Susceptibility and Occupational Radiation Risks

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Principal Investigator: David B. Richardson
Co-Investigator: Steven B. Wing
Project Director: Susanne H. Wolf

Department of Epidemiology, School of Public Health
University of North Carolina at Chapel Hill

Address for correspondence:

David Richardson
Department of Epidemiology
McGavran-Greenberg Hall
School of Public Health, CB#7435
University of North Carolina Chapel
Hill, NC 27599-7435

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Summary

We created a roster of approximately 24,000 Savannah River Site workers (SRS) by merging and resolving duplicate information from electronic files from the Center for Epidemiologic Research, Oak Ridge Associated Universities (ORAU) and from NIOSH files of SRS employment records. We submitted the roster to the Social Security Administration for a search of vital status through 12/31/2002. For decedents, we obtained cause of death information from death certificates and (for more recent decedents) from the National Death Index. Hardcopy employment history records were obtained and entered into an electronic data base in order to create a detailed work history file describing job titles and dates of employment. Job title information was coded into major groups. Information on annual assignments to health physics areas and departments was abstracted from quarterly printouts of dosimetry logbooks. We created an electronic file of annual external radiation dose estimates for these SRS workers by merging, and reconciling, information from the SRS HPAREH system (for workers employed in 1979 or later), information from an electronic dosimetry file created by DuPont (for workers terminated prior to 1979), and information abstracted by ORAU. We compared the computerized radiation dosimetry records from the Site to employment records on a year by year basis, and found that approximately 14,000 annual dosimetry records in the hardcopy logbooks were missing from the computerized dose files. Once identified, these records were abstracted, and added about 1.7 person-Sv of recorded dose. We standardized health physics areas and health physics departments into major categories, and, in conjunction with standardized job title information, developed the structure for a job exposure matrix. Building upon prior work, we assessed select non-radiological hazards. We enumerated a study cohort of 18,883 operations workers hired between 1950 and 1986, employed for at least 3 months, and not employed at another USDOE facility. As of 2002, 31% of the 15,264 men had died and 11% of the 3619 women had died. The total number of deaths was less than expected (SMR=0.8); 7 workers, all men, died due to pleural cancer SMR=4.25 (90CI: 1.99, 7.97) and there were 68 deaths due to leukemia among male workers (SMR=1.2). There was a positive association between a worker's recorded radiation dose and risk of death due to leukemia. (ERR/10 mSv=0.04). The association was largest for deaths due to myeloid forms of leukemia (ERR/10 mSv=0.12) and those exposures received 3-15 years prior to death were most strongly related to risk of leukemia.

Significant Findings

Results of this study show (1) a significant excess of mortality due to pleural cancer among male SRS workers; (2) a significant excess of leukemia mortality among male SRS workers; (3) low mortality rates due to most other causes of death, and substantial differences in lung cancer mortality by pay code; (4) cumulative radiation dose is positively associated with leukemia death rates, especially for myeloid forms of leukemia; and (5) cumulative dose is positively associated with non-Hodgkins lymphoma death rates under a 35 year lag assumption.

Usefulness of Findings

These findings add to the occupational literature on risks of chronic exposure to low-level ionizing radiation. Dosimetry findings and analyses of risks of exposures at different ages may be useful in implementation of the Energy Employees Occupational Illness Compensation Program Act (Publications 3, 4, 6).

Publications

1. Richardson DB. The impact on relative risk estimates of inconsistencies between ICD-9 and ICD-10. Occup Environ Med 2006;63(11):734-40.

2. Richardson DB. Use of multiple cause of death data in cancer mortality analyses. Am J Ind Med 2006;49(8):683-9.

3. Richardson DB, Wing S, Daniels RD. Evaluation of external radiation dosimetry records at the Savannah River Site, 1951-1989. J Expo Sci Environ Epidemiol 2006.

4. Hamra G, Nylander-French LA, Richardson D. Dose reconstruction for an occupational cohort at the Savannah River nuclear facility: evaluation of a hybrid method. Radiat Prot Dosimetry 2008;131(2):188-97.

5. Richardson DB, Wing S, Wolf S. Mortality among workers at the Savannah River Site. Am J Ind Med 2007;50(12):881-91.

6. Richardson DB, Wing S. Leukemia mortality among workers at the Savannah River Site. Am J Epidemiol 2007;166(9):1015-22.

Relevance to Specific Aims

Publications 1 and 2 provide methodological justification for the construction of the outcome categories used in these analyses. Publication 5 addresses mortality overall and for specific categories of cause of death. Publication 6 assesses variation in associations with exposure lag assumptions and models these temporal patterns. Assessments of non-radiological exposures are discussed in Publication 5; we found minimal ability to characterize workers by hydrazine exposure, solvent exposures were not substantial for the observed outcomes in excess, however, significant problems with asbestos exposure were identified in some time periods. Publications 3 and 4 address neutron and tritium exposures.

Publication Currently under Review:

Positive Associations between Ionizing Radiation and Lymphoma Mortality among Men. This publication gives further attention to the temporal patterns in association and examines comparability of patterns with those seen in the Life Span Study of atomic bomb survivors.

The impact on relative risk estimates of inconsistencies between ICD-9 and ICD- 10

D B Richardson

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Background: The 10th revision of the International Classification of Diseases (ICD) represents a in the ICD system. This paper investigates the impact on relative risk estimates of inconsistencies classification between ICD-9 and ICD-10, including scenarios in which occupational exposure levels are correlated with vear of death (and therefore with the ICD revision in effect at death). The setting cohort mortality study in which follow up spans the periods during which ICD-9 and ICD- 10 were in relative risk estimate obtained when death certificates are coded to the ICD revision in effect at compared to the relative risk estimate that would be obtained if all death certificates were coded to ICD revision (that is. ICD-10). The ratio of these relative risks is referred to as the coefficient of bias.

Methods: Simple equations relate the coefficient of bias to the sensitivity and specificity of the classification of decedents into categories of cause of death via ICD-9 (treating classifications based upon ICD-standard). Bridge coded mortality data for 2 296 922 decedents (that is, death certificates coded to ICD-9 and ICD-10 are used to derive estimates of sensitivity and specificity by category of cause of death. Numerical examples illustrate the application of these equations.

Results: Estimates of the sensitivity of classification of decedents into categories of death defined by ICD-9 ranged from 0.26-1.00. Specificity was above 0.98 for all categories of cause of death. Numerical examples illustrate that inconsistencies in outcome classification between ICD-9 and ICD- 10 may have substantial impact on relative risk estimates if there is a strong relation between exposure status and the proportion of deaths coded to a given ICD revision.

Conclusions: For analyses of mortality outcomes that exhibit poor comparability between ICD-9 may be prudent to recode cause of death information to a standard ICD revision in order to avoid bias that can occur when exposures are correlated with the proportion of deaths coded to a given ICD revision.

Appendix *I is* available the *OEM* website

Correspondence to: Assistant Richardson, Department of Epidemiolo y, School of Public Health, University of North Hill Hill, Chapel 27599 USA; david_ richardson@unc.edu

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Mortality outcomes for occupational cohort research often arc defined in terms of unde'rlying causes of death coded according to the International Classification of Diseases (ICD). The use of ICI) coding of cause of death information allows investigators to conduct analyses using a standardised methodology for coding the textual cause of death information on the death certificate and it provides investigators a standardised methodology for selection of a single underlying cause of death from a set of listed causes.'

However, roughly once every decade a new revision of the ICI) is adopted. As a result, methodologies for coding cause of death information change over time, as do rules for selection of the underlying cause of death. The adoption of the 10th revision of the ICD is particularly noteworthy, as ICD-10 marks a significant departure from the previous revisions both in form and structure. Consequently, the rationale that use of the ICD permits the conduct of epidemiological analyses following a standardised methodology for coding (and selection) of underlying cause of death information may be undermined by the periodic revisions to ICD, particularly substantial revisions such as that from ICD-9 to ICD-10.

One way for epidemiologists to address this problem is to code all death certificates for decedents in a study population to a standard revision of the ICD (for example, ICD-10). Such an approach ensures that death certificates with the same listed causes of death arc assigned to the same categories of death regardless of the ICD revision in effect at the time of death. However, there are often good reasons for not coding all death certificates to a single revision of the ICD. For example, for analyses that compare mortality rates in a study population to an external referent population via the standardised mortality ratio, cause of death information ispreferably tabulated to contemporaneous revisions of the ICD (as is done for calculation of referent rates at the state and national level). Furthermore, there arc practical obstacles to coding all death certificates to a standard lCD revision. The investigator must obtain copies of all death certificates so that these may be coded by a trained nosologist to a standard ICD revision. The collection of death certificates for epidcmiological research has become less common as access to national databases of cause of death information, such as the US National Death Index, have made it more efficient to obtain cause of death information from a national death registry. Since cause of death information in the US national death registry is coded to the contemporaneous revision of the ICD, the investigator may not have the ability to recode cause of death information to different versions of the ICD.

The objective of this paper is to evaluate the impact on relative risk estimates of the transition from ICD-9 to ICD-10. Data front a large comparability study are used to assess the classification of decedents into categories of' death defined by ICD-9 and -10 codes. Simple equations relate the impact on relative risk estimates to the sensitivity and specificity of the classification of decedents into categories of cause of death via ICD-9 (treating classifications based upon ICD-10 as the standard); numerical examples illustrate the impact on relative risk estimates of coding death certificates to contemporaneous revisions of ICD-9 and ICD-10, rather than coding all certificates to a standard ICD revision.

METHODS

Consider a hypothetical study comparing disease risk in two groups within a closed cohort followed to extinction. Let's say that study outcomes are classified in terms of categories of

cause of death using information on underlying cause of death coded to lCD-10; we can denote the observed risk in the exposed subgroup as r,, and the observed risk in the unexposed group as r_5, where r, and r_0 denote incidence proportions.

Now, consider the scenario in which some of the decedents have their underlying cause of death information coded to ICD-9 rather than ICD-10. Let's say that a proportion, P_1, of those in the exposed subcohort is coded to ICD-9, while the remainde[r] is coded to ICU-10; similarly, a proportion, P_5, of those in the unexposed subcohort is coded to ICD-9. If outcome classifications based upon ICD-10 serves as our standard then we can refer to the sensitivity *(Se)* and specificity (Sp) of outcome classifications that occur when using cause of death information coded to ICD-9.

Among the exposed subcohort, therefore, the sensitivity of case classification will be $Se_i = (1—P,)+Se* P,;$ the specificity of case classification among the exposed can be expressed as $Sp, = (1—P,)+Sp* P_1$. Similarly, among the unexposed the sensitivity and specificity of case classification can be expressed as $Se_5 = (1—Po)+Se' P_5$ and Spo = $(1—P_5)+Sp* P_0$, respectively.

An analysis of these data would yield an estimate of risk in the exposed subgroup, $r',=Se,(r,)+(I—.Sp,)(I—r,);$ an estimate of risk among the unexposed, r'_5 = Se5 (ro)+(1—Sp5)(I—r0); and a risk ratio estimate of RR' $=r',/r'5$.

Given that RR reflects the relative risk estimate that would be observed if all deaths were coded to ICD-10, and RR' reflects the relative risk estimate obtained when proportions P, and Po of the deaths in the exposed and unexposed subgroups, respectively, arc coded to ICI:)-9, the ratio, RR'/RR, may be referred to as a coefficient of bias in the relative risk estimate due to inconsistencies in outcome classification between ICD-9 and ICD-10.

Estimates of Se and Sp are shown in table 1. These values were obtained via analyses of comparability (that is, bridge coding) data. All US death certificates for 1996 were originally coded and classified according to ICD-9; a comparability file was created by appending ICD-10 codes to each record in the 1996 mortality file. 99.1% of the 2 318 212 records are coded by both ICD-9 and ICD-10. For the purposes of the comparability study 130 mortality outcomes were defined along with comparable ranges of ICD-9 and ICD-10 codes for each mortality outcome.' The list of outcomes and associated ICD-9 and ICD-10 codes is shown in the online Appendix I (see http://www.occcnvined.com/supplemental). Table 1 reports the numbers of decedents classified into disease categories by ICD-9 only, ICD-10 only, ICD-9 and -10, as well as estimates of *Se* and Sp (rounded to three decimal places) for 130 outcomes.

Numerical example

Numerical examples are provided for three categories of cause of death: lung cancer, renal failure, and essential hypertension. Coefficients of bias arc derived under assumptions that P_0 and P, took values equal to 0.0, 0.2, 0.4, 0.6, 0.$ and 1.0. For the purposes of these examples, the baseline risk (r_0) for each outcome was specified as 0.05 and RR (that is, r,/r,3) was specified as 2.0. Results are easily computed for alternative assumptions; however, estimates of the coefficient of bias are not influenced by assumptions about RR, and, for categories of cause of death with Sp near unity, estimates of the coefficient of bias are minimally influenced by assumptions about the magnitude of the baseline risk (see Appendix 11).

RESULTS

Table 1 reports estimates of sensitivity and specificity of outcome classifications made via ICD-9 relative to classifications made via ICD-10 coding of underlying cause of death information. The sensitivity of classification of decedents into categories of death defined by underlying cause of death

coded according to ICD-9 ranged from 0.26-1.00. For deaths due to external causes and infectious diseases sensitivity ranged from 0.26-1.00 and 0.6 —1.00, respectively; for cancer deaths, sensitivity tended to be fairly high (that is, greater than 0.90). Specificity was above 0.98 for all categories of cause of death.

Table 2 presents estimates of the coefficient of bias for estimates of the relative risk of lung cancer. The rows and columns of the table define various assumptions about the proportions of decedents for whom cause of death informa-tfon was coded to ICD-9. By definition, the coefficient of bias equals 1.00 for the cell defined by P_5 = 0.0 and P, = 0.0 (that is, no decedents were coded to ICD-9 in either the exposed or unexposed subgroups).

In an occupational setting, exposure status may be related to the proportion of deaths coded to ICD-9 versus ICD-10. For example, if occupational exposures tended to be higher in earlier calendar periods than in later calendar periods then exposure status may be related to year of death (and consequently, P, may be greater than P,,). An extreme scenario is one in which all deaths among the exposed are coded to ICD-9 (P_I = 1) and all deaths among the unexposed arc coded to ICD-10 ($P,_1$ = 0). Under this scenario, the estimate of the association between exposure and death due to lung cancer is very comparable to the relative risk estimate that would be obtained if all deaths were coded to ICD-f0 (coefficient of bias = 1.00). An alternative, equally extreme scenario is one in which all deaths among the exposed arc coded to ICD-10 (P, = 0) and all deaths among the unexposed are coded to ICD-9 (P_0 = I). Under the latter scenario, the estimate of the association between exposure and death due to lung cancer is only modestly attenuated when compared to the relative risk estimate that would be obtained if all deaths were coded to ICD-10 (coefficient of bias = 0.98). Such calculations illustrate how maximal and minimal values for the coefficient of bias may be obtained, permitting an investigator to evaluate the magnitude of bias potentially attributable to coding death certificates to contemporaneous revisions of the ICD rather than coding all certificates to a standard ICD revision.

Table 3 presents coefficient of bias for estimates of the relative risk of death due to essential hypertension. From table 3, maximal and minimal values for the coefficient of bias may be obtained. The minimal value for the coefficient of bias is 0.82 (for the scenario P, = 1 and $P_5 = 0)$, while the maximal value for the coefficient of bias is 1.22. Table 4 presents coefficient of bias for estimates of the relative risk of death due to renal failure. Under the scenario (P, = 1 and I',, = 0) the minimal value for the coefficient of bias is 0.72 while under the scenario $(P_I = 0$ and $P_5 = 1)$ the coefficient of bias is 1.39.

DISCUSSION

Over the last century, there have been 10 revisions of the ICD. Information about the degree of consistency in disease classification when cause of death information is coded to different revisions of the ICD is of direct relevance to understanding of potential bias in results obtained from epidemiological research on mortality outcomes. This paper focuses on the period spanned by ICD revisions 9 and t0;' this encompasses the period of coverage of the US National Death Index (NDI) and therefore is of direct relevance to US researchers who rely upon the NDI for collection of cause of death information. ICD-10 is much more.dctailed than ICD-9. Three additional chapters have been added to the ICD and some chapters rearranged, and cause of death titles (and some coding rules) have been changed.' The use of bridge coded data offers a way to assess the sensitivity and specificity of outcome classification using categories of death

Table 1 Classification of 2 296 922 deaths into categories defined by underlying cause of death coded to ICD-9 and ICD-10

Category of death	Number of decedents classified into disease category by ICD-9 and ICD-10	Number of decedents classified into disease category by ICD-9 only	Number of decedents classified into disease category by ICD-10 only	Sensitivity	Specificity
Salmonella infections	46	12	6	0.885	1.000
Shigellosis and amebiasis	6	2	1	0.857	1.000
Certain other intestinal infections	458	361	246	0.651	1.000
Respiratory tuberculosis	753	159	104	0.879	1.000
Other tuberculosis	169	120	32	0.841	1.000
Whooping cough	4	0	2	0.667	1.000
Scarlet fever and erysipelas	1	2	0	1.000	1.000
Meningococcal infection	270	18	15	0.947	1.000
Septicemia	20074	1262	5316	0.791	0.999
Syphilis	39	34	18	0.684	1.000
Acute poliomyelitis	0	0	1	-	1.000
Arthropod-borne viral encephalitis	2	1	0	1.000	1.000
Measles	1	0	0	1.000	1.000
Viral hepatitis	2567	1202	126	0.953	0.999
Human immunodeficiency virus (HIV) disease	30631	273	2810	0.916	1.000
Malaria	5	0	0	1.000	1.000
Other and unspecified infectious and parasitic diseases and their sequelae	3402	2876	2314	0.595	0.999
Malignant neoplasms of lip, oral cavity, and pharynx	7179	656	340	0.955	1.000
Malignant neoplasm of oesophagus	10914	285	225	0.980	1.000
Malignant neoplasm of stomach	12983	309	402	0.970	1.000
Malignant neoplasms of colon, rectum, and anus	54833	1458	1388	0.975	0.999
Malignant neoplasms of liver and intrahepatic bile ducts	10911	631	215	0.981	1.000
Malignant neoplasm of pancreas	26776	392	313	0.988	1.000
Malignant neoplasm of larynx	3706	201	221	0.944	1.000
Malignant neoplasms of trachea, bronchus, and lung	147147	4426	2059	0.986	0.998
Malignant melanoma of skin	6732	527	160	0.977	1.000
Malignant neoplasm of breast	42474	853	1170	0.973	1.000
Malignant neoplasm of cervix uteri	4394	140	123	0.973	1.000
Malignant neoplasms of corpus uteri and uterus, part unspecified	6054	238	390	0.939	1.000
Malignant neoplasm of ovary	12825	300	218	0.983	1.000
Malignant neoplasm of prostate	33044	964	1453	0.958	1.000
Malignant neoplasms of kidney and renal pelvis	10720	348	308	0.972	1.000
Malignant neoplasm of bladder	10926	480	424	0.963	1.000
Malignant neoplasms of meninges, brain, and other parts of central nervous system	11667	664	385	0.968	1.000
Hodgkin's disease	1309	95	99	0.930	1.000
Non-Hodgkin's lymphoma	21730	1135	647	0.971	1.000
leukaemia	19674	622	833	0.959	1.000
Multiple myelama and immunoproliferative neoplasms	9965	258	700	0.934	1.000
Other and unspecified malignant neoplasms of lymphoid, haematopoietic, and related tissue	0	0	72	-	1.000
All other and unspecified malignant neoplasms	54700	2261	10106	0.844	0.999
In situ neoplasms, benign neoplasms, and neoplasms of uncertain or unknown behaviour	6517	1090	5894	0.525	1.000
Anemias	3574	743	497	0.878	1.000
Diabetes mellitus	59674	1811	2999	0.952	0.999
Malnutrition	2492	1015	1043	0.705	1.000
Other nutritional deficiencies	117	54	187	0.385	1.000
Meningitis	681	64	73	0.903	1.000
Parkinson's disease	11263	534	653	0.945	1.000
Alzheimer's disease	20597	695	13070	0.612	1.000
Acute rheumatic fever and chronic rheumatic heart diseases	3911	1065	476	0.891	1.000
Hypertensive heart disease	20405	5568	334	0.984	0.998
Hypertensive heart and renal disease	2017	473	789	0.719	1.000
Acute myocardial infarction	207911	5081	2005	0.990	0.998
Other acute ischaemic heart diseases	2329	547	755	0.755	1.000
Atherosclerotic cardiovascular disease, so described	64335	3815	7896	0.891	0.998
All other forms of chronic ischaemic heart disease	251673	7037	6159	0.976	0.997
Acute and subacute endocarditis	735	103	129	0.851	1.000
Diseases of pericardium and acute myocarditis	650	64	100	0.867	1.000
Heart failure	45832	1220	3044	0.938	0.999
All other forms of heart disease	89569	16104	8577	0.913	0.993
Essential (primary) hypertension and hypertensive renal disease	11814	1070	2567	0.822	1.000
Cerebrovascular diseases	154524	4331	12313	0.926	0.998
Atherosclerosis	15363	1292	723	0.955	0.999
Aortic aneurysm and dissection	16011	350	360	0.978	1.000
Other diseases of arteries, arterioles, and capillaries	8119	2627	1014	0.889	0.999

