (1996).

34. E. S. Gilbert, Some confounding factors in the study of mortality and occupational exposures. *Am. J. Epidemiol.* **116**, 177–188 (1982).

35. G. R. Howe, A. M. Chiarelli and J. P. Lindsay, Components and modifiers of the healthy worker effect: Evidence from three occupational cohorts and implications for industrial compensation. *Am. J. Epidemiol.* **128**, 1364–1375 (1988).

36. L. Carpenter, V. Beral, P. Fraser and M. Booth, Health related selection and death rates in the United Kingdom Atomic Energy Authority workforce. *Br. J. Ind. Med.* **47**, 248–258 (1990).

37. G. M. Kendall, C. R. Muirhead, B. H. MacGibbon, J. A. O'Hagan, A. J. Conquest, A. A. Goodill, B. K. Butland, T. P. Fell, D. A. Jackson, M. A. Webb, R. G. E. Haylock, J. M. Thomas and T. J. Silk, Mortality and occupational exposure to radiation: First analysis of the National Registry for Radiation Workers. *Br. Med. J.* **304**, 220–225 (1992).

38. M. P. Little, G. M. Kendall, C. R. Muirhead, B. H. MacGibbon, R. G. E. Haylock, J. M. Thomas and A. A. Goodill, Further analysis, incorporating assessment of the robustness of risks of cancer mortality in the National Registry for Radiation Workers. *J. Radiat. Prot.* **113**, 95–108 (1993).

39. L. Carpenter, C. Higgins, A. Douglas, P. Fraser, V. Beral and P. Smith, Combined analysis of mortality in three United Kingdom nuclear industry workforces, 1946–1988. *Radiat. Res.* **138**, 224–238 (1994).

40. IARC, Study Group on Cancer Risk among Nuclear Industry Workers, Direct estimates of cancer mortality due to low doses of ionizing radiation: an international study. *Lancet* **344**, 1039–1043 (1994).

41. D. A. Pierce, Y. Shimizu, D. L. Preston, M. Vaeth and K. Mabuchi, Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. *Radiat. Res.* **146**, 1–27 (1996).