Table 1 Continued

Category of death	Number of decedents classified late disease category by ICD-9 and ICD-10	Number of decedent classified into disease category by ICD'9 only	Number of decedents classified into disease category by ICD-10 only	SenssYrvity"	Specificity'
Other disorders of circulatory system	2379	1828	1726	0.580	0.999
Influenza	712	31	31	0.958	1.000
Pneumonia	55687	26615	1485	0.974	0.988
Acute bronchitis and bronchiolitis	302	172	40	0.883	1.000
Unspecified acute lower respiratory infection	0	0	119	-	1.000
Bronchitis, chronic and unspecified	*1066*	2061	141	0.883	0.999
Emphysema	15457	1722	1064	0.936	0.999
Asthma	4687	927	284	0.943	1.000
Other chronic lower respiratory diseases	77435	2056	9612	0.890	0.999
Pneumoconioses and chemical effects	1074	61	80	0.931	1.000
Pneumonitiis due to solids and liquids	9685	579	1653	0.854	1.000
Other diseases of respiratory system	16293	2328	4383	0.788	0.999
Peptic ulker	4748	379	231	0.954	1.000
Diseases of appendix	367	54	43	0.895	1.000
Hernia	1257	134	151	0.893	1.000
Alcoholic liver disease	10420	1542	1551	0.870	0.999
Other chronic liver disease and cirrhosis	11972	927	1716	0.875	1.000
Cholelithiasis and other disorders of gall bladder	2565	251	141	0.948	1.000
Acute and rapidly progressive nephritic and nephrotic syndrome	182	138	26	0.875	1.000
Chronic glomerulonephritis, nephritis, and nephropathy not specified as acute or chronic, and renal sclerosis unspecified	603	1026	67	0.900	1.000
Renal failure	21255	969	8232	0.721	1.000
Other disorders of kidney	29	13	7	0.806	1.000
Infections of kidney	796	89	109	0.880	1.000
Hyperplasia of prostate	428	27	34	0.926	1.000
Inflammatory diseases of female pelvic organs	91	21	9	0.910	1.000
Pregnancy with abortive outcome	32	7	9	0.780	1.000
Other complications of pregnancy, childbirth, and the puerperium	214	32	70	0.754	1.000
Certain conditions originating in the perinotal period	12555	361	1337	0.904	1.000
Congenital malformations, deformations, and chromosomal abnormalities	9525	2215	989	0.906	0.999
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	22496	3010	2381	0.904	0.999
All other diseases (residual)	128432	32240	18414	0.875	0.985
Motor vehicle accidents	40525	2512	476	0.988	0.999
Other land transport accidents	678	51	1932	0.260	1.000
Water, air and space, and other and unspecified transport accidents and their sequelae	1967	320	208	0.904	1.000
Falls	10215	3701	528	0.951	0.998
Accidental discharge of firearms	1026	6	23	0.978	1.000
Accidental drowning and submersion	3312	128	230	0.935	1.000
Accidental exposure to smoke, fire, and fames	3539	110	108	0.970	1.000
Accidental poisoning and exposure to noxious substances	*7859*	*94*	377	0.954	1.000
Other and unspecified nontransport accidents and their sequelae	10107	489	5705	0.639	1.000
Intentional self-harm (suicide) bv discharge of firearms	17791	93	114	0.994	1.000
Intentional self-harm (suicide) by other and unspecified means and their uequelae	11927	96	142	0.988	1,000
Assault (homicide) by discharge of firearms	13809	46	72	0.995	1.000
Assault (homicide) by other and unspecified means and their sequeloe	6207	78	92	0.985	1.000
Legal intervention	297	31	10	0.967	1.000
Discharge of firearms, undetermined intent	220	2	2	0,991	1.000
Other and unspecified events of undetermined intent and their sequelae	2482	78	41	0.984	1.000
Operations of war and their sequeloe	5	7	2	0.714	1.000
Complications of medical and surgical care	1136	1897	776	0.594	0.999

'Treating classifications based upon ICD-10 as the standard.

defined in relation to *ICD-9* and 10 codes, specifically evaluating how events defined via death certificate information coded to *ICD-9* would be classified if the death certificate information were coded to *ICD-10*. *As* illustrated via numerical examples in this paper, maximal and minimal values for the coefficient of bias may be obtained, providing a sense of the magnitude of bias potentially attributable to coding death certificates to contemporaneous revisions of the *ICD.*

It can be shown (Appendix 11) that the maximal and minimal bounds for the coefficicnt, of bias are approximately *Se* and *1/Se,* corresponding to the extreme scenarios in which there is perfect concordance between exposure status and ICU revision. For most cancer outcomes, as illustrated by the numerical example for lung cancer, there is minimal potential for bias due to outcome misclassification. Even in scenarios where there is a strong correlation between exposure status and the proportion of deaths coded to a

Table 2 Hypothetical data. Coefficients of bias* for analyses of the relative risk of lung cancer mortality under varying assumptions about the proportion of exposed decedents *(P_t)* coded to ICD-9 rather than ICD- 10 and the proportion of unexposed decedents *(Pd* coded to ICD-9 rather than ICD- 10

	Po					
P_t	**0.0**	**0,2**	**0.4**	**0.6**	**0.8**	**1.0**
0.0	1.00	1.00	1.00	1.00	1.00	1.00
0.2	1.00	1.00	1.00	1.00	1.00	1.00
0.4	0.99	0.99	0.99	0.99	0.99	0.99
0.6	0.99	0.99	0.99	0.99	0.99	0.99
0.8	0.98	0.98	0.98	0.98	0.98	0,99
1.0	0.98	0.98	0.98	0.98	0.98	0.98

*The ratio of the relative risk estimate obtained when death certificates are coded to the ICD revision in effect at time of death to the relative risk estimate that would be obtained if all death certificates were coded to ICD-10.

Table 3 Hypothetical data. Coefficients of blase for analyses of the relative risk of mortality due to essential hypertension under varying assumptions about the proportion of exposed decedents *(P_t)* coded to ICD-9 rather than ICD-10 and the proportion of unexposed decedents (Po) coded to ICD-9 rather than ICD-10

	Pa					
P_t	**0.0**	**0.2 _ - - - 0.4**		**0.6**	**08**	**1.0**
0.0	1.00	0.96	0.93	0.89	0.86	0.82
0.2	1.04	1.00	0.96	0.93	0.89	0.85
0.4	1.08	1.04	1.00	0.96	0.92	0.89
0.6	1.12	1.08	1.04	1.00	0.96	0.92
0.8	1.17	1.12	1.08	1.04	1.00	0.96
1.0	1.22	1.17	1.13	1,09	1.04	1.00

'The ratio of the relative risk estimate obtained when death certificates ore coded to the ICD revision in effect at time of death to the relative risk estimate that would be obtained if all death certificates were coded to ICD-10.

given ICD revision, the coefficient of bias will be very near unity. For some non-cancer outcomes, in contrast, there is potential for substantial bias under scenarios in which exposure status is highly correlated with the proportion of deaths coded to ICD-9, as illustrated by the numerical examples for deaths due to essential hypertension and deaths due to renal disease.

For simplicity, our examples focused on the scenario of estimation of incidence proportions in a closed cohort followed to extinction. Often, of course, in a cohort mortality study incidence rates are estimated and a proportion of the cohort survives to the end of follow up. The equations presented in the Methods section are readily adapted from incidence proportions to incidence rates (Appendix 111) accommodating the scenario in which a portion of the cohort remains alive at the end of follow up. Following the arguments in Appendix II, it can be shown that the maximaland minimal bounds for the coefficient of bias in analyses of incident rate ratios are approximately Se and 1/Se. Also for simplicity, this paper focused solely on evaluating the impact on relative risk estimates of inconsistencies in outcome classification between ICD-9 and ICD-10. It is not uncommon for the period of follow up in a cohort study to span several ICD revisions (for example, ICD-8, -9, and -10). While the transition from ICD-8 to ICD-9 was not as significant as the transition from 1CD-9 to ICD-10, further work could be done to assess the impact on relative risk estimates of outcome misclassification when cause of death data are coded to a series of earlier ICD revisions. It is plausible that the sensitivity and specificity of classification of decedents (treating classifications based upon ICD-10 as the standard) would be progressively poorer as one considered deaths coded to progressively earlier ICD revisions. As observed in this paper, inconsistencies in outcome classification between ICD

Table 4 Hypothetical data. Coefficients of bias* for analyses of the relative risk of mortality due to renal failure under varying assumptions about the proportion of exposed decedents (P_t) coded to ICD-9 rather than ICD-10 and the proportion of unexposed decedents (Po) coded to ICD-9 rather than ICD- 10

	Po					
P_t	**0.0**	**0.2**	**0.4**	**0.6**	**0.8**	**1.0**
0.0	1.00	0.94	0.89	0.83	0.78	0.72
0.2	1.06	1.00	0.94	0.88	0.82	0.76
0.4	1.13	1.06	1.00	0.94	0.87	0.81
0.6	1.20	1.13	1.07	1.00	0.93	0.87
0.8	1.29	1.22	1.14	1.07	1.00	0.93
1.0	1.39	1.31	1.23	1.15	1.08	1.00

'The ratio of the relative risk estimate obtained when death certificates are coded to the ICD revision in effect at time of death to the relative risk estimate that would be obtained if all death certificates were coded to ICD-10.

revisions might have the greatest impact on relative risk estimates if there is a strong relation between exposure status and the proportion of deaths coded to a given ICD revision.

One approach to assess potential bias due to inconsistencies in outcome classification between ICD-9 and ICD-10 is to stratify analyses into time periods during which deaths were coded to a single standard IC!) revision. Under idealised conditions (including perfect specificity), stratification should control for this source of bias. In practice, of course, the results may be difficult to interpret because changes in effect estimates observed after stratification by calendar period of death (that is, ICI) revision) may be due to factors other than bias induced by lack of comparability between ICD revisions. Therefore, the formulae in this paper (and the empirical data on sensitivity and specificity) are useful because they provide information on the potential magnitude of this bias without having to resort to stratified analyses. For example, this paper demonstrates that for most categories of cause of death, including most cancer outcomes, the potential magnitude of this source of bias is very small, and analyses that follow the standard practice of defining a mortality outcome in terms of ranges of ICD codes that span revisions (and not stratifying analyses by calendar period of death) should be appropriate. Stratification by calendar time may also constrain analytical exploration of other temporal factors (such as variation in exposure effect with time since exposure). Therefore, for epidemiological investigations that focus on categories of cause of death that exhibit poor comparability of outcome classification between ICD revisions, recoding cause of death information to a standard ICD revision may be the most straightforward approach to eliminating this potential source of bias.

The analyses in this paper consider a list of categories of cause of death (defined in terms of ICD-9 and ICD- 10 codes) proposed by the US National Center for Health Statistics.' Sonic investigators have employed different definitions of mortality outcomes than those employed in this paper (for example, they have posited slightly different ranges of ICD-9 and/or ICD-10 codes associated with a category of cause of death). The LTAS program released by the US National Institute of Occupational Safety and Health, for example, defines 117 minor categories of cause of death in terms of ICD codes for revisions 7 through 10; and, the program OCMAP released by the University of Pittsburgh defines 60 categories of cause of death in terms of ICD codes for revisions 6 through 10.° The bridge coded data used in these analyses arc publicly available (http://ftp.cdc.gov/pub/Health Statistics/NCHS/Datascts/Comparability/icd9_icd10/); therefore, interested investigators can calculate sensitivities and specificities for different definitions of categories of cause of death. Use of different definitions of categories of cause of death could lead to estimates of sensitivity and specificity that differ from those values reported in table 1, and definitions of outcomes that exhibit greater consistency across ICD revisions should result in less overall bias. However, the general conclusions of this paper are unlikely to be substantially changed given that for many categories of death, such lung cancer and breast cancer, there is substantial consensus on the specified ranges of ICD codes associated with the category of death.

In addition to definitions of comparable ranges of ICD-9 and ICD-10 codes for a given category of cause of death, outcome classifications may differ depending upon the ICD revision used to code cause of death information as a result of changes between ICD revisions in rules for selection of the underlying cause of death.' ` Consequently, use of multiple cause coding of death information should lead to greater consistency in the classification of decedents into categories of death. We found that use of multiple cause coding slightlyimproved the consistency of classification of decedents into categories of death (results not shown).

The impact of using deaths coded to contemporaneous revisions of the ICD (and subsequently defining categories of cause of death via appropriate ranges of ICD-9 and ICD-10 codes) appears to be minimal for categories of cause of death that have high levels of comparability between ICD-9 and ICD-10 (that is, high sensitivity and specificity values in table 1). For such outcomes, even when exposures arc correlated with the proportion of deaths coded to one of the ICD revisions a small degree of bias is expected. In contrast, for categories of cause of death that exhibit low levels of comparability between ICD revisions, the relative risk estimates obtained when death certificates are coded to the ICD revision in effect at time of death may diverge substantially from the relative risk estimate that would be obtained if all death certificates were coded to a consistent ICD revision (that is, ICD-LO).

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REFERENCES

1 Israel RA, Rosenberg HM, Curtin IR. Analytical potential for multiple cause of death data. Am J Epidemiol 1986;124:161-79.
2 Anderson **RN,** Minino AM, Hoyert DL, et al. Comparability of cause of death between ICD-9 and ICD-10: preliminary estimates. Nail Vital Stat Rep 2001;49:1-32.
3 **Hetzel AM.** Histo*ry* and *organization* of the vital statistics *system.* Hyattsville, Maryland: National Center for Health Statistics, 1997.
4 **Steenland K,** Beaumont J, Spaeth *5,* eta!. New developments in the life Table Analysis System of the National Institute for Occupational Safety and Health. Journal *of* OccupationalMedicine 1990;32:1091-8.
5 Marsh GM, Youk AO, Stone RA, et al. OCMAP-PLUS: a program for the comprehensive analysis of occupational cohort data. J Occup Environ Med 199840:351-62.
6 **Steenland K,** Nowlin S, Ryan B, et al. Use of multiple-cause mortality data in epidemiologic analyses: US rate and proportion files developed by the National Institute for Occupational Safety and Health and the National Cancer Institute. Am J *Epidemiol* 1992;136:855-62.

APPENDIX II

If Sp very closely approximates unity (as is the case for the categories of cause of death shown fn table I) then the expression for *RR'* can be approximated as

$$RR' = S\sim(-r\sim \text{Seo(ro)}$$

The minimal value for the coefficient of bias occurs under the scenarios in which all deaths among the exposed study subjects are coded to ICD-9, while all deaths among the unexposed were coded to ICD-10 (that is, P, = 1 and $P_O = 0$). in this case

$$Se, \_ (I —P,)+Se" P, = Se, Sp, = (I—P,)+Sp*P, = Sp, \quad Se,)\_ (I—Po)+Se` P_0 = 1,$$

Spo 1—Po)+Sp" Ps = 1; therefore,

$$RR' = \frac{Se_t(\text{'tl} + (\text{l} - \text{SPI}(1 - \text{rml}}{ro}$$

which, as noted above, can be approximated by

$$\frac{Seth,)}{ro}$$

when $_{Sp}$— 1. Therefore, the minimal value for the coefficient of bias,

$$\frac{RR'}{RR}$$

can be approximated by Se, the sensitivity of the outcome classification under ICD-9 relative to ICD-10. Following a similar argument, if Sp very closely approximates unity, the maximal value for the coefficient of bias can be approximated by

$$\frac{1}{Se}$$

APPENDIX III

Consider a study comparing mortality rates, rather than incidence proportions, in two groups. Let's denote the observed mortality rate for a specified category of cause of death in the exposed subgroup as r_1, and the observed rate in the unexposed group as r,,, where r, and r_0 denote incidence rates. Let us further denote d, and d_5 as the death rates from all other causes. An analysis of these data would yield a rate estimate in the exposed subgroup, *r', = Se, (r,)+(* 1 *—Sp,)(d,);* a rate estimate among the unexposed, *r'5 = Sep) (rü)+(I—S,,)(d„);* and, a rate ratio estimate o1 RR' = *r' 1/,'0.*

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Use of Multiple Cause of Death Data in Cancer Mortality Analyses

David B. Richardson*

Background *In a cancer mortality study, the decision of whether to define a study outcome via underlying cause of death (UCD) or via multiple cause of death (MCD) information may impact relative risk (RR) estimates and associated confidence intervals.*
Methods *Simple equations are presented that relate RR estimates obtained in a cancer incidence study to the RR estimates obtained in mortality studies using UCD and MCD information. Data from the Surveillance, Epidemiology and End Results program were used to obtain information about the detection and confirmation rates of cancer diagnoses made via UCD. Data from US cause of death data tapes were used to obtain information on the ratio of UCD to MCD listings for cancer outcomes. Numerical examples illustrate the use of these equations.*
Results *In our examples, the RRs obtained via analyses of MCD were close to those obtained via analyses of UCD (but of'greater precision), even when assuming that the confirmation rate of cancer diagnoses made via MCD listing was substantially lower than that of diagnoses made via UCD.*
Conclusions *These finding are supportive of the use of MCD information in cancer mortality studies. Ain. J.* Ind. Med. 49:683-689, 2006. © *2006 Wiley-Liss, Inc.*

KEY WORDS: occupational mortality; multiple cause of death; death certificates; cancer; epidemiologic methods

INTRODUCTION

In cancer mortality studies, the outcomes under investigation are often defined in terms of the underlying cause of death (UCD) listed on the death certificate. Until 1968, cause of death information was routinely tabulated at the national level only for UCD; consequently, until recently an investigator necessarily had to define study outcomes in comparisons to national mortality rates (i.e., analyses of standardized mortality ratios).

However, in mortality studies that involve internal comparisons between groups with different exposures, the investigator has had the option of making use of all listed causes on the death certificate which may include contributory causes as well as other diseases not related to the underlying cause (listed as "other conditions" prevalent at death). The use of multiple cause of death (MCD) information may be particularly valuable for studies of chronic diseases, such as cancer, which tend to occur at older ages in patients with multiple morbid conditions prevalent at death [Israel et al., 1986]. Several previous authors have noted that entirely discounting available information on non-underlying causes of death may be a waste of information, and further argued that focus on a single underlying cause often provides an incomplete picture when there are multiple conditions present at death [Dorn and Moriyama, 1964; Markush and Seigel, 1968; Israel et al., 19861.

Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, North Carolina

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'Correspondence to: David B. Richardson, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7435. E-mail: david.richardson @unc.edu

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In this article, the decision of whether to define cancer mortality outcomes in terms of UCD or MCD information is framed in terms of the impact on relative risk (RR) estimates and associated confidence intervals. I focus on the scenario of a cancer mortality study that contrasts incidence proportions between two subgroups of the study population. My working assumption is that the aim of this hypothetical cancer mortality study is to approximate the RR that would be obtained in a study of cancer incidence. Equations are developed that permit one to contrast the RRs obtained via analyses of UCD and MCD information to the R.R that would be obtained via analyses of cancer incidence. These equations are formulated in terms of the sensitivity and positive predictive value of cancer diagnoses made via UCD and MCD information. These values are derived, where possible, from published data in which the "gold standard" was considered to be the ascertainment of cancer cases via a cancer registry [Percy eta]., 1990]. Therefore, the numerical examples contrast the RRs derived via analyses of UCD and MCD information to the RR that would be obtained in an incidence study that ascertained cases via a cancer registry.

MATERIALS AND METHODS

Consider a hypothetical study comparing cancer risk in two groups, with cancer incidence ascertained in a closed cohort via a cancer registry with characteristics comparable to those of the Surveillance, Epidemiology, and End Results (SEER) program. Let's say that the cancer risk in the exposed subgroup is r_1, the cancer risk in the unexposed group is r0, and the cancer risk overall is r., where r_1, r_0, and r. denote incidence proportions (see Appendix 1).

Now consider the same population examined in the context of a mortality study of cancer outcomes in a closed cohort followed to extinction. If case ascertainment via the cancer registry is our standard, we can then refer to information about the sensitivity (sometimes referred to as detection rate) and confirmation rate (sometimes referred to as positive predictive value) for cancer classifications based upon UCD information. Table I reports sensitivity and confirmation rates for three cancer outcomes; these values, denoted Se_{UC}:r, and Cfucn, were originally reported by Percy et al. [1990] and were obtained by linkage of cancer registry records with UCD information.

Using these reported values for the sensitivity and confirmation rate for cancer outcomes we can derive Spt!(.'o (see Appendix I), the specificity of cancer outcomes classified via UCD information, as

$$SPUCD = 1 - \frac{Se_{uct)(r,)} - SeUCD(r,)}{Cfucu(l-r.) + (1-r.)}$$

Assuming that Se_{UCD} and SP_{UCD} are equivalent in the exposure groups, an analysis in which cancer outcomes were defined via UCD would yield an estimate of cancer risk in the exposed subgroup,

$$r/_1 = SeUCD(r_l) + (1 - SPUCD)(I - rl)$$

an estimate of cancer risk among the unexposed,

$$r'o = Seuco(ro) + (I - SPUCO)(I - ro)$$

and a risk ratio estimate of r'1/r'0.

TABLE I. Estimates of the Sensitivity, $Seuco$, and Confirmation Rate, Cfuco, for Classification of Three Cancer Outcomes Via Underlying Cause of Death Information Derived From the US Death Certificate

Cancer category (international Classification of Diseases, Ninth Revision)	Seuco'	Cfuco[a]	xe
Leukemia (204-208)	0.74	0.94	0.30
Pancreas (157)	0.92	0.90	0.07
Lung and bronchus(1622-162.9)	0.95	0.94	0.09'

Also shown is the ratio of the number of cases listed as a non-underlying cause of death to the number of cases listed as the underlying cause,
'From Percy et al. [1990].
'From Steenland et al. [1992]. The ratio of cases listed anywhere on the death certificate to the number of cases listed as underlying cause minus one.
'Value reported by Steenland et al. [1992] is for lung, bronchus, and trachea

Multiple Cause of Death Information

Use of MCD information classifies as diseased all of those people classified as diseased via UCD information plus adds other people to the diseased category. If UCD information leads to the identification of t people with a disease, then use of MCD information leads to identification of (t + xt) cases, where x denotes the ratio of the number of deaths for which a cancer was listed anywhere on the death certificate to the number of deaths for which the cancer was listed as the UCD, minus one. In a cohort mortality study in which all cause of death information has been collected, x can be directly calculated. However, an estimate of x for a given cause of death can be obtained via analyses of US multiple cause of death data tapes (Table I).

The confirmation rate for the additional cancer cases listed as non-underlying causes may differ from the confirmation rate for cancer cases classified based upon UCD information. If the confirmation rate for the additional cancer cases listed as non-underlying causes is denoted Cf;,. then the sensitivity and specificity of outcome classification using MCD information can be expressed as,

$$SeMCD = SevCD + xCfae \quad \frac{Seucor.\ I\ I_{-.SPuC[D1(1\ ,...r.)}}{\llcorner}$$

and

$$SPMCD = SPUCD - x(1 - Cfac) \quad \frac{se_{\sim}.l,r.+(i..spucu)tl\ r.)}{1\ \_r.}$$

Assuming that Se_{MCD} and SP_{MCD} are equivalent in the exposure groups, an analysis in which cancer outcomes were defined via MCD would yield an estimate of cancer risk in the exposed subgroup,

$$r'' = SeMCD\ (^{r}i) + (1 - SpMCD)\ (I - rt)$$

an estimate of cancer risk among the unexposed,

$$^{r}{}''o = {}^{Se}MCD(^{r}o) + (I - SPMCD)(1 - ro)$$

and a risk ratio estimate of r" r /r"0.

Numerical Examples

These relationships are illustrated for several scenarios. Numerical examples are presented for analyses of leukemia, pancreatic cancer, and lung cancer. 1 specify that ru is 0.010 for leukemia, 0.014 for pancreatic cancer, and 0.080 for lung cancer.

Results are presented for three values for RR (1.5, 2.0, 4.0), where RR = r_1/rr,. I applied the sensitivity and confirmation rate for outcome classification via UCD using the values in Table I; and, I specified the ratio of the number of deaths for which a cancer was listed as a non-underlying cause to the number of deaths for which the cancer was listed as the UCD using the values in Table 1.

Results are shown for the scenario in which the confirmation rate for the cases ascertained via non-underlying cause of death information (Cf,,,,) is equal to the confirmation rate for cases ascertained via UCD, CfUCD• Results are also shown for scenarios in which Cf_{lc} is lower than Cf_{UCD}; specifically, I specified that Cf_{ac} = 0.90(CfucD) and Cf_{ac} = 0.75(CftrcD)•

In order to illustrate the precision of risk estimates derived via analyses of UCD information relative to the precision of risk estimates derived via analyses of MCD information, I calculated 95% confidence intervals for the relative risk estimates for the scenario of a cohort study with 1,000 exposed and 1,000 unexposed subjects. The standard deviation for the log relative risk was estimated as

SD = (loa~r ˉcoat + rouo,, - 000)1 and Wald 95% confidence limits were obtained as exp(log (r'_1 /r'u) ± 1.96 SD) [Greenland and Rothman, 1998].

RESULTS

Table II presents numerical examples for three hypothetical cohort studies comparing leukemia risk in two exposure groups. In the first example the risk of leukemia incidence among the exposed is specified to be 1.5 times the risk of leukemia in the unexposed; in the second and third examples the relative risk is 2.0 and 4.0, respectively. In each example, the sensitivity of leukemia classification via UCD information is 0.74 and the confirmation rate of leukemia diagnoses in the full cohort is 0.94. In each of the three examples the risk ratios obtained via analyses of UCD are biased towards the null when compared to the RR specified for leukemia incidence.

TABLE II. Relative Risks for Three Cancer Causes in Analyses Using UCD (^{R}Ruco) and MCD (RR_{MCO}) Information*

Outcome	RR	$RR_{uco'}$	95%CI"	$RR_{MC}O$	95%CI"
Leukemia	1.5	1.46	(0.60,3.58)	1.46	(0.67,3.20)
	2.0	1.91	(0.82, 4.45)	1.91	(0.91, 4.00)
	4.0	3.58	(1.69,7.58)	3.58	(1.85,6.90)
Pancreatic cancer		1.44	(0.74, 2.78)	1.44	(0.76, 2.72)
	2.0	1.85	(1.00, 3.45)	1.85	(1.02, 3.38)
	4.0	3.33	(1.93, 5.72)	3.33	(1.97, 5.62)
Lung cancer	1.5	1.46	(1.12,1.90)	1.46	(1.13,1.88)
	2.0	1.90	(1.48, 2.44)	1.90	(1.50, 2.41)
	4.0	3.49	(2.81, 4.34)	3.49	(2.84, 4.30)

Confirmation rate for cases listed as non-underlying cause of death ($Cf_{,,}$) is assumed to be the same as the confirmation rate for cases listed as underlying cause of death.
"Given values for $_{Cfuco}$ and $_{SeUCD}$ listed inTable I.
[b]Given values for x listed in Table ıand assuming Cf_{cf} - CfucD.
959 confidence interval calculated for the scenario in which there are 1,000 exposed cohort members and 1,000 unexposed cohort members.

Table 11 also reports the relative risk obtained via analyses of MCD, under the assumption that the confirmation rate for cases ascertained via non-underlying cause of death information was the same as for cases ascertained via UCD. The relative risks derived in analyses of cases identified via MCD information are identical to those obtained in analyses of cases identified via UCD; however, use of MCD information results in slightly tighter confidence intervals than obtained via analyses of UCD.

The results shown for numerical examples of analyses of pancreatic cancer and lung cancer are similar to those shown for leukemia (Table 1I). Risk ratios based upon analyses of UCD are biased towards the null when compared to the RR specified for incidence in each example. The relative risks derived via MCD information are the same as that obtained via UCD although use of MCD information results in slightly tighter confidence intervals than obtained via analyses of UCD.

In Tables III and IV, the confirmation rate for cases ascertained via non-underlying cause of death information was less than the confirmation rate for cases ascertained via UCD. Specifically, for the numerical examples in Table II1 the confirmation rate for cases ascertained via non-underlying cause of death information was 90% of the confirmation rate for cases ascertained via UCD; and, for the numerical examples in Table IV the confirmation rate for cases ascertained via non-underlying cause of death information was 75% of the confirmation rate for cases ascertained via

TABLE III. Relative Risks for Three Cancer Causes in Analyses Using UCD (RR_{UCO}) and MCD (RR_{MCD}) Information'

Outcome	RR	RR_{UCO}	95%CI'	RR_{MCO}[b]	95%CI"
Leukemia	1.5	1.46	(0.60, 3.58)	1.45	(0.66, 3.17)
	2.0	1.91	(0.82, 4.45)	1.88	(0.90, 3.93)
	4.0	3.58	(1.69, 7.58)	3.44	(1.80, 6.59)
Pancreatic cancer	1.5	1.44	(0.74, 2.78)	1.43	(0.76, 2.71)
	2.0	1.85	(1.00,3.45)	1.85	(1.01,3.36)
	4.0	3.33	(1.93,5.72)	3.29	(1.95,5.55)
Lung cancer	1.5	1.46	(1.12,1.90)	1.45	(1.13,1.87)
	2.0	1.90	(1.48, 2.44)	1.89	(1.49, 2.40)
	4.0	3.49	(2.81,4.34)	3.44	(2.80,4.22)

Confirmation rate for cases listed as non-underlying cause of death (Cf_{ac}) is assumed to be 90% of the confirmation rate for cases listed as underlying cause of death.
[a]Given values for C_{fuco} and S_{euco} listed in Table I.
[b]Given values for x listed in Table I and assuming Cf_{ac} - 0.90(Ctucol.
`95% confidence interval calculated for the scenario in which there are 1,000 exposed cohort members and 1,000 unexposed cohort members.

UCD. The relative risks obtained in analyses of MCD are slightly more attenuated than the relative risk estimates obtained in analyses of cases ascertained via UCD. This occurs because the confirmation rate for the additional cancer cases ascertained via non-underlying cause of death information is lower than the confirmation rate for cases ascertained via UCD. However, even under these scenarios the relative risks obtained in analyses of MCD are similar in magnitude to the relative risks obtained in analyses of UCD (differing by less than 10%); and, use of MCD information results in tighter confidence intervals than those obtained via analyses of UCD.

TABLE IV. Relative Risks for Three Cancer Causes in Analyses Using UCD (RR_{UCC}) and MCD (RR_{MCD}) Information*

Outcome	RR	RR_{UCO}'	95%CI'	RR_{MCD}[b]	95%CI'
Leukemia	1.5	1.46	(0.60,3.58)	1.43	(0.65,3.13)
	2.0	1.91	(0.82, 4.45)	1.84	(0.88, 3.83)
	4.0	3.58	(1.69, 7.58)	3.25	(1.71, 6.17)
Pancreatic cancer	1.5	1.44	(0.74, 2.78)	1.43	(0.76, 2.70)
	2.0	1.85	(1.00, 3.45)	1.83	(1.01, 3.34)
	4.0	3.33	(1.93, 5.72)	3.24	(1.93, 5.46)
Lung cancer	1.5	1.46	(1.12,1.90)	1.45	(1.12,1.86)
	2.0	1.90	(1.48, 2.44)	1.87	(1.48, 2.37)
	4.0	3.49	(2.81, 4.34)	3.35	(2.73, 4.11)

Confirmation rate for cases listed as non-underlying cause of death (Cf_{ac}) is assumed to be 75% of the confirmation rate for cases listed as underlying cause of death.
'Given values for C_{fuco} and S_{euco} listed in Table I.
[b]Given values for x listed in Table I and assuming Cf_{ac} – 0.75(Cfuco).
'95% confidence interval calculated for the scenario in which there are 1,000 exposed cohort members and 1,000 unexposed cohort members.

The numerical examples presented here are generally supportive of the use of MCD data for cancer mortality analyses. The equations and numerical examples suggest that use of MCD information should result in RR estimates that are similar to those obtained via use of UCD information but of slightly greater statistical precision. Ideally, a decision about whether to define a study outcome via UCD or via MCD information would be informed by empirical data about the sensitivity and specificity of disease diagnoses using UCD and MCD information. Unfortunately, there is minimal information available in the published literature on the reliability of MCD information for classification of cancer outcomes. Therefore, numerical examples have been used to illustrate the likely impact on relative risk estimates of use of UCD and MCD information. It is shown that, even in scenarios in which the confirmation rate of the cases ascertained via non-underlying cause information is 75% of the confirmation rate for cases ascertained via UCD information, the relative risk estimate obtained in analyses of MCD typically is only modestly attenuated relative to that obtained in analyses of UCD. It should be noted that there is little empirical evidence to suggest that cancer diagnoses noted as non-underlying conditions are markedly less reliable than those noted as the UCD.

DISCUSSION

For simplicity, examples focused on the scenario of a closed cohort followed to extinction. Often, of course. in a cohort mortality study a large proportion of the cohort survives to the end of follow-up. Among those alive at the end of follow-up, the sensitivity of the death certificate for ascertaining cancer incidence is, by definition, 0; and, the specificity of the death certificate for ascertaining cancer incidence is, by definition, I (since false positive cases can only be ascertained among the members of the cohort who are deceased). Appendix 11 presents equations for calculating the sensitivity and specificity classifications of cancer cases for the scenario in which a portion of the cohort remains alive at the end of follow-up.

The equations and numerical examples presented here are premised on the assumption that outcome misclassification is non-differential with respect to exposure (i.e., sensitivity and specificity of case classification does not differ by exposure status). There are scenarios, of course, in which differential misclassification may occur. For example, deaths that occur at a hospital are more likely to have multiple causes listed than deaths that occur in other settings [Wall et al., 2005]; therefore, Se_{MCD} and SPMCD may vary with place of death. If place of death was related to exposure status then this would be a scenario in which differential outcome misclassification would he more likely to arise in analyses that define outcomes via MCD information than in analyses that defined the study outcome via UCD. Of course concerns about differential outcome

misclassification are not unique to analyses of MCD data; if place of death is related to exposure then differential case misclassification may occur in analyses based upon UCD as well, since UCD tends to be more accurately recorded for deaths that occur at a hospital (i.e., Seuw and SpucD may also vary with place of death). There are also scenarios in which differential misclassification of case status may be less likely in analyses that utilize MCD information than in analyses that utilize UCD information. For example, often in cohort mortality studies cause of death information is coded to the ICD revision in effect at time of death (this is the case, for example, in studies that obtain cause of death information from the US National Death Index). The rules for selection of a single UCD from the listed causes of death have changed between revisions of the ICD. Therefore, for a given cause of death SeUCD and SPUCD may vary over calendar time; if calendar year of death were related to exposure then this could be a source of differential misclassification in analyses based upon UCD information; in contrast, this is not an issue if study outcomes are defined in terms of MCD information.

This discussion has been framed in terms of analyses of mortality risk ratios. However, analyses of cohort data often involve estimation of rate ratios. Previous authors have noted that for non-differential outcome misclassification, the relationship between sensitivity/specificity and attenuation bias in relative risk and relative rate estimates is similar as long as one assumes that false positive cases do not result in much improper truncation of follow-up time for truly non-diseased subjects [Rothman and Greenland, 1998]. For analyses in which case classification is based upon death certificate information, this assumption is held since follow-up time is truncated for deceased subjects regardless of their case status (therefore, false positive cases never result in improper truncation of follow-up time). Consequently, by reference to sensitivity and positive predictive value of case classification one might describe the apparent rate ratio in a similar manner to that illustrated in this paper for analyses of risk ratios.

In these numerical examples, the use of MCD information typically resulted in a modest increase in precision of relative risk estimates over that achieved in analyses that used UCD information. In order to achieve a comparable increase in precision in a cohort study that utilized UCD information to that achieved via analyses of MCD information, however, an investigator would need to increase the study size in proportion to the ratio of cases listed as MCD to the number listed as UCD (Table 1). For the example of leukemia mortality shown in the first row of results in Table II, the analysis using UCD information resulted in a $RR_{tjCD} = 1.46$ (95% Cl 0.60, 3.58) and was based upon a hypothetical cohort of 2,000 subjects. In order to obtain a RRu estimate with confidence intervals as narrow as those obtained viaanalyses of MCD information (0.68. 3.20), an investigator would require a cohort study of approximately 2,600 subjects. The gain in efficiency obtained via use of MCD information will be greater for outcomes that have a high ratio of multiple cause listings to underlying cause listing [Steenland et al., 1992]. In general these include diseases that tend to have a long morbidity period and low case fatality rate, yet are serious enough to he noted by the certifier on the death certificate.

It is assumed that the aim of an investigator conducting a hypothetical cancer mortality study is to approximate the RR that would be obtained in a study of cancer incidence. Of course, a study that relies upon death certificate data assesses an association that is different from the association assessed in a cancer incidence study. Mortality studies are open to potential confounding by treatment quality, for example, and may underestimate the role of risk factors that influence the incidence of less severe or non-fatal disease. From this perspective, as well, the use of MCD information in cancer studies might be expected to minimize these limitations and increase the comparability of RR estimates obtained in cancer mortality and incidence studies. Analyses based upon MCD information will typically encompass some of the cases of disease that were prevalent at death but not selected as the UCD. Of course, an investigator has the option of considering results obtained via analyses of outcomes defined via MCD and via UCD information. Further empirical evaluation of the detection and confirmation rates for cancer classifications based upon MCD information would be a useful addition to the literature and provide further information about the appropriateness of using MCD information to define outcomes in cancer mortality studies.

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REFERENCES

Dorn HF, Moriyama IM. 1964. Uses and significance of multiple cause tabulations for mortality statistics. Am J Public Health Nations Health 54:400-406.

Greenland S, Rothman *K.* 1998. Introduction to categorical statistics. In: Rothman *K,* Greenland S, editors. Modern epidemiology, 2nd ed. Philadelphia: Lippincott, Williams, & Wilkins.

Israel RA, Rosenberg HM, Curtin LR. 1986. Analytical potential lot multiple cause of death data. Am J Epidemiol 124:161-179.

Markush RE, Seigel DG. 1968. Prevalence at death. 1. A new method for deriving death rates for specific diseases. Am J Public Health Nations Health 58:544-557.

Percy CL, Miller BA, Gloeckler Ries LA. 1990. Effect of changes in cancer classification and the accuracy of cancer death certificates on trends in cancer mortality. Ann NYAcad Sci 609:87-97.

Rothman KJ, Greenland S. 1998. Modern epidemiology. 2nd ed. Philadelphia, PA: Lippincott-Raven. xiii, 737 p.

Steenland K, Nowlin S, Ryan B, Adams S. 1992. Use of multiple-cause mortality data in epidemiologic analyses: Us rate and proportion files developed by the national institute for occupational safety and health and the national cancer institute. Am J Epidemiol 136:855-862.

Wall MM, Huang J, Oswald J, McCullen D. 2005. Factors associated with reporting multiple causes of death. BMC Med Res Methodol 5:4.

APPENDIX

Consider a hypothetical study comparing cancer risk in two groups, where the case classification based upon cancer registry data conforms to Table Al. The risk in the exposed subgroup is denoted $r_J = A1n_1$; the cancer risk in the unexposed group is denoted ro = $B/n_{i)}$; and, the overall risk is denoted r. = mJ/N.

A mortality study that uses underlying cause of death (UCD) information to classify subjects with respect to cancer case status has sensitivity, $SeLIcn$, and specificity, SP_{UCD} would result in the classification shown in Table All.

The overall classification of subjects in the study with respect to disease status would conform to Table A111.

TABLE AL Distribution of Subjects by Disease Status and Exposure Status

	Exposed	Unexposed	
Diseased	A	B	m1
Non-diseased	C	D	
	mo		
	n,	no	N

The confirmation rate (i.e., positive predictive value) would be:

$$Cf_{UCD} = \frac{Seuc;e\ (A+B)}{.Sp1)(CID)}$$

Dividing the numerator and denominator by N, the confirmation rate can be expressed in terms of the average risk in the study population,

$$Cf_{UCD} = Seuco(r.) + \frac{Seucu(r.)}{t - S_{Pucu}\ I - rJ}$$

So, given $Se_{U}cn$ and $Cf_{U}cn$, the specificity can then be expressed as,

$$S_{PUCD} = 1 - \frac{Seucu(r_{,})}{Cruc.lI\ r. + (t - r'.)}$$

APPENDIX II

Consider a study of cancer mortality in a closed cohort in which aproportion, S, of the cohort is alive at the end of study. We wish to contrast the risk ratio for cancer incidence to the risk ratio obtained via analyses in which cancer cases were ascertained via UCD and via MCD.

Let's say that P is the ratio of deceased cases to incident cases ascertained over the follow-up period. Then, the sensitivity of case classification based upon UCD information will be Seu_{CD}*P. Similarly, the sensitivity of case classification based upon MCD information will be Se_{MCD}*P. If most incident cases are followed to extinction (e.g., the disease under study is rapidly fatal) then P — 1, Se_{UCD}*P — $Se_{U\ CD}$, and $Se_{M(,}$n*P' SeMCD•

The specificity of case classification based upon UCD information can be expressed as $Sp_{tJCD,}s$ = [S+(1 — S — r•) Sp_{U}cnj/(I — r.), where r. is the average risk in the study population. When the disease risk is low, $SPUCD.s$ is well approximated by $SPUCD,s$ = S+(1 — S) $Spu_{J}cn$. Similarly, the specificity of case classification based upon MCD

TABLE AII. Expected Distribution of Subjects By Exposure Status, Disease Status Defined by Cancer Registry Information, and Disease Status Defined by Underlying Cause of Death Information

	Exposed		Unexposed	
	Classification based upon registry Information		Classification based upon registry Information	
	Diseased	Non-diseased	Diseased	Non-diseased
Classification based upon UCD	Diseased	Seuco A	(1 —SPuco)C	Seuw B (1 — Spuco)D

Non-diseased $(1 - S_{euco})^{A}$ SPUCD C $(1 - S_{euco})^{B}$ SPucD D

TABLE All!. Expected Distribution of Subjects by Disease Status Defined by Cancer Registry Information and Disease Status Defined by Underlying Cause of Death Information

		Classification based upon registry Information	
		Diseased	**Non diseased**
Classification based upon UCD	Diseased	SeucD (A + B)	(1 — Spuco)(C + D)
	Non-diseased	(1 — $Se_{UCD)(A}$ + B)	$_{SPUCO\ (C}$ + D)

information can be expressed as $S_{pMCD,s}$ = [S+(l — S — r.) Similar to the numerical examples shown in Tables 11- Sp_{MCD}J/(l — r.). Consequently, as the proportion of the IV, with the additional specification of values P and S, one can cohort alive at the end of follow-up increases $_{SPUCD,s}$ and derive RRuov and RR_{MCD} for a study of mortality in a closed $S_{PMCD,s}$ approach unity. cohort that is not followed to extinction.

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Evaluation of external radiation dosimetry records at the Savannah River Site, 1951-1989

DAVID B. RICHARDSON', STEVE WING[a], ROBERT D. DANIELSb

'Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[b]Health-related Energy Research Branch, National Institute for Occupational Safety and Health, Cincinnati, OH 45226, USA

The Savannah River Site (SRS) is one of the largest facilities in the nation's nuclear weapons complex. To date, little information has been published regarding radiation risk estimates derived from epidemiological studies of SRS workers. As part of an ongoing epidemiological cohort study of SRS workers, we have assessed the suitability of the Site's personnel radiation dosimetry information for use in epidemiological analyses. This paper provides information on historical dosimetry methods, recording practices, and the completeness of computerized dosimetry information for workers employed at SRS during the period 1951-1989, when the site was operated by the du Pont Company. The study includes 18,883 workers hired at SRS between 1951 and 1987 who were employed for at least 90 days. Documents relating to external radiation dosimetry methods were reviewed, recorded doses were examined to evaluate recording practices, and the completeness of monitoring was assessed by comparing employment history and computerized dosimetry records, and by implementing a "nearby" procedure for estimating values for missing annual dosimetry records. Dosimeter technology evolved over this period from two-element film dosimeters to multielement thermoluminescent dosimeters. Dosimetry measurements were recorded consistently in 0.05 millisievert (mSv) increments. Prior to 1973, recording thresholds of 0.10-0.) 5 mSv were used while from 1973 to 1989 a recording threshold of 0.05 mSv was used. We abstracted nearly 3 person-Sv of dosimetry information that was available in hardcopy but not in computerized format. The collective dose from the computerized and abstracted records totaled 512.1 person-Sv. A "nearby" method was used to estimate dose values for 13,812 employment-years for which dosimetry information was not available. The average estimated value was 0.6 mSv and the assigned collective dose derived via the "nearby" procedure was 8.7 person-Sv. The consistency of dosimetry practices at SRS and the completeness of historical dosimetry records are supportive of their use in epidemiologic research.

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Introduction

The Savannah River Site (SRS) is a 310-square mile facility located near Aiken, SC and Augusta, GA. In 1950, the E.I. du Pont Nemours and Company contracted with the Atomic Energy Commission to design, construct, and operate a facility to produce materials, primarily tritium and plutonium, for the government's nuclear weapons program. Construction of temporary facilities was completed in May 1951; these served as the headquarters for the Construction Division. By August 1952, a heavy water plant at SRS had become operational, and in December 1953 the Site's first production reactor went critical. In 1954, the first separations facility became operational and three additional production reactors were brought on line. By December, 1954 the first plutonium was shipped from the plant. The Site's tritium facilities were completed in October 1955. Production activities at the Site have involved the operation of five large reactors, two chemical separation areas, a heavy water extraction plant, nuclear fuel and target fabrication plants, as well as test reactors, power plants, and laboratories. E.I. du Pont Nemours and Company managed and operated the site through March 31, 1989. More recent activities at the site include recycling and reloading tritium in the nation's nuclear weapons, as well as nuclear waste management and environmental restoration.

Previous epidemiological studies of SRS workers have reported evidence of an excess number of leukemia deaths among hourly-paid male employees compared to the expected number based upon US mortality rates and evidence of a positive relationship between cumulative external radiation dose and leukemia mortality (Cragle et al., 1988, 1998; Wartenberg et al., 2001). We are currently conducting an updated study of SRS workers utilizing historical records of annual whole body radiation dose estimates. These dosimetry records originally were collected and maintained for radiation protection and compliance purposes rather than for research purposes. Decisions

1. Address all correspondence to: Dr. David B. Richardson, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. Tel: + 1 919 966 2675. Fax: + 1 919 966 2089. E-mail: david.richardson@unc.edu

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regarding monitoring policies or recording practices that were appropriate in the context of monitoring for compliance may differ from those that would ideally be used if monitoring were conducted for research purposes. Therefore, as part of our study, we have assessed the suitability of using SRS historical records of annual whole body radiation dose estimates for epidemiologic purposes.

The objectives of this paper are the following: to provide a summary of historical external radiation dosimetry methods employed at SRS during the period when the Site was operated by E.I. du Pont Nemours and Company; to evaluate the recording practices used by the SRS personnel dosimetry program during these years; to utilize employment history information in conjunction with computerized dosimetry records in order to assess the potential for exposure measurement error due to incomplete radiation dosimetry information; and, to apply a previously developed method for estimating radiation doses in unmonitored employment periods in order to assess the impact of using imputed values on worker dose estimates.

Materials and methods

The analyses in this report focus on a cohort of 18,883 Savannah River Site workers who were hired by the du Pont Company prior to 1987 and who worked at least 90 days. Workers without complete information on name, SSN, date of birth, and date of first hire were excluded. This cohort of workers expands upon the cohort examined by Cragle et al. (1988, 1998) by including white males hired between 1975 and 1986 and by including white females and. non-white males and females.

A file containing work history information was constructed by manually entering du Pont payroll records that describe dates of employment and job title changes into a computer file. Job titles were standardized and grouped. Using this information a file was created that describes the number of days that a worker was employed during each calendar year (1951-1989), and the longest held occupation during each calendar year. Our analyses of the completeness of computerized whole body dose estimates refer to "employment-years." A person contributed one employment-year of observation for each calendar year in which they were employed, regardless of the number of days that they were employed in that year. A worker who has computerized annual dosimetry information for their entire employment period, therefore, would have one annual dosimetry record for each employment-year.

Health Physics Area

The health physics staff classified workers according to the "health physics area" in which they worked. This corresponded to a defined area at the Site in which the occupational exposure of personnel to radiation was under the supervision of radiation protection staff. In some cases, a health physics area corresponded to a specific location (such as a specific nuclear reactor), while in other cases it corresponded to a defined area encompassing a number of work locations dedicated to a specific process (e.g., separations). We abstracted information used to classify workers according to the health physics area in which they worked in each calendar year from quarterly dosimetry logbooks (1958-1989). If a worker was missing information on health physics area for a given employment-year, but had a known health physics area for an adjacent time period during which they were employed in the same job, then, for the purposes of exposure imputations, we assigned that health physics area to the employment-year.

Computerized Radiation Dosimetry Records

In 1979 a computerized personnel dosimetry system, referred to as the Health Protection Annual Radiation Exposure History (HPAREH) system, was implemented at SRS. For all Site employees who were actively employed in 1979, a history file of annual radiation exposure information was entered into the HPAREH system from hardcopy personnel folders and logbooks (1951-1964), magnetic tapes of logbooks (1965-1972), and HP Master File magnetic tapes (1973-1979). Since 1979 dosimetry information has been routinely entered into the HPAREH system. Recorded values include estimates of shallow dose (i.e., skin dose), notably from beta particles, that was evaluated via the personnel dosimetry system by including an uncovered, or open-window, reading; deep (penetrating) dose, such as doses from medium- to high-energy photons, that was evaluated by including shielded-window readings; neutron dose that was measured by a separate neutron dosimetry system; and tritium dose measured via bioassay methods.

Workers who terminated employment at SRS prior to 1979 are not included in the HPAREH system. However, an electronic file of annual radiation dose estimates for the period 1951-1979 was constructed for the purposes of epidemiological research conducted by the DuPont Corporation (Appendix, available with the electronic version of this article); we refer to this as the Fayerweather file. Recorded values in the Fayerweather file include estimates of shallow and deep doses; these estimates include contributions from tritium intakes and neutron exposures. Dosimetry information for an additional 1058 workers was identified and computerized during the course of an epidemiological cohort study of SRS workers conducted by Oak Ridge Associated Universities; we refer to this as the SRPABST file. The previous epidemiological analyses of radiation-mortality associations among SRS workers reported by Cragle et al. (1998) utilized information from the HPAREH, Fayerweather, and SRPABST files. For the sake of consistency

with contemporary nomenclature, dose estimates that were

originally expressed in units of rem are discussed and reported in this article in units of sievert (Sv), where I Sv = 100 rem.

Our preliminary examination of these data revealed that all workers hired after 1964 who terminated prior to 1979 were lacking computerized dosimetry information. We abstracted and manually entered dosimetry information from historical dosimetry logbooks into a computer file for 854 workers who were employed in the period 1964-1979; this resulted in an additional 1.2 person-Sv of recorded dose for the workers in our study cohort. In addition, we identified 15,752 annual dosimetry records in the historical dosimetry logbooks that were not included in the HPAREH, Fayerweather, or SRP_ABST computerized files. We manually-entered dosimetry information from historical logbooks into a computer file for 5686 of these employment-years (an additional 1.7 person-Sv of recorded dose for the workers in our study cohort). The recorded annual deep and shallow dose estimates were 0.0 mSv for nearly all of the remaining 10,066 employment-years. These were dosimetry records for workers who terminated after January 1, 1979 and appear in the historical SRS logbooks but not in the HPAREH file. We assigned an estimated annual deep and shallow dose of 0.0mSv to these years and classified them as employment-years for which monitoring information is available. Figure 1 summarizes the number of computerized annual dosimetry records available from each source, by calendar period.

Dosimetry Methods

A review of historical documents related to personnel dosimetry at SRS was conducted. We reviewed documents obtained from the published literature, as well as technical reports available from the Site. Of particular value were the Site's history of the personnel radiation dosimetry program and the technical basis document for the Savannah River Site produced for the Energy Employees Occupational Illness Compensation Program Act (Taylor et al., 1995; Scalsky, 2004).

Evaluation of Recording Thresholds

When recording dosimeter measurements, a decision is often made to define a recording threshold (i.e., the dose level above which a positive entry would be made in the dose record). Measurement results at or below this recording threshold may be indicated by a specified value such as a zero, or equivalent "null" value. Different practices may be used over time at a facility to record dosimetry results with values at or below recording threshold (Inskip et al., 1987).

Using data from the HPAREH system, we empirically evaluated dosimetric recording practices used at SRS during the period 1951-1989, and investigated the value(s) used to indicate dosimeter results below the recording threshold. This was carried out by examining the distributions of annual recorded dose, tabulated as the proportion of dosimetry records for each calendar year with dose values in specified, non-overlapping, ranges. We focused on the recording of dose values <, 0.30 mSv, the value previously reported as the recording threshold for film badge dosimeters (Taylor et al., 1995). Annual dose values were analyzed, rather than detailed weekly, biweekly, and/or monthly dosimetry results, because the former were available in computerized form whereas the latter were not. As these analyses examine annual external dosimetry data (which are the sum of more frequent periodic dosimetry measurements) the findings

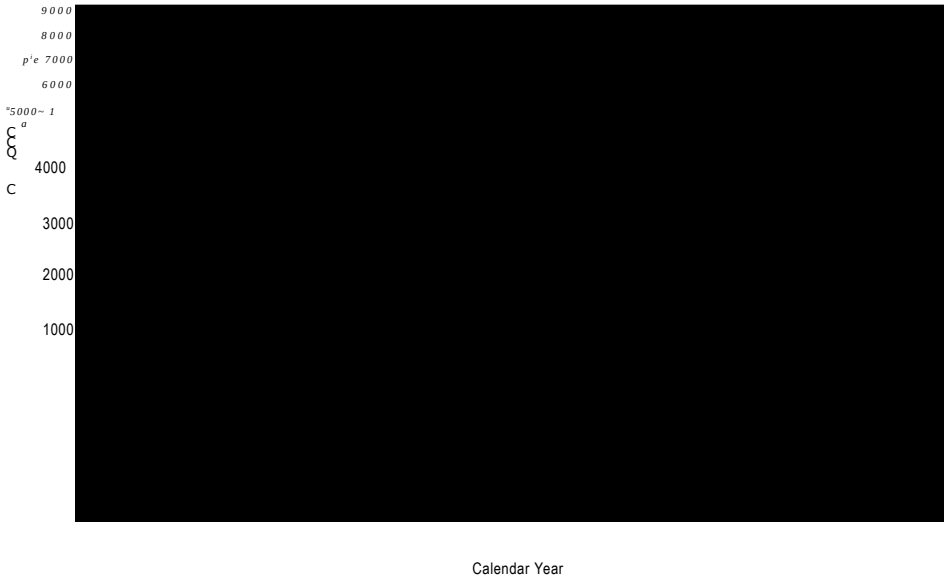

Figure 1. SRS computerized annual external dosimetry records by source, 1951-1989.

provide indirect evidence about recording practices. However, as illustrated in prior studies (Wing et al., 1994; Richardson et al., 2000), useful inferences can be drawn about recording practices from analyses of annual dosimetry data.

Completeness of Monitoring

A worker may have employment-years without computerized annual dosimetry information due to an administrative decision not to include the worker in the Site's radiation dosimetry program. Not all workers were included in the Site's radiation dosimetry program in all years; however, since the start of operations, Site policy has been to monitor external radiation exposure for workers who entered a controlled area. Other reasons why a worker may have employment-years without computerized annual external dosimetry information are data entry errors, errors in computerized record linkages, or lost records. Evidence of the latter problems comes from previous investigators who have located hardcopy annual dosimetry records for SRS workers that were not originally included in computerized dosimetry files (i.e., the SRPABST file). In order to identify workers who were employed but had no dosimetry information for a given calendar year, we compared employment history and computerized dosimetry information.

Nearby Estimation Procedure

In previous studies of workers employed at US Department of Energy sites, estimated dose values were derived for person-years of employment that were missing annual dosimetry information via a "nearby" method (Watson et al., 1994; Richardson et al., 1999). Under this method, a series of hierarchical steps are followed in order to calculate an estimated value for each missing annual dosimetry record (i.e., if there were no adequate data to calculate an estimated value using the first step in the procedure, an estimated value was calculated using a subsequent step). The first steps of the nearby algorithm use the worker's own annual dosimetry data from adjacent time periods as a basis for calculating an estimated dose. If there were adequate data, the average of the annual doses recorded within 2 years of the missing value was used to calculate an estimated value for the missing annual dosimetry record. Each annual dose was weighted by the number of days employed in that calendar year. In order to ensure stable estimates, the person-time weighted mean annual dose in neighboring years had to be based on at least 180 days of employment. If there were not adequate data in the nearby years, the average annual dose for all similar workers (defined by occupation, health physics area, gender, and calendar year of employment) was used to calculate an estimated value for the missing annual dosimetry record. The nearby approach was used to derive annual whole body dose estimates (the shielded dose, as defined by SRS, which includes tritium and neutron exposures). We evaluated the relative reliability of each step in the nearby estimation procedure by comparing observed annual doses with estimated values (results available at http://www.unc.edu/`davidr/srs).

Results

Dosimetry Technology

Initially, the personnel dosimetry program at SRS used dosimeters, processing technology, and support provided by the Oak Ridge National Laboratory (ORNL). ORNL provided SRS with a small number of beta/photon film badge dosimeters, as well as neutron nuclear track, type A (NTA) emulsion dosimeters during the period 1951-1952. Around 1953, SRS implemented their own in-house dosimetry capabilities (Taylor et al., 1995).

The original two-element film dosimeter used at SRS had a 1 mm sterling silver filter (i.e., shield) and a Vi inch diameter open window. DuPont X-ray film (Types 552, 558, and 555) was used as the radiation sensor. In November, 1959 a multielement film dosimeter was placed in general use at the Site. The multielement dosimeter held a single pack of standard dosimeter film in a plastic (Nylon) body with the top portion of the film badge covered by indium foil (0.005 inch), lead foil (0.010 inch) and a Mylar protective layer (Wright, 1959). The lower portion of the film badge had a 1 mm silver filter, a 2 mm aluminum filter, and an open window (Taylor et al., 1995) The indium foil was for "screening" use in case of a nuclear incident. Routine badge interpretation at the time of introduction of the new dosimeter was not changed from previous methods; only readings from the open window and silver-shielded window were routinely used (Wright, 1959). Film badge dosimeters were exchanged on a weekly schedule until October, 1957, on a biweekly schedule from October 1957 to 1964, on a 4-week cycle in 1965, and on a monthly schedule beginning in 1966 (Scalsky, 2004). It has been reported previously that a 0.30 mSv recording threshold was used at SRS for all film badge dosimetry during the period 1951-1970 (Taylor et al., 1995).

The SRS multielement film dosimeter was used until April, 1970 when a thermoluminescent dosimeter (TLD) with two lithium fluoride chips (an open window and aluminum shield) began to be used in place of film badge dosimeters. The SRS TLD had an estimated MDL of 0.15 mSv (Scalsky, 2004). In July, 1983 the **SRS** TLD was replaced by Panasonic TLD in large part because of breakdowns in the one-of-a-kind SRS TLD badge reader (Taylor et al., 1995). Workers who were judged to have neutron exposure potential wore NTA film dosimeters (1951-1970), or neutron TLDs (1970–). It has been reported that a 0.05 mSv recording threshold has been used during the period of thermoluminescent dosimetry (1970–) (Taylor et al., 1995). TLDs were exchanged on a

Table 1. Summary of dosimeter technologies and conclusions about recording practices for low-dose measurements

Years	Dosimeter material and type	Filters	Recording threshold (mSv)"	Recording increment (mSv)"	Indication of below threshold dosimeter (shallow dose)"
1951	DuPont 552 Film	Open, Ag	n.d.	n.d.	Blank
1952-57	DuPont 552 Film	Open, Ag	0.10/0.15	0.05	Blank
1958-70	DuPont 552 Film	Open, Al, Ag	0.10	0.05	Blank
1970-72	Li based TLD	Open, Al	0.10	0.05	Blank
1973-82	Li based TLD	Open, Al	0.05	0.05	Blank
1982-89	Panasonic UD-802 Li and Ca based TLD	Mylar, Plastic+ Mylar, Pb	0.05	0.05	Blank

'Based upon results in Tables 2 and 3.

n.d. - Not determined (n.b. very little individual external radiation monitoring was done at SRS in 1951)
External radiation dosimetry at the Savannah River Site, 1951-1989.

Table 2. Percentages of annual shallow doses in specified ranges, by calendar year 1951-1969

mSv Year	=.a	=0	>0-<0.05	=0.05	>.05-<0.10	=0.10	>0.10-<0.15	=0.15	>0.15-<0.20	=0.20	>0.20-<0.25	=0.25	>0.25-<0.30	=0.30	>0.30
1951	100.0														
1952	28.2			0.4				7.0		7.9		1.8		2.2	52.4
1953	39.0					0.5		11.4		0.6		2.3		7.3	39.0
1954	49.9	0.0		0.0		0.0		7.3		2.9		0.3		6.9	32.6
1955	37.2	0.0		0.1		0.1		0.4		10.7		1.5		2.1	47.8
1956	15.2					1.7		6.3		0.9		1.7		3.4	70.8
1957	9.0					2.8		0.5		2.1		1.1		2.2	82.3
1958	10.5					4.7		2.3		3.0		2.8		2.7	74.1
1959	10.4					7.4		2.6		3.4		2.7		1.7	71.9
1960	4.1					2.1		0.6		1.9		1.0		1.6	88.8
1961	4.3					1.6		0.9		1.1		0.8		1.3	89.9
1962	3.8					1.7		0.6		1.4		0.7		1.3	90.5
1963	8.1			0.0		2.3		0.7		1.7		1.2		1.8	84.2
1964	11.2					3.2		1.0		2.1		1.3		1.0	80.2
1965	5.1					1.9		1.0		2.1		1.3		1.9	86.7
1966	9.4					5.0		1.5		3.7		1.6		2.9	76.0
1967	4.7					2.2		0.9		2.0		1.6		1.8	86.8
1968	2.8					1.1		0.7		0.7		0.4		0.6	93.8
1969	2.0					0.7		0.2		0.5		0.4		0.4	95.9

"A "blank" value for recorded shallow dose.

Note: "0.0" indicates <0.05% of records with values in this range
Data from HPAREH file.

quarterly cycle for personnel judged to have low-exposure potential and on a monthly cycle for other employees (Table 1).

Recording Practices

Table 2 presents the percentage of annual shallow dose estimates reported each year during the period 1951-1969 (i.e., the period of film badge dosimetry) in increments between 0.0 and 0.30 mSv. Each row of the table reports the distribution of recorded dose values for a given calendar year; therefore, the reported percentages in each row sum to 100%. Inferences about the recording practices in each calendar year can be made by examination of the distribution of recorded dose values in that year. In most years during the period 1951-1969, the lowest non-missing recorded value is 0, l O mSv, although in 1953, 1954, and 1955 few annual shallow dose records have a value <0.15mSv. During this period, dosimeter results were recorded in 0.05 mSv increments. Dosimeter results for shallow doses <O.lOmSv appear to have been uniformly recorded as a "blank" value. This "blank" value was treated as a zero dose when calculating a worker's total cumulative dose accrued at the plant (i.e., in the Site's dosimetry logbooks).

During the period 1953-1957 film badge dosimeters were exchanged on a weekly schedule, while during the period

Table 3. Percentages of annual shallow doses in specified ranges, by calendar year, 1970-1989

mSv =.a Year	=0	>0- <0.05	=0.05	>0.05- <0.10	=0.10	>0.10- <0.15	=0.15	>0.15- <0.20	=0.20	>0.20- <0.25	=0.25	>0.25- <0.30	=0.30	>0.30
1970 8.8					5.9		1.7		4.4		2.5		2.5	74.2
1971 15.6			0.0		4.4		2.4		2.5		2.0		1.3	71.8
1972 18.4			0.1		8.3		2.8		3.6		2.6		1.9	62.4
1973 17.9			4.4		6.7		4.1		3.2		2.8		2.6	58.3
1974 13.4			8.6		6.0		4.5		3.5		2.6		2.5	58.9
1975 12.0			6.1		6.1		5.2		4.3		3.4		3.3	59.6
1976 11.0			6.8		6.4		5.8		5.0		3.7		3.0	58.4
1977 15.5			6.9		5.4		4.7		3.8		3.2		2.7	57.7
1978 16.6			7.7		6.4		4.6		3.9		3.4		2.5	55.1
1979 15.4	0.0		7.3		6.0		4.9		3.9		3.8		3.0	55.7
1980 16.8			7.8		6.4		5.4		4.3		3.5		3.2	52.5
1981 22.1			7.8		6.3		4.6		3.8		2.9		2.9	49.6
1982 26.3			9.8		6.5		4.6		3.6		2.9		2.0	44.2
1983 27.3			9.7		6.6		3.8		3.3		3.1		2.5	43.7
1984 41.8			8.0		4.7		3.0		2.2		2.4		2.1	35.8
1985 40.9			9.4		5.0		3.2		2.0		2.3		1.8	35.3
1986 22.0	0.0		7.1		8.1		5.4		4.6		3.3		3.4	46.1
1987 12.8			4.8		6.5		5.4		5.5		5.2		4.6	55.1
1988 14.0			4.8		6.8		5.9		5.8		4.9		4.5	53.3
1989 21.2	0.0		7.3		8.4		6.6		6.6		5.8		4.9	39.3

"A "blank" value for recorded shallow dose.

Note: "0.0" indicates <0.05% of records with values in this range
Data from HPAREH file.

1958-1964 the dosimetry program switched to a biweekly exchange schedule. There is no substantial evidence of a change in recording practices accompanying this switch in the badge exchange rate. Similarly, the switch in 1959 from a two-element to a multielement film badge dosimeter, and from manual to automated dosimeter processing, appears to have had minimal effect on the distribution of annual recorded deep dose values.

Table 3 presents the percentage of annual shallow dose estimates reported for the period 1970-1989 in increments between 0.0 and 0.30 mSv. The lowest non-zero, non-missing recorded value is 0.05 mSv, suggesting a recording threshold value of 0.05 mSv, although in the period 1970-1972 few annual shallow dose records have a value <0.10 mSv. All dosimeter results were recorded in 0.05 mSv increments. During the period 1970-1989, dosimeter results for shallow doses <0.05 mSv were recorded as a "blank" value.

Table I summarizes our conclusions about dosimetry recording practices at SRS during the period 1951-1989 derived from these analyses of recorded shallow dose values. An examination of recording practices for deep doses suggests similar recording practices to those used to record shallow doses (results not shown), although in the HPAREH file "blank" values and zeros were used to indicate deep dose estimates below the recording threshold. Specifically, a zero was recorded to indicate a deep dose value below the recording threshold if the shallow dose estimate for that year was non-missing.

Completeness of Monitoring

Between 1951 and 1989 the 18,883 workers accumulated 242,043 employment-years. Computerized annual external radiation dose estimates were available for 206,416 (85%) of these employment-years from the HPAREH, Fayerweather, and SRP_ABST files. An additional 15,752 employment-years of dosimetry data were assigned dose estimates based upon our abstraction of hardcopy SRS dosimetry records (Table 4).

Figure 2 shows the percentage of the workforce, by sex, with computerized monitoring information in each calendar year (1951-1989). By 1955 approximately 90% of the male workers employed each year have computerized annual external radiation doses estimates available, and, by 1972 there was essentially complete radiation monitoring information for all male SRS workers in the study cohort. In contrast, among female SRS workers <60% of those employed each year between 1954 and 1965 have computerized dose records. The percentage of female workers with computerized annual dosimetry records increased from 60 to 70% over the period 1966-1971; from 1972 onwards computerized annual dosimetry records were nearly complete for female SRS workers.

Estimating Values for Employment Years Lacking Computerized Dosimetry Information

While monitoring information during the period 1951-1953 was highly incomplete, radiological exposures were minimal

Table 4. Number of SRS workers by gender, number of calendar years of employment, and sources of external radiation dose estimates

	Male number (percent)	Female number (percent)	Total number (percent)
Workers employed at least 90 days, hired between 1951 and 1987	15,264	3619	18,883
Total employment-years for workers in the SRS study cohort, 19511989	211099 (100%)	30944 (100%)	242043 (100%)
Employment-years that had computerized dosimetry information, 1951-1989'	187750 (89%)	18666 (60%)	206416 (85%)
Additional employment-years of dosimetry information assigned based upon review of historical dosimetry logbooksb	9704 (5%)	6048 (20%)	15752 (7%)
Employment-years that were not monitored, 1951-1953`	5159 (2%)	904 (3%)	6063 (3%)
Employment-years of dosimetry information that were estimated via nearby methods, 1954-1989	8486 (4%)	5326 (17%)	13812 (6%)

[a]Dosimetry records from the HPAREH, Fayerweather, and SRP_ABST files.

'Values abstracted from historical dosimetry logbooks; and, based upon a review of a sample of employment-years for workers who terminated after January 1, 1979 whose dosimetry records appear in the historical SRS dosimetry logbooks but not in the HPAREH file, an estimated dose of zero was assigned to 10,066 employment-years.

`We did not estimate dose values for employment-years that were unmonitored during the period 1951-1953 since relatively few workers had potential for occupational exposure to ionizing radiation prior to December 1953.

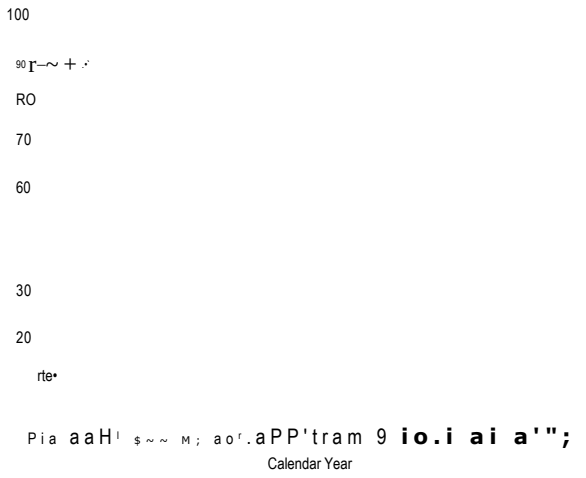

Figure 2. Percentage of workforce with computerized annual whole body doses by sex, 1951-1989.

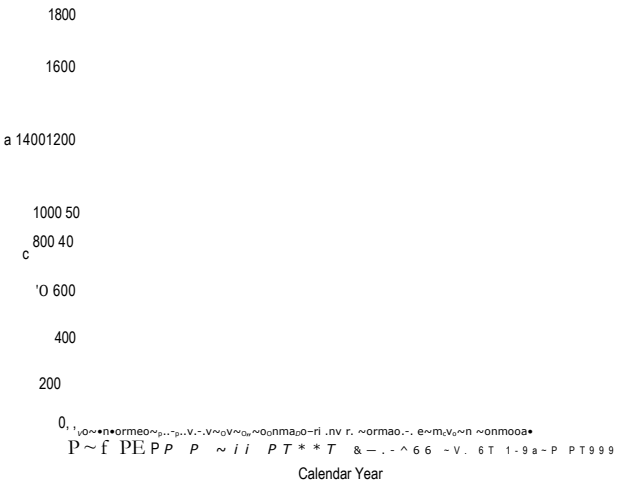

Figure 3. Number of employment-years for which estimated dose values were derived by calendar year.

for most workers during this period as the first production reactor at SRS went critical in December 1953. We did not estimate dose values for years of employment in the period 1951-1953.

Figure 3 shows the number of annual dose values estimated via the nearby approach by calendar year. Estimated dose values (52%) were for employment-years in the period 1954-1959, and 89% of all estimated dose values were for employment-years prior to 1970. Of the 13,812 employment-years without monitoring data during the period 1954-1989, 6772 (49%) of these employment-years occurred among clerical and kindred workers (Table 5); the majority of these employment-years were accrued among female workers (constituting the 85% of all employment-years among female workers with missing dosimetry information). In contrast, people employed as reactor operators, production operators, and raw materials operators had computerized dosimetry information for nearly all employment-years in these jobs (Table 5).

Figure 4 shows the total estimated dose by calendar year. With the exception of 1954, the estimated dose constitutes a small percentage of the total dose for the calendar year. Estimated annual dose values (16%) were equal to OmSv (Table 6), and 75% of the estimated doses were <0.5mSv. The highest estimated annual dose was 37.8 mSv. The average estimated annual dose was 0.6 mSv; and, the assigned collective dose was 8.7 person-Sv. This may be contrasted to the average recorded annual dose value of

Table 5. Employment-years with missing dosimetry data by occupation, 1954-1989a

	No. of employment-years without dose records	% Of employment-years without dose records	Mean estimated annual dose (in mSv)	Estimated collective dose (in person-mSv)
Other operator	1392	10	1.5	2144.5
Clerical and kindred non-manual workers	6772	24	0.2	1656.8
Other skilled manual	1364	3	1.2	1653.7
Students/unknown	899	7	0.7	671.6
Technicians, analysts, and assistants	379	3	1.8	670.7
Production/shift supervisor	192	2	1.7	322.3
Other semiskilled workers	876	5	0.4	319.5
Other supervisors	476	3	0.5	229.0
General service operator	199	2	1.0	190.3
Chemists	113	5	1.5	171.5
Engineering technicians and trainees	146	4	1.0	148.2
Engineers	215	2	0.4	80.2
Heavy water operator	60	7	1.3	75.8
Rigger	18	1	3.8	69.3
Radiation monitor, health physicist	15	0	4.1	60.9
Auxiliary operator	34	1	1.7	57.3
Power operator	187	4	0.3	52.3
Life scientists and medical services	213	12	0.1	24.4
Crane operator	21	1	1.0	22.0
Junior physicist	19	4	1.1	20.2
Senior engineers	56	1	0.4	19.8
Laboratory supervisor	17	2	1.1	18.7
Managers, specialist, and associates	55	2	0.2	10.2
Separations/process operator	23	0	0.4	9.4
Carpenter	14	14	0.6	8.6
Reactor operator	13	0	0.6	7.5
Senior physicist, process physicist	8	I	0.7	5.9
Raw materials operator	6	0	0.8	4.7
Utility operator	3	1	1.5	4.5
Administrators and professionals	18	4	0.1	1.6
Production operator	4	1	0.4	1.5
Senior chemist, process chemist	4	0	0.1	0.2
Metallurgists	I	0	0.1	0.1
	13,812	6	0.6	8733.3

'The period 1951-1953 was excluded from this description since radiological exposures were minimal during this period and we therefore did not estimate dose values for workers who were unmonitored during the period.

2.3 mSv during this period, and the recorded collective dose of 512.1 person-Sv.

The nearby method uses the worker's recorded dose information from adjacent years, if available, to derive an estimated dose value. Of the estimated values, 5224 (38%) were derived using recorded values for the same worker in the neighboring calendar years. The remainder of estimated dose values were derived using average values (typically the mean dose for other workers of the same sex, in the same occupation group and health physics area, in that calendar year).

Given the large percentage of estimated dose values for clerical and kindred workers, we examined these estimated dose values in detail. Sixteen percent of the estimated dose values for clerical and kindred workers (1066 employment-years) were equal to 0 mSv, 89% of estimated dose values for clerical and kindred workers were <0.5 mSv, and 98% of the estimated dose values for these workers were < 1.0 mSv. Twenty-six percent of the estimated dose values for clerical and kindred workers were derived using neighboring dose values; the remainder were derived using average values (typically the mean dose for other workers of the same sex, in the same occupation group and health physics area, in that calendar year).

Discussion

In this paper, we have focused on exposure measurement errors that may arise due to historical radiation dosimetry

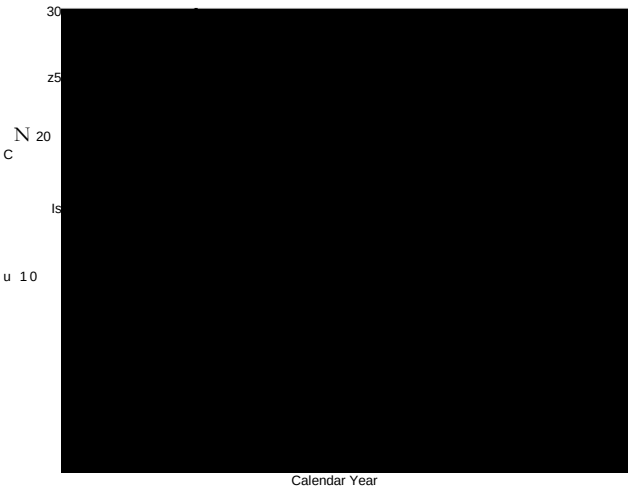

Figure 4. Recorded and estimated collective dose by calendar year

Table 6. Distribution of estimated annual doses by dose level

Estimated dose (mSv)	Number employment-years without dose records
=0	2221
>0-<l	9426
-<2	972
2-<3	464
3-<4	310
4-<5	169
5-<6	83
6-<7	43
7-<8	55
8-<9	17
9-<l0	12
10-37.8[a]	40
Total	13,812

[a]The highest estimated dose value.

recording practices and due to incomplete information in the available computerized radiation dosimetry files. There is a substantial literature on errors in external radiation dose estimation due to readings below a detection or recording threshold (Gilbert and Fix, 1995; Mitchell et al., 1997; Richardson and Ciampi, 2003; Xue and Shore, 2003; Shin et al., 2005). The validity of statistical investigations of the impacts of recording practices depends, in part, upon the validity of assumptions about historical recording practices; consequently, empirical evaluations of recording practices contribute to this literature.

Previous reports have stated that during the period of film badge dosimetry at SRS (1951-1970) there was a recording threshold of 0.30 mSv (Taylor et al., 1995). Table 1 summarizes our conclusions about the recording practicesemployed at SRS during this period. A recording threshold of 0.10-0.15 mSv was employed during this period, and a "blank" value was routinely used to indicate below-threshold dosimetry results. It appears that measurements derived from film badge dosimeters were recorded in 0.05 mSv increments (i.e., there was rounding when reading/recording values based on the optical density of the film).

For epidemiologic purposes, this recording practice is preferable to the practices suggested by previous investigators (i.e., recording a null value for all dosimetry measurements below a threshold of 0.30 mSv), and it suggests that the problem of "missed dose" due to below threshold measurements was minimized by the use of relatively low recording thresholds at SRS. Nonetheless, when dosimeters were exchanged frequently a worker's exposure history may still be characterized by a large number of below threshold dosimetry measurements.

It is notable that recording practices at SRS appear relatively consistent over time, with annual dose values as low as 0.10 mSv routinely recorded during the period 1953-1972. In contrast, during the same period at the USDOE Hanford Site, analyses suggest a recording threshold of 0.30 mSv in the years 1953-1956, a recording threshold of 0.10 mSv during the period 1957-1963, and a recording threshold of 0.20mSv during the period 1964-1971. At the USDOE Oak Ridge National Laboratory, evidence suggests that although doses of <0.30 mSv were set to zero during the period 1948-1951, recording thresholds varied during the rest of the 1950s and 1960s (Wing et al., 1994). Compared to these other nuclear facilities with external radiation monitoring programs during the same historical periods, SRS recording practices were more complete, consistent and reliable, at least for employees of the prime contractors. During later time periods, the introduction of TLD dosimeters at SRS resulted in the recording of even lower dose estimates, with values as low as 0.05 mSv routinely recorded as of 1973.

The use of a missing value in the dosimetry records, rather than a designated indication of a below threshold measurement, creates difficulties for evaluating the completeness of radiation monitoring at the site. For historical abstraction of these records, DuPont memoranda indicate that "blanks for a person indicates a zero dose" (McMahan, 1984). Similarly, in computerized records blanks were treated as a zero dose when summing quarterly or yearly dose values to obtain plant totals.

While much of the literature on the topic of exposure measurement error in epidemiological studies of workers in the nuclear industry has focused on issues of calibration, angular response, energy response, and laboratory errors, less attention has been given to the more generic issue of incomplete information on historical exposures (National Research Council and Committee on Film Badge Dosimetry in Atmospheric Nuclear Tests, 1989; Fix et al., 1994;

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Thierry-Chef et al., 2002; Daniels and Schubauer-Berigan, 2005; Shin et al., 2005). As shown in this paper, even for a well-monitored cohort at a facility where operations effectively started a decade after the commencement of the Manhattan Project, a sizable fraction of the work force in the early years of operation did not have computerized dosimetry information available. At SRS, the errors related to incomplete dosimetry information may be as important to an evaluation of measurement error as the issues of dosimeter response and calibration.

By comparing employment history and dosimetry records we identified and assigned dose estimates to 15,752 employment-years that had been monitored but were not included in previous computerized files, contributing 2.9 person-Sv of dose that had been omitted from the computerized files. In a previous study of workers employed at Oak Ridge National Laboratory, an evaluation of historical trends in the completeness of computerized monitoring information also led to the identification of historical dosimetry records that had not been previously incorporated in computerized dosimetry files (Wing et al., 1994). These examples underscore the importance of a critical evaluation of the completeness of computerized dosimetry records.

We used a "nearby" method to estimate the magnitude of "missed dose" due to periods of employment without external dosimetry information for the period 1954-1989. We did not estimate dose values for workers who lack dosimetry information for employment-years during the period 1951-1953. Given the relatively localized potential for radiation exposures in these years, we assumed that the available monitoring information encompassed those most likely exposed during that period. A large proportion of the employment-years for which we estimated dose values were for females employed in clerical and kindred non-manual jobs. It is likely, therefore, that a large proportion of the workers with missing dosimetry information had little or no occupational exposure to radiation. This is reasonably well reflected by the estimated dose values for clerical and kindred workers derived via the "nearby" method: 16% of the estimated annual dose values for individuals employed as clerical and kindred workers are 0 mSv, half are < 0.14 mSv (i.e., a dose range near the recording threshold for dosimeters prior to 1972), and three-quarters of all estimated annual doses for clerical and kindred workers are <0.3 mSv. One aspect of the "nearby" method is important to recognize in order to understand why small positive dose values have been assigned to a large number of workers who were likely to have had little or no true exposure. If a worker's true dose was zero then the nearby approach will tend to assign a value that is a slight overestimate of the "true" zero value. Based upon our validation of the nearby method applied to SRS data (see http://www.unc.edu/~davidr/srs) when the true value for an annual dose was zero, the mean and median estimated values derived via the nearby approach were 0.26 and 0.02 mSv, respectively. The reason for this is that an estimated dose value may be greater than zero but it cannot be less than zero. In contrast, if the true dose is greater than zero then the nearby method tends to produce a positive estimate that will slightly underestimate the true dose. So, the nearby estimation procedure tends to lead to a small overestimate of the value for an unmonitored dose year in which the true dose was zero and a small underestimate of the value for an unmonitored year in which the true dose was greater than zero. These findings are similar to patterns reported in a previous application of the nearby procedure to data for workers from the Hanford Site (Richardson et al., 1999). If we had information that indicated that a clerical worker was employed in an area in which the dose rate was zero then we could assign a zero dose to that year. In effect, however, the nearby method does this: if the worker was employed in a job/area where the average monitored value was zero or near zero then the worker gets assigned a zero (or near zero) value for that year. Rather than the relatively extreme assumption that the true dose value for all unmonitored years was zero, the nearby approach offers an approach to imputing a distribution of estimated dose values for unmonitored years using the workers' own data from adjacent years as well as information on occupation and area of employment. Our analyses suggest that while the recorded collective dose for the period 1951-1989 was 512.1 person-Sv a reasonable "adjusted" estimate of the collective dose for this period is 520.8 person-Sv.

Similar to findings from evaluations of the dosimetry programs at ORNL and Hanford, coverage of the SRS workforce was more complete for male workers than for female workers. The percentage of missing annual external dosimetry records among male SRS workers (4%) is comparable to the 6% missing annual external dosimetry records among male Hanford workers (Richardson et al., 1999) and the 5% missing annual dose records reported among white males employed at ORNL (Wing et al., 1991). Also similar to previous findings from evaluations of the dosimetry programs at ORNL and Hanford, we found that coverage was more complete in later historical periods than in earlier years of operation. The majority of the estimated dose values were for employment-years in the period 1954-1969 (Figure 3). During the 1950s and 1960s the radiation protection program at SRS was in a state of evolution with the health physics staff progressively growing in size and experience (Taylor et al., 1995). Despite the relatively large percentage of estimated dose values for these years of operation, however, it appears that even in these years computerized dosimetry records are essentially complete for workers in jobs with the greatest exposure potential. For example, we found that computerized dosimetry information was essentially complete for people employed as reactor operators, raw materials operators, radiation monitors, and separations/process operators (jobs in which workers tended

to receive higher annual radiation doses). The notable increase in completeness of computerized annual dosimetry records for female SRS workers in the early 1970s corresponds in time roughly with the introduction of routine monitoring of employees by TLD badges and enrolling low-exposure personnel into a quarterly badge cycle.

Although the available dose files had already been carefully examined during the course of several previous epidemiologic studies, our additional examination led to the discovery of 2.9 person-Sv missing from the electronic files. This missed dose pertained to the primary workforce from a facility where superior monitoring practices were demonstrated, which suggests that a greater proportion of missing doses may exist at other facilities where monitoring programs were not as complete and for subcontractors whose employees were not monitored as carefully.

Epidemiological studies of cancer risk among workers in the nuclear industry provide a method for directly assessing the effects of low level protracted radiation exposures. SRS is among the largest of the USDOE facilities with a history of operation that spans more than five decades. While the average external radiation dose accrued by SRS workers was relatively low, studies of SRS workers are important to this literature given the historical importance of the facility, its size, and the length of operation. In addition to analyses of this single cohort, data from epidemiological studies of SRS workers have the potential to make a substantial contribution to multifacility (i.e., pooled) analyses which aim to increase the precision of risk estimates derived from nuclear worker studies by the aggregation of data.

Conclusion

Overall, the recording practices for external radiation monitoring at SRS provide a basis for deriving reliable estimates of radiation dose. The recording thresholds employed at SRS were relatively low when contrasted with the thresholds used at other USDOE sites at comparable periods and there is evidence of a high-level of consistency over time in SRS dosimetry recording practices (Wing et al., 1994; Richardson et al., 2000). Identifying employment-years with missing annual external dosimetry information is an important step in the assessment of potential exposure misclassification bias. We identified 15,752 employment-years in which workers had been monitored and yet records were not available in the computerized files used in previous epidemiological analyses. In addition, via a nearby estimation approach we have estimated values for an additional 13,812 annual external dosimetry records. The use of this estimation procedure for missing dosimetry information may help to reduce exposure misclassification in future epidemiological analyses. The impact of these estimated values on the results of analyses of quantitative radiation dose-mortality associations for the SRS cohort will be assessed.

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References

Cragle D.L., McLain R.W., Qualters J.R., Hickey J.L., Wilkinson G.S., Tankersley W.G., and Lushbaugh C.C. Mortality among workers at a nuclear fuels production facility. *Am J Ind Med 1988: 14: 379-401.*

Cragle D.L., Watkins J.P., and Robertson-DeMers K. Mortality among workers at the Savannah River nuclear production facility. American Statistical Association: Section on Statistics in Epidemiology Dallas, TX: American Statistical Association. *1998.*

Daniels R.D., and Schubauer-Berigan M.K. Bias and uncertainty of penetrating photon dose measured by film dosimeters in an epidemiological study of us nuclear workers. *Radial Prot Dosimetry 2005: 113: 275-289.*

Fix J.J., Gilbert E.S., and Baumgartner W.V. An assessment *of* bias and uncertainty in recorded dose from external sources *of* radiation for workers at the hanford site Richland, WA: Pacific Northwest Laboratory, *1994.*

Gilbert E.S., and Fix J.J. Accounting for bias in dose estimates in analyses *of* data from nuclear worker mortality studies, *Health Phys 1995: 68: 650-660.*

Inskip H., Beral V., Fraser P., Booth M., Coleman D., and Brown A. Further assessment of the effects of occupational radiation exposure in the united kingdom atomic energy authority mortality study. *Br J Ind Med 1987: 44: 149-160.*

McMahan S.R. Exposure data extraction procedures (three interoffice memos *3/l/84, 3/12/84, 3/18/84).* In: Fayerweather, W.E. (Ed). Savannah River Plant, Aiken, SC, *1984.*

Mitchell T.J., Ostrouchov G., Frome E.L., and Kerr G.D. A method for estimating occupational radiation dose to individuals, using weekly dosimetry data. *Radial Res 1997: 147: 195-207.*

National Research Council, Committee on Film Badge Dosimetry in Atmospheric Nuclear Tests. *Film Badge Dosimetry in Atmospheric Nuclear Tests.* National Academy Press: Washington, DC, *1989.*

Richardson D., Wing S., Watson J., and Wolf S. Missing annual external radiation dosimetry data among hanford workers. *J Expo Anal Environ Epidemiol 1999: 9: 575-585.*

Richardson D., Wing S., Watson J., and Wolf S. Evaluation of annual external radiation doses at values near minimum detection levels of dosimeters at the hanford nuclear facility. *J Expo Anal Environ Epidemiol 2000: 10: 27-35.*

Richardson D.B., and Ciampi A. Effects of exposure measurement error when an exposure variable is constrained by a lower limit. *Am J Epidemiol 2003: 157: 355-363.*

Scalsky E.D. Technical basis document for the savannah river site: to be used for eeoicpa dose reconstructions. In: Neton, J.W. (Ed). *ORAU Team Dose Reconstruction Project for NIOSH Cincinnati: National Institute for Occupational Safety and Health 2004.*

Shin H., Ramsay T., Krewski D., and Zielinski J.M. The effect of censoring on cancer risk estimates based on the canadian national dose registry *of* occupational radiation exposure. *J Expo Anal Environ Epidemiol 2005: 15: 398-406.*

Taylor G.A., Crase K.W., La Bone T.R., and Wilkie W.H. *A History of Personnel Radiation Dosimetry at The Savannah River Site. U.S.* Department *of* Energy, Springfield, VA, *1995.*

Thierry-Chef I., Pernicka F., Marshall M., Cardis E., and Andreo P. Study of a selection of 10 historical types of dosemeter: Variation of the response to hp(10) with photon energy and geometry of exposure. *Radial Prot Dosimetry 2002: 102: 101-113.*

Wartenberg D., Brown S., Mohr S., Cragle D., and Friedlander B. Are african-american nuclear workers at lower mortality risk than Caucasians? *J Occup Environ Med 2001: 43: 861-871.*

Watson J.E., Wood J.L., Tankersley W.G., and West C.M. Estimation of radiation doses for workers without monitoring data for retrospective epidemiologic studies. *Health Phys 1994: 67: 402-405.*

Wing S., Shy C.M., Wood J.L., Wolf S., Cragle D.L., and Frome E.L. Mortality among workers at oak ridge national laboratory. Evidence of radiation effects in follow-up through *1984. JAMA 1991: 265: 1397-1402.*

Wing S., West C.M., Wood J.L., and Tankersley W. Recording of external radiation exposures at oak ridge national laboratory: Implications for epidemiological studies. *J Expo Anal Environ Epidemiol 1994: 4: 83-93,*

Wright C.N. *Packet of Assembled Data on srp Film Badge (for Easy Reference).* Savannah River Plant, Aiken, SC, *1959 p 14.*

Xue X., and Shore R.E. A method for estimating occupational radiation doses subject to minimum detection levels. *Health physics 2003: 84(1): 61-71.*

Appendix

An electronic file of annual radiation dose estimates for the period 1951-1979 was constructed for the purposes of epidemiological research conducted by the DuPont Corporation; this is referred to as the Fayerweather file (after the principal investigator of that study). Values recorded in the Fayerweather file require reference to indicator flags associated with each annual dose estimate in order to properly characterize whether a worker was monitored (and if so, whether the recorded dose is zero or some non-zero value).

A flag is associated with each annual dose record. Historical dosimetry information for the period 1952-1964 was abstracted from hardcopy personnel folders and logbooks. Detailed abstraction procedures are documented in three DuPont memoranda (McMahan, 1984). There are two primary flags associated with records for the period 1952-1964. A flag value of "?" indicates a calendar year with unknown monitoring status (i.e., a year for which no dosimetry record was located) (McMahan, 1984). Essentially all of the dosimetry records (99.46%) flagged with a "?" have recorded values of 0 mrem; these are treated as unmonitored calendar years. A small number (n = 230) of records flagged with a "?" have non-zero recorded values that were confirmed by review of SRS logbooks; these records are treated as monitored years. A flag value of "R" is associated with 36% of these records and is taken to denote an annualdose value that was entered into the Fayerweather system from the hardcopy dosimetry records. Finally, several flag values were defined to indicate errors encountered during manual data abstraction. The most common of these (assigned to 9% of records) is the flag value "9" which denotes no dosimetry information for the calendar year (McMahan, 1984); these are treated as unmonitored calendar years. The flag value "7" was used (4% of records) to indicate that no exposure information for the calendar year was found in the worker's folder (McMahan, 1984); this flag value was only used during the period 1952-1957 (when dosimetry information was maintained in file folders). These years are treated as unmonitored calendar years. The flag value "8", intended to denote illegible information in the worker's folder, was never used (McMahan, 1984). Flag values of "1", "2", "3", and "4" were used to indicate incorrect information about the open window, shielded window, neutron, and tritium fields, respectively; the flag value "5" indicates that the name on the exposure collection data sheet does not agree with the name in the exposure logbook but the roll and payroll number agree, and flag "6" denoted that a neutron-tritium worksheet was used in data abstraction (McMahan, 1984). Flag values "1"–"6" were seldom used (in total they are associated with 0.2% of records) and dose records with these flags are treated as monitored calendar years.

For the period 1965-1978 dosimetry information was entered into the Fayerweather file from magnetic tapes. Each annual dose record for this period is associated with a flag value of either "T" or "?". A flag of "T" denotes a dose estimate that was entered into the Fayerweather system (n = 13,528) while a flag of "?" denotes a calendar year for which monitoring status is unknown. During this period 99.95% of the 84,174 dosimetry records flagged with a "?" have recorded values of 0 mrem and are treated as unmonitored calendar years; 43 of these dosimetry records (representing 18 workers) have non-zero dose values which were confirmed by review of SRS dosimetry logbooks and are treated as monitored years.

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DOSE RECONSTRUCTION FOR AN OCCUPATIONAL COHORT AT THE SAVANNAH RIVER NUCLEAR FACILITY: EVALUATION OF A HYBRID METHOD

Ghassan Hamra', Leena A. Nylander-French' and David Richardson2,*

'Department of Environmental Sciences and Engineering, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7400, USA

[2]Department of Epidemiology, School of Public Health, The University of North Carolina at Chapel Hill, CB #7435, McGavran-Greenberg, Chapel Hill, NC 27599-7400, USA

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The Savannah River Site (SRS) is the only nuclear facility in the United States that produces tritium, a radioactive isotope of hydrogen. The purpose of the study was to derive annual tritium dose estimates for SRS employees through the development of a job-exposure matrix. The proposed method is unique in that along with qualitative information on job, area and time of employment, it utilises recorded annual whole-body dose measures, when available, in order to estimate doses from tritium intakes of the monitored workers. Using information from 75 253 dose measures for the period 1954-1978, the average proportion of the whole-body dose that was due to tritium intake was calculated; these proportions were allowed to vary by job, area and time period. This information was used to assign tritium dose levels for 43 590 employment-years. The collective estimated tritium dose was 4319 mSv compared with the total known tritium dose of 17 382 mSv. The correlation (R^2) of estimated tritium dose with known tritium dose was 0.68.

INTRODUCTION

Savannah River Site (SRS) is a 315-mile^2 nuclear fuel facility located in Aiken, SC, USA. Originally operated by E.I. duPont de Nemours & Company (DuPont), SRS has produced nuclear fuels, mainly tritium and ^{23}9Pu, for > 50 y. Since SRS is solely a nuclear fuels facility, radiological hazard protection is integrated into everyday operations. Although this may help reduce occupational exposures, it does not eliminate them. About 85`%0 of the total occupational dose is characterised as external exposure, while the remaining 15'%, are attributable to internally deposited radionuclides(').

One of these radionuclides is tritium, an isotope of hydrogen that emits beta radiation as it decays into helium~^{2}~. Since it acts like hydrogen, tritium gas is capable of binding to oxygen molecules to form tritiated water (HTO). HTO may enter the body via inhalation, ingestion, or absorption through the skin[13)]. Once absorbed, HTO will readily diffuse through cellular membranes, uniformly integrating itself into the water present in the human body[(2)]. While tritium has a physical half-life of 12.3 y, ingested HTO has a biological half-life of about 10 d[t4] . In that time, tritium is capable of producing genetic mutations via beta-radiation or the energy release associated with transformation from ^{3}H to ^{3}He[(2)]. Animal tests have shown that acute exposure to HTO can lead to malformations and death[(3)]. However, little is known about the effects of chronic low-level exposure. One study by Joksic and Spasojevic-Tisma[(5)] found that low-level exposure to tritium caused chromosomal damage in human lymphocytes, but direct estimates of human cancer risk following tritium exposure are not available

Savannah River Site is the only nuclear fuel facility in the US that produces tritium. Although tritium is a by-product of processes at most other nuclear facilities, the fact that SRS has the explicit task of producing tritium necessitates an examination of exposure to tritium among SRS employees. Historically, tritium dose was measured via biological monitoring at SRS. Since the late 1970s, dose measures have been maintained in an electronic format that facilitates their use for research purposes. However, dose measures for earlier time periods have only been computerised in summation with the other components of a worker's whole-body dose (i.e. summed together with penetrating dose from external irradiation).

The goal of the research was to develop a predictive model of the tritium dose component of annual recorded whole-body dose (AWBD). This research is unique in that principles of job-exposure matrix development with quantitative measures of AWBD were combined to estimate personal tritium dose for SRS employees without a known tritium dose. Often in occupational settings, a researcher has very little information with which to derive individual

***Corresponding author: david.richardson@unc.edu**

quantitative exposure estimates. In this case, there are records of annual tritium dose measures for a large proportion of the workers in the study cohort. In addition, for those without records of annual tritium dose measures (e.g. the tritium component of the whole body dose was not available in computerised form) the records of AWBD have been computerised. The proposed model provides quantitative tritium dose estimates, which may be utilised in further research of health effects of tritium exposure among this population of workers.

METHODS

Cohort

A roster of 21 204 individuals hired by DuPont between 1950 and 1986 was enumerated. Those workers without a known (i) date of birth (n = 57), (ii) date of first hire (n = 184) or (iii) gender (n = 10) were excluded from the study. In addition, individuals who were employed <90 days (n = 1355) were also excluded since they may differ from long-term employees with respect to mortality risk and cumulative dose estimates. Finally, SRS workers previously employed at another Department of Energy facility (n = 715) were excluded since information on occupational radiation exposure that occurred outside of employment at SRS was not known. This left 18 883 SRS workers who met the entry criteria for inclusion in the study cohort.

Occupation and health physics area categories

A file containing work-history information was created from DuPont payroll records that contained information about dates of employment and job-title changes. Job titles were standardised and coded to 34 major occupational groups. On the basis of this information, a file was created that describes the number of days that a worker was employed during each calendar year (1951-1999). If a worker held more than one job in a calendar year, for simplicity, a single occupation for that worker was assigned based on the longest held occupation in that year.

The term `health physics area' (HPA) represents a system defined by health physicists at SRS for classifying workers based on location and similarity of procedure. In each HPA, which are specific to the SRS facilities, occupational exposure to radiation among employees was under the supervision of radiation monitors or health physics stall. HPA represented a single location (such as an administrative building) or a number of work locations, which are physically separated but take part in similar processes (such as '100-Reactors', which consists of five reactors at SRS, some of which are miles apart). Information on HPA was ascertained from quarterlydosimetry logbooks for the years 1958-1989. If a worker was missing information on HPA for a given employment-year, but had a known HPA for an adjacent time period during which they were employed in the same job, then, for the purposes of exposure imputations, it was assigned that HPA to the employment-year. For those employment-years for which HPA could not be assigned, there was established an `Unknown' category.

Tritium dosimetry program at SRS

Tritium dose records at SRS represent the annual sum of internally deposited tritium measured via urinalysis. Calcium was added to HTO in urine samples and the evolved hydrogen from this was passed through an ionisation chamber. This practice was standard from the start of operations until 1958, and the analysis had a minimum detectable activity (MDA) level of I μCi/l. The reporting level was set at I μCi/l for a number of years, and was eventually reduced to match the current MDA of 0.1 μCi/1. Including urinalysis results, the calculation of tritium-equivalent dose (expressed in rem or Sv) took a number of factors into consideration including biological half-life, target tissue, default mass of body water, a quality factor for tritium and the mean energy of tritium beta particles

When converting urinalysis results to dose estimates, the presumed patterns of exposure were taken into consideration in order to properly represent the body burden of tritium (i.e. acute exposure episodes versus chronic low-dose exposure). The details of conversion of urinalysis results are summarised by Taylor *et al.* [7] and Scalskyts).

Annual tritium dose was recorded as a component of the annual whole-body dose and represented a fraction of the AWBD. Since tritium was measured via biological monitoring after it had been distributed in the body, tritium was referred to as a dose based on the International Society of Exposure Analysis (ISEA) definition of dose as `the amount of agent that enters a target after crossing an exposure surface'[9] .

External dosimetry recording practices at SRS

During the beginning of operations at SRS, dosimetry services were provided by Oak Ridge National Laboratory (ORNL). ORNL processed films for SRS, and dosemeter exchange took place on a weekly basis. In 1951, personal ionisation chambers were used in addition to film dosemeters to measure exposure among SRS workers. In 1952, SRS initiated an on-site dosimetry programme. Dosemeters were the same two-element film dosemeters used by ORNL and were collected on a weekly basis. In March

1953, SRS began processing film using the ORNL film badge dosemeter. In 1957, SRS

beta/photon dosemeter exchange practice was changed to occur on a biweekly basis. In 1959, SRS began using a multi-element film dosemeter. This dosemeter allowed for individual analysis of beta, gamma and X-ray exposures among personnel. In 1965, SRS implemented a 4-week exchange programme for beta/photon dosemeters, which was changed to a monthly exchange program in 1966. This monthly exchange programme remains in use today. In 1970, SRS thermoluminescent dosemeters (TLDs) replaced film as the means for recording beta/photon dose. The laboratory minimum detection limit (MDL) for this method was 0.15 mSv, as compared with 0.4 mSv for the previous method. In 1983, the use of commercial Panasonic beta/photon TLDs was implemented. This new dosimetry method reduced the MDL from 0.15 to 0.05 mSvt7~.

Employment-year dosimetry **records**

The term 'employment-year' is used to describe the unit of observation contributed by a person each year he/she was employed at SRS, regardless of the number of days employed. A worker who had computerised annual dosimetry information for his/her entire employment period provided one annual dosimetry record for each employment-year.

In 1979, a computerised personal dosimetry system, referred to as the Health Protection Annual Radiation Exposure History (HPAREH) system, was implemented at SRS. The HPAREH system was developed in order to produce a file of annual radiation-exposure data for all SRS employees who were actively employed in 1979. Historical dosimetry information was entered into the HPAREH system from hardcopy personnel folders and logbooks (1951-1964), magnetic tapes of logbooks (19651972) and HP Master File magnetic tapes (19731979). Since 1979, dosimetry information has been routinely entered into the HPAREH system. The HPAREH file includes some records for years in which workers were not monitored for external radiation exposure using personal dosemeters at SRS. These records were entered into the HPAREH system in order to record information about offsite doses and internal doses from radionuclides other than tritium. If the only information for a monitoring year pertained to an estimate of offsite dose or an estimate of effective dose from an internal deposition (other than tritium), then the record was excluded from the analyses.

Dosimetry information for an additional 1058 workers was identified and computerised during the course of an epidemiological cohort study of SRS workers conducted by Oak Ridge Associated Universities, known as the SRPABST file.

Workers who terminated employment at SRS prior to 1979 were not included in the HPAREH system. An electronic file of annual radiation-dose estimates for the period of 1951-1979 was constructed for the purpose of epidemiological research conducted by the DuPont Corporation, called the Fayerweather file. In the Fayerweather file, abstraction of annual tritium-dose information was incomplete. If a non-zero tritium dose value was recorded in the Fayerweather file, it could, in most cases, be validated; however, relatively few such values were recorded.

As part of the research, dosimetry information was derived from historical dosimetry logbooks for an additional 854 workers who were employed during the period of 1964-1979. In addition, 15 752 annual dosimetry records were identified in the historical dosimetry logbooks that were not included in the HPAREH, Fayerweather or SRPABST computerised files. From these files, it is possible to abstract dosimetry information from historical logbooks for an additional 5686 employment-years. The recorded annual deep- and shallow-dose estimates were 0 rem for nearly all of the remaining 10 066 employment-years. These were dosimetry records for workers whose employment terminated after 1 January 1979 and appeared in the historical SRS logbooks but not in the HPAREH file. An estimated annual deep- and shallow-dose of 0 rem was assigned to these years. Lastly, a 'nearby' method was used to estimate annual whole-body dose for 13 812 employment-years for which dosimetry information was not available (i.e. 6`Yo of the employment-years for SRS workers during the period 1954-1989). These data are described in a previous work by Richardson *et a!.* [10]. In the present analysis, these estimates were treated as known annual whole-body dose records.

Radiation exposure records at SRS have been maintained by a combination of manual and computer efforts following procedures to ensure data quality[t7] . For most of its history, SRS has used an automatic system for recording and archiving external exposure data from personnel monitoring badges in a computerised master file°[1]. Supplemental abstraction of data from hardcopy and magnetic tapes followed a protocol for data entry and error checkingt12.13)

Modern radiation dose information is expressed in sieverts, which represents the biological equivalent dose based on Joules per kilogram multiplied by weighing factors for the exposed organism and radiological agent of interest. For the sake of consistency with contemporary nomenclature, dose estimates that were originally expressed in units of rem are discussed and reported here in sieverts, where 1 Sv = 100 rem.

Estimation of tritium dose

The objective was to estimate the tritium component of the AWBD in order to impute a value for those

employment-years in which recorded tritium doses were missing. The technique applied combined an industrial hygiene approach to develop a job-area-exposure matrix (JEM) with empirical methods for exposure prediction using regression modelling.

Typically, a JEM will utilise qualitative information about the area of employment, occupation and time of employment for assignment of a level of exposure (or dose) based on expert knowledge of where and when an exposure was likely to occur[14 17]. This level of exposure may be dichotomous, with an employee assigned a `yes/no' to exposure, or ordinal, with exposure described as `low/medium/high'(la~ The proposed method of dose reconstruction differs in that this qualitative information was combined with quantitative data about estimated whole-body dose in order to provide quantitative estimates of annual tritium dose.

Previous studies of workers at SRS were focused on classifying dose level according to job and area description alone and it was shown that workers receive the highest tritium dose in one of the three processes: neutron irradiation of lithium–aluminium targets or heavy water (DO) and fission due to reprocessing of reactor fuels[69j]. However, the combinations of job-area that may have led to tritium exposure were not consistent over time. For example, there were changes over time in the type and number of reactors operating at SRS. In addition, individuals with an occupation for which tritium exposure was not expected, but who were also assigned an HPA code for working in an area where tritium exposure was expected, may not have been properly assigned a level of tritium dose, as may have been suggested in previous studies. Thus, information on occupation, HPA and calendar year has been incorporated into consideration in developing the predictive model of tritium dose.

Statistical analysis

The proportion of a worker's AWBD due to intake of tritium was estimated by fitting a linear regression model in which the dependent variable was the annual tritium dose and the independent variable was the annual whole-body dose using Statistical Analysis Software (SAS, v. 8.2, Cary, NC, USA). The model was stratified by occupational group, HPA and calendar year, thereby allowing for different estimates of the fraction of AWBD due to tritium within each stratum defined by these factors.

In addition, strata by categories of AWBD were defined. This stratification accounted for potential differences in the relationship between tritium and AWBD within subgroups defined by occupation, area and calendar year. A major concern when developing a JEM. is that job titles do not provide substantive distinctions between tasks at a facility,since job titles and area codes may represent information used for administrative tasks, rather than for research purposes[16]. Further dividing groups of workers who share similar occupational titles and areas into subgroups based on AWBD serves to create subgroups that have greater similarity in job activities (and therefore in their relationships between tritium dose and AWBD).

A general model was developed assuming a linear relationship between tritium dose and AWBD.

$$Y_{ijkl} = a_{ijkl} + Q_{ijkl}x + e_{ykj}$$

for i = 1,2,..., *in* year, j = 1,2,..., Farea, *k = 1,2,.. ., n* occupation and *1= 1,2,..., p* AWBD group, where $Y_{;jk}$; represents tritium dose for the Ith AWBD group in the kth occupation of the jth area in the ith year, as_{k}; the intercept for the /th AWBD group in the kth occupation of the jth area in the ith year, x the fixed effect for amount of AWBD exposure, $R_{;jk/}$ amount of AWBD exposure for the Ith AWBD group in the kth occupation of the jth area in the ith year and $e_{;jk}$, is the random effect for the Ith AWBD group in the kth occupation of the jth area in the ith year.

This model is fit using a complete data analysis; therefore, the regression coefficients are estimated for all workers who have known (i.e. computerised) tritium dose values. The parameter estimates obtained from this linear regression model were then used in conjunction with covariate patterns observed for employment-years with missing tritium-dose values in order to derive a predicted tritium dose for that year. This predictive model helped to derive estimates of an individual's tritium dose based on the known tritium dose levels of his/her coworker.

The reliability of this estimation procedure was evaluated by comparing observed tritium doses with estimated values. For these evaluations, all observed annual tritium-dosimetry records were utilised. A predicted value was derived for each annual tritium-dosimetry record using the estimation procedure described above. The correlation of observed and predicted values was calculated as a direct assessment of the model. Further evaluations of this estimation procedure were conducted in order to examine how reliably the values were estimated when observed doses were of differing magnitudes. Box-plots were created of the difference between estimated and observed by the level of the observed dose.

RESULTS

Cohort data

During the period 1951-1999, the 18 883 workers in the study cohort contributed a total of 277 735 employment-year records (Table 1). Recorded tritium doses were available for 224 357 of these

Table 1. Description of employee records for the entire SRS occupational cohort from 1951-1999.

	Number of records			
	1951–1953	1954–1978	1979–1999	Total
Total employment years	9014	155 281	113 440	277 735
Known tritium dose	2294	109 956	112 107	224
Missing tritium dose	6720	45 325	1333	53
Employment years with aAWBD>0	1457	117 991	58 772	178 220
Known tritium dose	800	74 610	58 206	133
Missing tritium dose	657	43 381	566	44

employment-years. Thus, there were 53 378 employment-years for which tritium-dose information was unknown.

Tritium exposures were minimal for most workers during the period 1951-1953 as the first production reactor at SRS went critical in December 1953. Therefore, tritium-dose values for employment years for the period 1951-1953 were not estimated. From 1979 onwards, tritium-dose estimates were routinely computerised at SRS via the HPAREH system. As indicated in Table 1, nearly complete information on annual tritium dose estimates was obtained for workers employed during the period 1979-1999. By definition, if the AWBD was equal to 0 mSv then the annual tritium-dose component was equal to 0 mSv. Therefore, for those employment-year records in which the AWBD was equal to 0 mSv, the tritium dose was considered as known and equal to 0 mSv.

For the period 1954-1978, 155 281 employment-year records were observed and computerised tritium doses were available for 71'%, (109 956) of these employment-years (Table 1). Since estimation of tritium dose was not necessary for those with an AWBD of 0 mSv, computerised tritium-dose values were estimated for 43 381 employment-years.

Evaluation

There were 74 610 recorded tritium-dose values for employment-years during the period 1954-1978 on which was based the estimation of the tritium dose for the employment-years with missing tritium dose records. For the evaluation of the predictive model, the observed and estimated tritium values were compared for these employment-years. The 75th, 90th, 95th, 99th and 100th percentile of known tritium doses were 0.00, 0.65, 1.65, 3.90 and 86.45 mSv, respectively. The corresponding values for the estimated tritium dose for those individuals with a known tritium dose were 0.07, 0.73, 1.63, 3.03 and 86.45 mSv, respectively.

Figure 1 shows a box-plot of the error for the predictive model as observed tritium dose minus expected tritium dose by categories defined by observed tritium dose. Most of the estimated tritium values matched well with the observed tritium dose, since the errors for each observed dose group were near zero. However, the model over-predicted lower values and under-predicted higher values. The mean and median errors for the lowest dose category (observed dose equal to zero) were -0.06 and 0 mSv, respectively (95% of values fall in the range -0.61-0.00). For the highest observed dose category (observed dose >3.0 mSv), the mean and median of error were 1.89 and 1.36 mSv, respectively *(95%* of values fall in the range - 0.50-9.07).

Estimation of tritium values for employment-years lacking computerised tritium records

A total of 43 381 missing tritium values with a mean of 0.10 mSv and median of 0.00 mSv were estimated. The collective sum of the estimated tritium values was 4319 mSv. When compared with the collective measured tritium dose for the period 1954-1978, the collective sum of estimated tritium values represents 20`%, of the collective sum of measured tritium dose. Like the distribution of known dose values, the lower 75th percentile of the estimated values is equal to zero. Tritium values for the 90th, 95th, 99th and maximum percentile were 0.121, 0.508, 2.135 and 74.533 mSv, respectively.

The mean 75th and 95th percentile of those employees with known tritium dose records are presented by area and occupation (Table 2) for comparison with the estimated tritium dose records for those without a known tritium dose record (Table 3). Data are presented in this fashion due to the skewness of predicted tritium dose values, The dose from the estimation did not match the order of the dose for the known tritium dose. For example. the estimated tritium dose was highest for the areas 100-Reactors and 232-234-H (Tritium Process/ Reservoir), respectively, while the known tritium dose was highest for areas 100-Reactors and 400-D Heavy Water Plant. The fraction of tritium dose to AWBD was highest for 232-234-H (Tritium Process/ Reservoir), which may explain the higher estimated tritium dose.

In addition, the upper bounds of the range distribution of the estimated tritium doses (i.e. the 97.5th percentile of the distribution) by area and occupation for employment-years without a known tritium dose were lower than the same boundary for the upper bounds of the distribution of the estimated tritium dose for area and occupation groups with known tritium-dose records. A few

occupations did

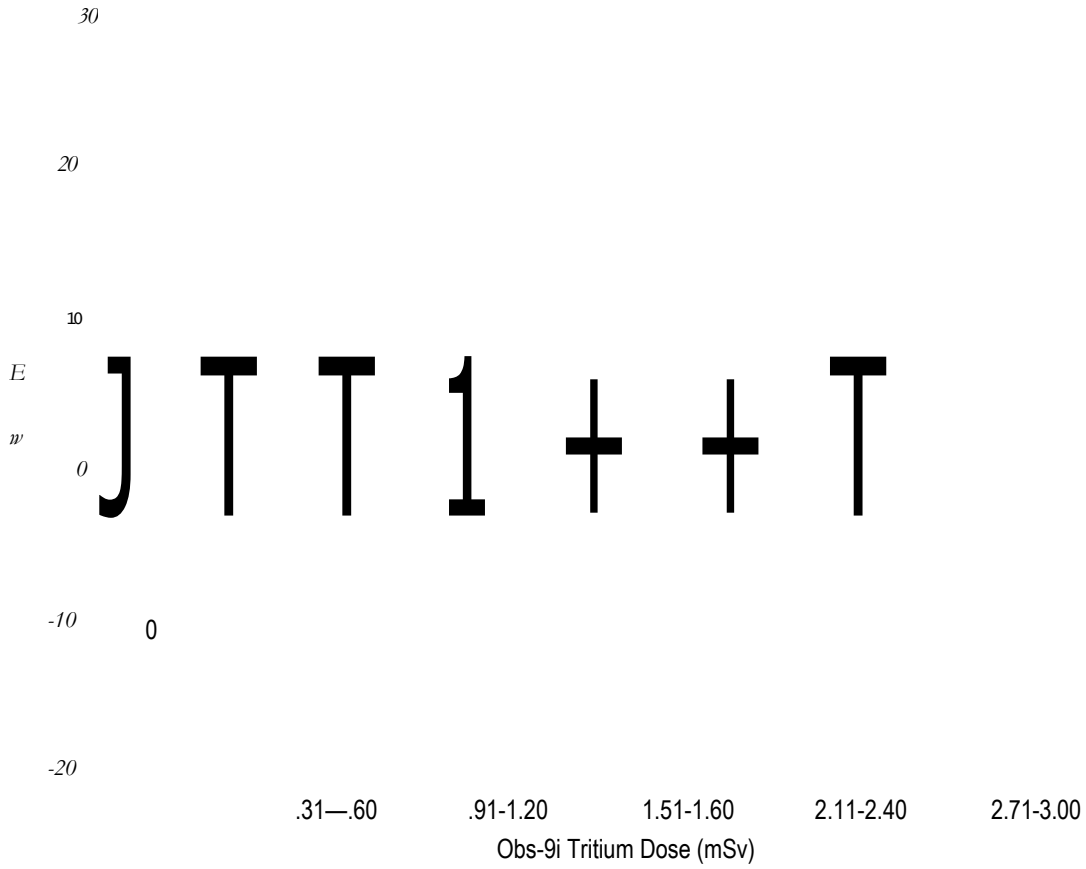

Figure 1. Box-plots of the difference between estimated tritium dose and observed tritium dose (error) by groups of observed tritium dose 1954-1978.

not follow this trend, including general service operator, engineering technician and trainee, engineer, junior physicist, chemist, raw materials operator, student, laboratory supervisor, senior/process chemist, senior/process physicist, life sciences and medical services, clerical and kindred non-manual workers and administrators and professionals (Tables 2 and 3). Some of these occupations had higher upper bound estimates than others, and may be the result of overestimation due to a few high exposure events For individuals within the same exposure category (defined in the model) as a few other workers.

DISCUSSION

This paper presents an innovative hybrid of traditional approaches to exposure assessment based upon the method of JEM in conjunction with a quantitative dose estimation approach using a stratified regression model.

A large proportion of the employment-years for which tritium dose was estimated were for workersemployed in areas other than reactor operations and tritium loading/recycling. It is likely, therefore, that a large proportion of the workers with missing tritium dosimetry information had little or no occupational exposure to tritium. This is reasonably well reflected by the estimated tritium dose for workers outside the reactor and tritium areas; 79`%, of estimated tritium doses were 0 mSv and 90`%, of all estimated doses were <0.121 mSv. An important aspect of the estimation method to recognise is that small positive dose values were assigned to a large number of workers who were likely to have had little or no true exposure. If a worker's true dose was zero, the estimation approach had a tendency to assign a value that was a slight overestimate of the `true' zero dose. Based upon evaluation of the proposed model when the true value for the annual tritium dose was zero, the mean and median estimated values derived were 0.057 and 0 mSv, respectively. The reason for this is that an estimated dose value may be greater than zero but it cannot be less than zero. In contrast, if a true dose was high relative to the other dose

records (i.e. the dose was in the 99th and higher

Table 2. Mean and the 75th and 97.5th percentiles of the distribution of the annual measured tritium dose (in mSv) by health physics area and occupation 1954-1978 (n = 74 610).

Area	Mean	Percentile	
		75th	97.5th
100 (Reactors)	0.702	1.050	4.050
400-D (Heavy Water Plant)	0.451	0.350	3.650
232-234-H (Tritium Process/Reservoir)	0.404	0.350	2.550
Administration	0.159	0.000	1.500
200-H (H-Main Gate and H-Trit)	0.106	0.000	1.150
773-A (experimental fuel and target fabrication)	0.088	0.000	0.250
T&T, E&I, other plant services	0.079	0.000	0.900
Unknown	0.075	0.000	0.600
200-F (F-Main Gate)	0.058	0.000	0.450
777-M (Experiment Physics Lab) and CMX Administration and services	0.054	0.000	0,300
Physical plant	0.052	0.000	0.450
300-M (raw materials/fuel and target fabrication) Occupation	0.046	0.000	0.650
Reactor Operator	0.024	0.000	0.000
Heavy Water Operator	1.298	1.950	4.150
Auxiliary Operator	1.280	2.050	5.000
Radiation Monitor, Health Physicist	0.733	1.200	4.050
Rigger	0.539	0.150	4.250
Other skilled manual	0.426	0.600	2.500
Separations/Process Operator	0.311	0.000	3.000
Unknown	0.263	0.000	2.750
Technicians, analysts and assistants	0.241	0.000	2.450
Carpenter	0.228	0.000	1.150
Production/shift supervisors	0.198	0.000	2.150
Utility operator	0.188	0.000	2.200
Other operator	0.186	0.000	2.050
General service operator	0.184	0.000	1.500
Other supervisors	0.086	0.000	0.700
Production	0.085	0.000	1.050
	0.085	0.000	0.900
	0.081	0.000	1.150
	0.065	0.000	0.800
	0.047	0.000	0.550
	0.040	0.000	0.000
	0.031	0.000	0.200
	0.026	0.000	0.150
	0.025	0.000	0.000
	0.023	0.000	0.350
	0.021	0.000	0.200
	0.018	0.000	0.050
	0.018	0.000	0.000
	0.016	0.000	0.250
	0.008	0.000	0.000
	0.006	0.000	0.000
	0.005	0.000	0.000
	0.004	0.000	0.050
	0.003	0.000	0.000
	0.000	0.000	0.000

percentile range), then the method had a tendency to produce a positive estimate that slightly underestimated the true dose. Therefore, the model produced a small overestimate of the level for an unrecorded year for which the true dose was zero and a small underestimate of the value for an unmonitored year for which the true dose was greater than zero. If the information indicates that a worker was employed in an area in which the tritium dose rate was zero, then it is possible to assign a zero dose to that year.

Table 3. Mean and the 75th and 97.5th percentiles of the distribution of, the estimated annual tritium dose (in mSv) by health physics area and occupation 1954-1978 (n = 43 381).

Area	Mean	Percentile	
		75th	97.5th
100 (Reactors)			
400-D (Heavy Water Plant)			
232-234-H (Tritium Process/Reservoir)	0.344	0.327	2.595
Administration	0.140	0.000	1.752
200-H (H-Main Gate and H-Trit)	0.297	0.265	2.195
773-A (experimental fuel and target fabrication)	0.040	0.000	0.300
T&T, E&I, other plant services	0.055	0.000	0.521
Unknown	0.020	0.000	0.111
200-F (F-Main Gate)	0.101	0.000	0.651
777-M (Experiment Physics Lab) and CMX	0.038	0.000	0.195
Administration and services	0.031	0.000	0.298
Physical plant	0.017	0.000	0.064
300-M (Raw Materials/Fuel and Target Fabrication)	0.016	0.000	0.088
Occupation	0.046	0.000	0.170
Reactor operator	0.011	0.000	0.052
Heavy water operator	0.733	1.050	3.170
Auxiliary operator	0.716	1.192	3.450
Radiation Monitor, Health Physicist	0.449	0.558	2.835
Rigger	0.762	0.369	4.739
Other skilled manual	0.453	0.450	4.150
Separations/process operator	0.188	0.064	1.781
Unknown	0.104	0.074	0.837
Technicians, analysts and assistants	0.047	0.000	0.298
Carpenter	0.095	0.000	1.250
Production/shift supervisors	0.000	0.000	0.000
Utility operator	0.130	0.025	1.422
Other operator	0.065	0.027	0.705
General service operator	0.123	0.000	1.184
Other supervisors	0.028	0.000	0.096
Production operator	0.019	0.000	0.206
Engineering technicians and trainees	0.000	0.000	0.000
Managers, specialists and associates	0.019	0.000	0.075
Engineers	0.001	0.000	0.000
Junior physicist	0.010	0.000	0.080
Chemists	0.000	0.000	0.000
Raw materials operator	0.001	0.000	0.000
Students	0.053	0.000	0.537
Crane operator	0.001	0.000	0.000
Senior engineers	0.004	0.000	0.024
Laboratory supervisors	0.001	0.000	0.000
Senior chemist, process chemist	0.000	0.000	0.000
Senior physicist, process physicist	0.000	0.000	0.000
Life scientists and medical services	0.011	0.000	0.000
Other semi-skilled workers	0.000	0.000	0.000
Clerical and kindred non-manual workers	0.002	0.000	0.006
Metallurgists	0.001	0.000	0.000
Power operator	0.000	0.000	0.000
Administrators and professionals	0.001	0.000	0.000
	0.000	0.000	0.000

In effect, however, the proposed estimation method the annual whole body dose groups assisted with this did just this. If the worker was employed in a occu- by clustering individuals based on their known pation/area where the average recorded value was AWBD, since workers with zero (or near zero) zero or near zero then the worker was assigned a AWBD had a propensity for similar tritium doses zero (or near zero) value for that year. Inclusion of depending on the occupation/area combination.

The proposed method offers an approach to imputing a distribution of estimated tritium doses for employment-years with missing information using the available data from monitored workers during that year as well as information on occupation and area of employment. For the ultimate future goal of the project, which is to examine associations between tritium exposure and potential adverse health effects in workers at SRS, this predictive model provides useful information about occupational exposures to tritium.

JEMs have a number of limitations to overcome. First, utilising qualitative information to provide ordinal or dichotomous exposure classification is not always ideal for examination of exposure-disease relationship. Job and area classifications are not necessarily created for the purpose of distinguishing between tasks or exposures. Rather, they may represent distinctions created simply for administrative purposes[t16]. In addition, since within job variation cannot be taken into account, JEMs suffer from non-differential misclassification of exposure~20~.

The proposed model attempts to overcome these obstacles by combining an industrial hygiene approach to evaluate exposure with an empirical method of exposure prediction. This provides an understanding about exposure to tritium at SRS that may otherwise have been overlooked. First, providing quantitative estimates of tritium exposure will benefit further studies of workers exposed to this radionuclide. The estimation of tritium dose is based on known tritium and annual whole-body dose exposure. Combining estimated and known tritium doses provides a complete exposure history for employees at SRS. This level of detail about exposure is more useful than that obtained in a typical JEM. Second, the proposed method attempts to overcome the obstacle discussed by Loomis *et al.*[06] concerning codes that do not provide substantive distinctions between different jobs and areas. For example, one might assume 'administration' is an area of employment that would not lead to a high level of tritium exposure. However, the average tritium dose and fraction of WBDS in this area was higher than the areas of `experimental fuel and target fabrication' and `200-H (H-Main Gate and H-Trit)' two areas that may be expected to have a higher tritium exposure. This fact may have been overlooked, possibly leading to misclassification of the area administration as a low or no exposure area, or even 200-H (H-Main Gate and HTrit) as a high-exposure area.

Occupation and area descriptions for SRS employees may not provide an ideal distinction between different employees' true area and occupation. This is seen when comparing the number of known area and occupation categories compared with the ORAU Team Dose Reconstruction Projectfor NIOSH at SRS, which contains more specific and detailed descriptions of facilities and processes. Although the technique of dose reconstruction can help overcome this problem, the data set of the study is limited in the picture it paints of exposure scenarios for tritium at SRS.

Although there are limits to what dose reconstruction can tell us about tritium dose, it is important to estimate the exposure for employees at SRS. Increasing knowledge of tritium exposure will help to better evaluate potential relationships between exposure and disease. In addition, the estimated tritium dose records could be used to adjust available estimates of annual whole-body dose in order to take into account changes over time in tritium dose estimation methods, including International Commission on Radiological Protection models and quality factors for tritium. It is hoped that this study provides useful information for future studies at SRS, and perhaps for other facilities where worker exposure to tritium is of concern.

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REFERENCES

1. Cragle, D., McLain, R., Qualters, J., Hickey, J., Wilkinson, G., Tankersley, W. and Lushbaugh, C. *Mortality among workers at a nuclear fuels production facility.* Am. J. Ind. Med. **14,** 379-401 (1988).
2. Hill, R. and Johnson, J. *Metabolism and dosimetry of tritium.* Health Phys. 65(6), 628-647 (1993).
3. Okada, S. and Momoshima, N. *Overview of tritium: characteristics, sources and problems.* Health Phys. **65(6),** 595-609 (1993).
4. Elliot, A. *Tritium dosimetry.* Nuclear Med. Commun. **26,** 481-482 (2005).
5. Joksic, G. and Spasojevic-Tisma, V. *Chromosome analysis of lymphocytes from radiation workers in tritium-applying industry.* lnt. Arch. Occup. Environ. Health 71, 213-220 (1998).
6. Straume, T. *Tritium risk assessment.* Health Phys. **65(6),** 673-682 (1993).
7. Taylor, G. A., Crase, K. W., La Bone, T. R. and

Wilkie, W. H. A history of personnel radiation dosimetry at the Savannah River Site (Springfield, VA, USA: US Department of Energy) (1995).

8. Scalsky, E. D. *Technical basis document for the Savannah River Site: to be used for EEOICPA dose*

reconstructions. In: ORAU Team Dose Reconstruction Project for NIOSH. Neton, J. W., Ed. (Cincinnati: National Institute for Occupational Safety and Health) (2005).

Zartarian, V., Bahadori, T. and KcKone, *T. Adoption of an official ISEA glossary. J.* Expo. Anal. Environ. Epidemiol. **15,** (2005) 1-5.

10 Richardson, D., Wing, S. and Daniels, R. D. *Evaluation of external radiation dosimetry records at the Savannah River Site, 1951-1999.* J. Expo. Sci. Environ. Epidemiol. 17, 13-24 (2007).

Boiter, H. P. *Radiation Exposure Records Management.* pp. 13. (Aiken, SC: Savannah River Plant) p. 13 (1975).

12. Plant, S. R. *Exposure Data Protocol.* pp. 13. (Aiken, SC: Savannah River Plant) p.13 (1984).
13. McMahan, S. R. *Exposure Data Extraction Procedures.* Fayerweather, W. E. Ed. (Aiken, SC: Savannah River Plant) (1984).
14. Hoar, *S. Job exposure matrix methodology. J.* Toxicol. Clin. Toxicol. 21(1/2), 9-26 (1983-1984).
15. Kromhout, H., Heederik, D., Dalderup, L. and Kromhout, D. *Performance of two general job-exposure matrices in a study of lung cancer morbidity in the Zutphen cohort.* Am. J. Epidemiol. 136, 698-711 (1992).
16. Loomis, D., Peipins, L., Browning, S., Howard, R., Kromhout, H, and Savitz, D. *Organization and classification of work history data in industry-wide studies: an application to the electric power industry.* Am. J. Ind. Med. **26,** 413-425 (1994).

17 Goldberg, M., Kromhout, H., Guenel, P., Fletcher, A., Gerin, M., Glass, D. C., Heederik, D., Kauppinen, T. and Ponti, A. *Job exposure matrices in industry.* lnt. J. Epidemiol. 22(Suppl. 2), S10–S15 (1993).

18. McGuire, V., Nelson, L., Koepsell, T., Checkoway, H. and Longstreth, W. T. *Assessment of occupational exposures in community-based case–control studies.* Annu. Rev. Public Health **19,** 35-53 (1998).
19. Hickey, J. and Cragle, D. *Occupational Exposures of Workers to Chemicals at the Savannah River Plant 1952-1984* (Oak Ridge, TN, USA: Oak Ridge Associated Universities) (1985).
20. De Vocht, F, Zock, J. P., Kromhout, H., Sunyer, J., Anto, J., Burney, P. and Kogevinas, M. *Comparison of self reported occupational exposure with a job exposure matrix in an international community-based study on asthma.* Am. J. Ind. Med. 47, 434-442 (2005).

Mortality Among Workers at the Savannah River Site

David B. Richardson, PhD,* Steve Wing, PhD, and Susanne Wolf, MPH

Background *Workers employed at the Savannah River Site (SRS) were potentially exposed to a range of chemical and physical hazards, many c#f which are poorly characterized. We therefore compared the observed deaths among workers to expectations based upon death rates for referent populations.*

Methods *The cohort included 18,883 SRS workers hired between 1950 and 1986. Vital status and cause of death information were ascertained through 2002. Sex-specific standardized mortality ratios (SMR) were computed using U. S. and South Carolina mortality rates. SMRs were tabulated separately for monthly-, weekly-, and hourly-paid men.*

Results *Males had fewer deaths from all causes I SMR = 0.80, 90% confidence interval (Cl): 0.78, 0.82], all cancers (SMR = 0.85, 90% Cl: 0.81, 0.89), and lung cancer (SMR = 0.88, 90% Cl: 0.82, 0.95) than expected based upon US mortality rates. The SMR for cancer of the pleura was 4.25 (90% CI: 1.99, 7.97) for men. The SMR for leukemia was greater than unity for monthly-paid (SMR = 1.33, 90% CI: 0.88, 1.93) and hourly-paid (SMR= 1.36, 90% CI: 1.02, 1.78) men. Female workers had fewer deaths from all causes (SMR = 0.75, 90% CI: 0.69, 0.82) than expected, but more deaths than expected, from cancer of the kidney (SMR = 2.58, 90% Cl: 1.21, 4.84) and skin (SMR = 3.90, 90% CI: 2.11, 6.61).*

Conclusions *While the observed numbers of deaths in most categories of cause of death were less than expected, there are greater than expected numbers of deaths due to cancer of the pleura and leukemia, particularly among hourly-paid male workers. It is plausible that occupational hazards, including asbestos and ionizing radiation, contribute to these excesses. Am. J.* Ind. Med. 2007. © *2007 Wiley-Liss, Inc.*

KEY WORDS: cohort studies; mortality study; Savannah River Site; occupational diseases

INTRODUCTION

In 1950, the E.I. du Pont Nemours and Company (DuPont) contracted with the Atomic Energy Commission to construct and operate a facility to produce nuclear materials. The facility, located near Aiken, South Carolina, became known as the Savannah River Site (SRS). Over its history, the site has operated five large reactors, two chemical separation areas, a heavy water extraction plant, nuclear fuel, and target fabrication plants, as well as test reactors, power plants, and laboratories. DuPont managed and operated the site through March 1989, when the Westinghouse Corporation took over operations.

Cragle et al. [1998] compared cause-specific mortality in a cohort of 9,860 white male SRS workers who had vital status and cause of death information ascertained through 1986 with mortality of US white men. They found that salaried workers had substantially fewer deaths due to all

The supplemental table appendices described in this article can be found at http://www.interscience.wiley.com/jpages/0271-3586/suppmat.

Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

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'Correspondence to: David B. Richardson, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599.
E-mail: david.richardson @unc.edu

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causes [standardized mortality ratio (SMR) = 0.60, 95% Cl: 0.54, 0.67], all cancers (SMR = 0.71, 95% Cl: 0,58, 0.87), and lung cancer (SMR = 0.60,95% Cl: 0.41, 0.85) than white

males in the US population. Non-salaried workers had slightly lower all cause and all cancer mortality rates than the general population (SMRs = 0.85 and 0.86, respectively) but had slightly higher mortality rates for lung cancer (SMR = 1.08, 95% Cl: 0.91, 1.28). Leukemia mortality was in excess among salaried (SMR = 1.10, 95% CI: 0.40, 2.40) and non-salaried (SMR = 1.34, 95% Cl: 0.80, 2.09) workers when compared to expectations based upon US mortality rates [Cragle et al., 1988, 1998].

Comparison of cause specific mortality of an occupational cohort to an external referent population, usually implemented through indirect adjustment for age and calendar time using SMRs, can help in etiologic research on occupational exposures. This method of analysis is useful in settings in which there is little or no ability to accurately discriminate between workers in a study cohort with respect to exposure level (either because exposure estimates are unreliable or because historical exposures were similar for most workers). Although there are relatively good historical records of SRS workers' exposures to ionizing radiation [Richardson et al., 2006], there is little information about exposures to other chemical and physical hazards at the site, which include acids, solvents, asbestos, and hydrazine [Hickey and Cragle, 1985; Makie et al., 2005].

Interpretation of the SMR as an effect measure that represents the independent effect of occupational exposures requires comparability (or "exchangeability") of the study population and the external referent population. It is widely recognized that this condition is not met for analyses of most common causes of death because of the "healthy worker effect (HWE)," which involves: (1) exclusion of people too sick to work from employment, (2) termination of employment for people who become sick once employed, and (3) socioeconomic and lifestyle differences between people who work and those who don't, particularly in studies of workers employed by corporations that pay their workers relatively well and provide pension and health benefits [McMichael, 1976; Wilcosky and Wing, 1987; Arrighi and Hertz-Picciotto, 1994]. In studies of workers employed in the nuclear industry deficits in all cause and all cancer mortality are often observed when contrasts are drawn to the general population [Vrijheid et al., 2007]. However, for analyses of diseases that are not strongly related to socioeconomic and lifestyle factors, that do not cause symptoms affecting ability to work for long periods prior to death, and that are caused by exposures that occur primarily in the workplace under study and rarely elsewhere, there may be a reasonable degree of exchangeability between the study and referent populations and relatively little bias due to the "HWE." Alternatively, to the extent that SMRs for leading causes of death reflect living conditions, they provide clues about generalized susceptibility of the working population and they may provide useful contrasts with SMRs for specific causes of death that may be related to occupational exposures.

The aim of this article is to report on SMR analyses of an expanded cohort of SRS workers followed through 2002. Analyses contrast mortality rates in the study population to mortality rates for the US and South Carolina.

MATERIALS AND METHODS

We report on a cohort of 18,883 SRS workers who were hired by DuPont prior to 1987. and who worked at least 90 days. Workers without complete information on name, SSN, date of birth, and date of first hire were excluded. The original study cohort analyzed by Cragle et al. [1988] (n = 9,860) was defined as all white male workers who were hired by DuPont prior to 1974 and employed for at least 90 days. We have expanded the cohort to include males and females of all races hired by DuPont prior to 1987; we did not include workers hired in more recent years given the low mortality expected among more recently-hired workers and the changes in record keeping that occurred when Westinghouse Corporation took over as the prime operations contractor from DuPont.

The names and social security numbers of cohort members who had not previously been identified as deceased by Cragle et al. [1998] were submitted to the Social Security Administration (SSA) and the National Death Index (NDI) for determination of vital status through December 31, 2002. We used the NDI-Plus service to obtain underlying and contributing causes of death for deceased workers identified by the NDI. For deaths occurring prior to 1979, cause of death information was coded according to the Eighth revision of the International Classification of Diseases (ICD); for deaths occurring in 1979 and later, cause of death information was coded to the 1CD revision in effect at the time of death. If there was no death indication for a worker and they were confirmed to be alive on January 1, 1979 or later by the SSA or by the site's employment records then they were assumed to be alive as of December 31, 2002. Those lost to follow-up before January 1, 1979 were only considered alive until the date last observed. Decedents for whom the underlying cause of death was unknown contributed to the calculation of the SMR for all causes of death.

The mortality experience of the cohort was analyzed using the N1OSH modified life table analysis system (LTAS) [Steenland et al., 1990; Robinson et al., 2006]. Each cohort member accumulated person-time from their date of entry (completion of 90 days of employment) until the earliest of the following: the date of death for deceased cohort members, the date last observed for persons lost to follow-up or the ending date of the study (December 31, 2002). Person-time at risk was multiplied by the appropriate U.S. age-, sex-, race-(white or non-white), calendar period-, and cause-specific mortality rates to calculate the expected number of deaths. The ranges of 1CD codes associated with each of the categories of cause of death used in these analyses are

described by Robinson et al. [2006]. The ratio of observed to expected number of deaths 'was expressed as the SMR. A 90% confidence interval was computed using exact methods when the number of observed deaths was less than or equal to live (but greater than zero) and an approximation when the number of observed deaths was six or more [S teenland et al., 1990]. If the number of observed deaths was zero, neither an SMR nor a confidence interval was calculated; rather, we report the observed and expected numbers of deaths. The mortality analysis was repeated using South Carolina state mortality rates for the period 1960-2002; person-time and deaths occurring prior to 1960 were excluded from these analyses.

Analyses were conducted with and without stratification by race. Tables of race-specific results are not reported in this paper as SMRs for non-white workers tended to be highly imprecise. Analyses of male workers were conducted stratified by pay code, which was defined as monthly-paid workers, weekly-paid workers, or hourly-paid workers and was based upon the worker's pay code at time of hire. Information on pay code was derived from historical employment history records that were available in hard copy form and were computerized for the purposes of this research project. Monthly-paid workers were primarily engineers, chemists, physicists, and supervisors. Weekly-paid workers were primarily clerical and kindred workers, security personnel, analysts, and technicians. Hourly-paid workers were primarily employed as operators and skilled manual workers. Since over 90% of female decedents were weekly-paid, analyses of female workers were not conducted with stratification by pay code.

Analyses were conducted stratified by duration of employment and calendar period at risk. Duration of employment was treated as a time-varying variable which increased during the interval from the date of first hire in operations at SRS until the date of last employment [Steenland et al., 1990; Cassinelli et al., 1998].

RESULTS

The cohort included 15,264 men and 3,619 women (Table 1). With follow-up through 2002, 27% of the study cohort was deceased (5,098 workers), 72% of the cohort was alive at the end of follow-up (13,590 workers), and 1% was lost to follow-up (195 workers). Information on underlying cause of death was collected for 99% of decedents (5,047 workers).

Table I.1 shows SMRs for male and female SRS workers, using US mortality rates as referents. The number of deaths due to all causes was less than expected based upon national rates for male (SMR = 0.80) and female (SMR = 0.75) SRS workers. The categories of cancer mortality with SMRs above unity among males were cancer of the pleura (SMR = 4.25), breast (SMR = 2.11), eye (SMR = 2.41), connective tissue (SMR = 1.32), and leukemia (SMR = 1.20). None of the non-malignant categories of cause of death were in excess among male SRS workers. Among females, the categories of cancer mortality with SMRs greater than unity were cancer of the tongue, buccal cavity, esophagus, intestine, ovary, kidney, skin, brain, and Hodgkin's disease. The non-malignant categories of cause of death for which SMRs were greater

TABLE I. Cohort Description

	Male		Female	
	n	%	n	%
Total	15,264	100	3,619	100
Vital status				
Alive	10,486	68.7	3,106	85.8
Dead	4,709	30.9	389	10,8
Losttofollow-up	69	0.4	124	3.4
Pay code				
Monthly	4,026	26.4	496	13.7
Weekly	3,388	22.2	2,576	71.2
Hourly	7,850	51.4	547	15.1
	Mean	SD	Mean	SD
Year of birth	1935	15	1943	14
Year of hire	1963	13	1970	13
Age at entry (years)	28	7	26	7
Duration of employment	16	13	12	11
Length of follow-up (years)	34	13	30	13

Savannah River Site (SRS) workers who were hired by DuPont prior to 1987 and who worked at least 90 days

TABLE II. Standardized Mortality Ratios by Sex, Based Upon US Mortality Rates (1950-2002)

Cause of death	Sex (number of workers)					
	Male (N =15,264)			Female (N = 3,619)		
	Ohs	*SMR*	90% CI	Ohs	*SMR*	90% CI
Tuberculosis	3	0.23	0,06, 0.59	**0**	**-**	[0.77]a
Malignant neoplasms						
Lip	**0**	**-**	[0.48]	**0**	**-**	[0.01]
Tongue	7	0.83	0.39,1.56	1	2.16	0.11,10.23
Other buccal cavity	6	0.63	0.27,1.25	1	1.75	0.09, 8.29
Pharynx	12	0.63	0.37,1.03	0	0.00	[0.91]
Esophagus	20	0.42	0.28,0.62	2	1.25	0.22,3.95
Stomach	28	0.58	0.41,0.80	2	0.63	0.11,1.99
Intestine except rectum	107	0.83	0.70, 0.97	15	1.09	0.67,1.68
Rectum	18	0.64	0.42, 0.95	**0**	**-**	[2.43]
Biliary	29	0.71	0.51,0.97	2	0.55	0.10,1.72
Pancreas	75	0.99	0.81, 1.19	5	0.66	0.26,1.39
Peritoneum	4	0.76	0.26. 1.73	**0**	**-**	[0.65]
Larynx	9	0.46	0.24, 0.80	**0**	**-**	[0.62]
Trachea, bronchus, lung	497	0.88	0.82, 0.95	27	0.68	0.48, 0.94
Pleura	7	4.25	1.99, 7.97	**0**	**-**	[0.06]
Breast	4	2.11	0.72, 4.82	29	0.80	0.58,1.10
Cervix uteri	-	-	-	2	0.38	0.07,1.18
Other parts of uterus	-	-	-	3	0.74	0.20,1.91
Ovary,fallopiantube,andBr	-	-	-	13	1.22	0.72,1.93
Other female genital organs	-	-	-	**0**	**-**	[0.61]
Prostate	114	0.97	0.82,1.13	-	-	-
Other male genital organs	1	0.19	0.01, 0.89	-	-	-
Kidney	23	0.59	0.40, 0.83	7	2.58	1.21, 4.84
Bladder	30	0.83	0.60, 1.12	1	0.64	0.03, 3.05
Skin	27	0.82	0.58,1.13	10	3.90	2.11, 6.61
Mesothelioma	2	0.92	0.16, 2.89	**0**	**-**	[0.07]
Eye	2	2.41	0.43,7.61	**0**	**-**	[0.09]
Brain and other CNS	42	1.00	0.76,1.29	5	1.09	0.43, 2.29
Thyroid	**0**	**-**	[2.68]	**0**	**-**	[0.41]
Bone	1	0.27	0.01, 1.28	**0**	**-**	[0.36]
Connective	11	1.32	0.74, 2.19	1	0.81	0.04, 3.84
Other and unspecified	92	0.83	0.69, 0.99	5	0.44	0.17, 0.92
Non-Hodgkin's lymphoma	51	0.88	0.69,1.11	5	0.85	0.33,1.78
Hodgkin's disease	5	0.53	0.21,1.11	1	1.14	0.06,5.40
Leukemia and aleukemia	68	1.20	0.97,1.47	5	0.94	0.37,1.98
Multiple myeloma	19	0.74	0.48,1.09	1	0.39	0.02,1.83
Benign and unspecified neoplasms	15	0.81	0.50,1.25	3	1.24	0.34, 3.21
Diabetes	61	0.50	0.40, 0.62	11	0.71	0.40,1.18
Diseases of the blood	20	0.98	0.65,1.42	1	0.40	0.02,1.91
Mental disease	56	0.89	0.70,1.11	9	1.61	0.84, 2.81
Diseases of the nervous system	88	0.93	0.77,1.11	8	0.70	0.35,1.26
Diseases of the heart	1,598	0.80	0.77, 0.84	74	0.61	0.50, 0.74
Other diseases of the circulatory sys	396	0.90	0.83, 0.98	26	0.56	0.39, 0.78
Respiratory diseases	310	0.69	0.63,0.76	40	1.01	0.76, 1.32
Diseases of the digestive system	158	0.59	0.52, 0.68	15	0.63	0.39, 0.97
Diseases of the genitourinary system	53	0.64	0.51, 0.81	5	0.55	0.22,1.15

TABLE II. *(Continued)*

	Sex (number of workers)					
	Male(N =15,264)			Female (N = 3,619)		
Cause of death	Obs	SMR	90%CI	Obs	SMR	90% CI
Diseases of the skin	5	0.98	0.39, 2.06	1	1.25	0.06, 5.92
Diseases of the musculoskeletal sys	10	0.76	0.41,1.29	5	1.35	0.53, 2.84
Symptoms and ill-defined conditions	48	0.75	0.58, 0.95	1	0.17	0.01, 0.82
Accidents	279	0.81	0.73, 0.89	19	0.86	0.57,1.27
Violence	134	0.68	0.58,0.78	10	0.78	0.42, 1.33
Other causes	164	0.98	0.86,1.12	18	0.90	0.58,1.33
All cancers	1,311	0.85	0.81, 0.89	143	0.83	0.72, 0.96
All deaths	4,709	0.80	0.78, 0.82	389	0.75	0.69, 0.82

SRS workers who were hired by DuPont prior to 1987 and who worked at least 90 days.
Obs, observed deaths; SMR, standardized mortality ratio; CI, confidence interval; CNS, central nervous system.
'The bracketed value is the expected number of deaths. SMRs and associated confidence intervals were not calculated if the observed number of events was zero.

than unity were benign neoplasms, mental disease, respiratory diseases, diseases of the skin, and diseases of the muscoskeletal system among female workers.

Analyses of SMRs for male and female SRS workers using South Carolina (SC) mortality rates as referents produced similar results to those obtained in analyses using US mortality rates as the referent, although the SMR for cancer of the pleura among males was of smaller magnitude (SMR = 2.82) when based upon SC referent rates (Table A1, available with the electronic version of this article).

Table III shows SMRs for male SRS workers with stratification by pay code, using US mortality rates as the referent. There is substantial variation in the magnitude of the SMR for all cause mortality by pay code. All cause mortality rates were well below national rates (SMR = 0.59) among monthly-paid males. Among weekly-paid male workers all cause mortality rates were 19% below national rates (SMR = 0.81), while among hourly-paid workers all cause mortality rates were closest to national rates (SMR = 0.90). A similar pattern is observed in the SMRs for all cancer mortality when examined by pay code (Table 111). Lung cancers constituted the single largest cancer cause of death in this cohort. There is a substantial deficit of lung cancer deaths among salaried male workers (SMR = 0.52), a moderate deficit of lung cancer among weekly-paid males (SMR = 0,75), and an excess of lung cancer mortality among hourly-paid male workers (SMR = 1.12). The SMR for cancer of the pleura was greater than unity for monthly-paid (SMR = 2.28), weekly-paid (SMR = 5.34), and hourly-paid male workers (SMR = 4.79).

Leukemia mortality was in excess among monthly- and hourly-paid men (SMRs = 1.33 and 1.36, respectively) when compared to expectations based upon national referent rates. The majority of cases were myeloid forms of leukemia, withacute myeloid leukemia constituting the largest number of cases. SMRs were also above unity for mesothelioma, cancer of the pancreas, breast, prostate, eye, and connective tissue in hourly-paid men, non-Hodgkin's lymphoma and cancer of the tongue, intestine, eye, brain, bone, connective tissue, and other and unspecified sites in weekly-paid workers, and cancer of the pancreas, larynx, and Hodgkin's disease among monthly-paid men (Table 111).

The pattern of SMRs by pay code was similar for many non-malignant causes of death: SMRs for diseases of the heart, respiratory system, digestive system, and external cause of death were lowest among monthly-paid male SRS workers and highest (near unity) for hourly-paid males. The only non-malignant categories of cause of death for which observed deaths exceeded expectation were diseases of the nervous system and disease of the skin among hourly-paid males, and mental diseases, other diseases of the circulatory system, and diseases of the skin among weekly-paid workers.

Use of SC mortality rates as referents led to relatively modest changes in SMRs from the values derived via analyses using US referent rates (Appendix Table A2, with the electronic version). The lung cancer SMR among hourly-paid male workers was below unity rather than above as in analyses based upon US national referent rates. Notable excesses of leukemia mortality among monthly-paid (SMR = 1.46) and hourly-paid (SMR = 1.50) male workers were observed in analyses using SC referent rates.

Separate SMR analyses, using US mortality rates as the referent, were conducted stratified by race and pay code. The majority of non-white males were hourly-paid workers. The SMR for prostate cancer was greater than unity in analyses of hourly-paid non-white men (SMR = 1.65, 90% Cl: 1.13, 2.34) while less than unity in analyses of hourly-paid white males (SMR = 0.86, *90%* Cl: 0.66, 1.12). The

TABLE III. Standardized Mortality Ratios Based Upon US Mortality Rates (1950-2002) by Pay Code

	Pay code (number of workers)								
	Monthly-paid (N = 4,026)			Weekly-paid (N = 3,388)			Hourly-paid (N = 7,850)		
Cause of death	Ohs	SMR	90%CI	Obs	SMR	00%CI	Ohs	SMR	90%CI
Tuberculosis	0	-	[2.74]a	1	0.43	0.02, 2.03	2	0.25	0.04, 0.79
Malignant neoplasms									
Lip	0	-	[0.14]	0	-	[0.11]	0	-	[0.24]
Tongue	1	0.48	0.02,2.27	3	1.63	0.45,4.22	3	0.67	0.18,1.72
Other parts of buccal cavity	2	0.84	0.15, 2.65	2	0.96	0.17, 3.04	2	0.40	0.07,1.25
Pharynx	2	0.44	0.08,1.39	4	0.99	0.34, 2.26	6	0.58	0.25,1.15
Esophagus	6	0.53	0.23,1.05	7	0.69	0.33,1.30	7	0.27	0.13, 0.51
Stomach	7	0.58	0.27,1.09	5	0.50	0.20,1.04	16	0.61	0.39, 0.93
Intestine except rectum	20	0.58	0.39,0.85	30	1.05	0.75,1.42	57	0.86	0.68,1.07
Rectum	2	0.27	0.05, 0.85	5	0.80	0.32,1.69	11	0.77	0.43,1.27
Biliary	4	0.39	0.13, 0.89	6	0.68	0.30,1.35	19	0.88	0.58,1.29
Pancreas	20	1.01	0.67,1.47	11	0.65	0.37,1.08	44	1.11	0.85, 1.43
Peritoneum	1	0.72	0.04, 3.40	1	0.86	0.04, 4.06	2	0.73	0.13, 2.31
Larynx	5	1.03	0.41, 2.16	1	0.24	0.01,1.12	3	0.28	0.08, 0.73
Trachea, bronchus, lung	75	0.52	0.43,0.64	94	0.75	0.63,0.89	328	1.12	1.02,1.22
Pleura	1	2.28	0.12,10.82	2	5.34	0.95,16.83	4	4.79	1.64,10.96
Breast	0	-	[0.49]	0	-	[0.42]	4	4.02	1.38, 9.20
Prostate	31	0.98	0.71,1.32	18	0.76	0.49,1.13	65	1.04	0.84,1.28
Other male genital organs	0	-	[1.30]	0	-	[1.30]	1	0.37	0.02,1,75
Kidney	3	0.29	0.08, 0.75	3	0.33	0.09, 0.86	17	0.85	0.54,1.28
Bladder	8	0.79	0.39,1.42	6	0.75	0.33,1.48	16	0.88	0.55,1.34
Skin	8	0.91	0.45,1.64	4	0.51	0.17,1.17	15	0.93	0.57,1.43
Mesothelioma (1999-2002)	0	-	[0.60]	0	-	[0.52]	2	1.89	0.34, 5.96
Eye	0	-	[0.23]	1	5.16	0.26, 24.44	1	2.45	0.13,11.63
Brain	9	0.81	0.42,1.42	13	1.30	0.77, 2.07	20	0.95	0.63,1.37
Thyroid	0	-	[0.71]	0	-	[0.61]	0	-	[1.36]
Bone	0	-	[0.96]	1	1.18	0.06, 5.62	0	-	[1.89]
Connective	1	0.A6	0.02,2.19	4	2.09	0.72,4.79	6	1.42	0.62,2.80
Other and unspecified	15	0.53	0.33, 0.81	28	1.14	0.81,1.57	49	0.84	0.66,1.07
Non-Hodgkin's lymphoma	15	0.97	0.60,1.49	14	1.05	0.64,1.64	22	0.76	0.51,1.08
Hodgkin's disease	3	1.28	0.35, 3.32	0	-	[2.27]	2	0.41	0.07,1.30
Leukemia and aleukemia	20	1.33	0.88,1.93	9	0.70	0.37,1.22	39	1.36	1.02,1.78
Multiple myeloma	5	0.77	0.30,1.61	5	0.90	0.36,1.90	9	0.66	0.34,1.15
Benign and unspecified neoplasms	3	0.62	0.17,1.60	4	0.98	0.34, 2.24	8	0.84	0.42,1.52
Diabetes	12	0.39	0.22,0.63	14	0.53	0.32,0.83	35	0.54	0.40,0.72
Diseases of the blood	5	0.92	0.36,1.94	4	0.92	0.31, 2.10	11	1.03	0.58,1.71
Mental diseases	15	0.94	0.58,1.44	16	1.22	0.77,1.86	25	0.74	0.51,1.03
Diseases of the nervous system	20	0.76	0.50,1.10	18	0.87	0.56,1.29	50	1.05	0.82,1.33
Diseases of the heart	328	0.61	0.56, 0.67	371	0.86	0.79, 0.94	899	0.87	0.83, 0.92
Other diseases of the circulatory sys	72	0.62	0.50, 0.75	102	1.13	0.95,1.33	222	0.96	0.86,1.08
Respiratory diseases	48	0.39	0.30, 0.50	73	0.77	0.62, 0.93	189	0.83	0.73, 0.94
Diseases of the digestive system	28	0.42	0.30, 0.57	37	0.63	0.47, 0.83	93	0.66	0.55, 0.78
Diseases of the genitourinary system	9	0.42	0.22, 0.74	8	0.48	0.24, 0.87	36	0.81	0.60,1.07
Diseases of the skin	0	-	[1.24]	2	2.02	0.36, 6.39	3	1.05	0.29, 2.71
Diseases of the musculoskeletal system	2	0.59	0.10,1.84	2	0.70	0.12, 2.21	6	0.87	0.38,1.72
Symptoms and ill-defined conditions	13	0.85	0.50,1.34	5	0.38	0.15,0.80	30	0.84	0.61,1.14
Accidents	44	0.52	0.40,0.67	49	0.61	0.47,0.77	186	1.03	0.91,1.16

TABLE III. ***(Continued)***

	Pay code (number of workers)								
	Monthly-paid (N = 4,026)			Weekly-paid **(N** = 3,388)			Hourly-paid **(N = 7,850)**		
Cause of death	**Obs**	**SMR**	**90%CI**	**Obs**	**SMR**	**90%CI**	**Obs**	**SMR**	**90%CI**
Violence	18	0.38	0.25, 0.57	24	0.54	0.38, 0.77	92	0.86	0.72,1.03
Other causes	32	0.75	0.55,1.01	37	1.06	0.79,1.39	95	1.07	0.89,1.27
All cancers	264	0.66	0.59, 0.73	277	0.81	0.73, 0.89	770	0.95	0.90,1.01
All deaths	913	0.59	0.56, 0.62	1,044	0.81	0.77, 0.86	2,752	0.90	0.87, 0.92

Male SRS workers who were hired by DuPont prior to 1987 and who worked at least 90 days.
Obs, observed deaths; SMR, standardized mortality ratio; CI, confidence interval; CNS, central nervous system.
1fhe bracketed value is the expected number of deaths. SMRs and associated confidence intervals were not calculated if the observed number of events was zero

SMR for lung cancer was greater than unity for hourly-paid white men (SMR = 1.18, 90% Cl: 1.07, 1.30) but not for non-white men (SMR = 0.74, 90% CI: 0.54, 0.99). The SMR for leukemia was greater than unity for both non-white (SMR = 1.56, *90%* Cl: 0.62, 3.28) and white (SMR = 1.34, 90% Cl: 0,98, 1.78) hourly-paid males.

Table IV shows SMRs for categories of cancer mortality among male SRS workers by duration of employment. The SMR for leukemia was less than unity for those employed <10 years (SMR = 0.93) and greater than unity for workers employed 10 to <20 years (SMR = 1.57), 20 to <30 years (SMR =1.06), and 30+ years (SMR = 1.63). SMRs for cancer of the pleura were above unity for workers employed <10 years (SMR = 3.26), 10 to <20 years (SMR = 3.56), 20 to <30 years (SMR = 2.33), and 30+ years (SMR = 9.23). Analyses of all cancers and other specific categories of cancer deaths indicated no notable variation in SMRs with duration of employment.

Table V shows SMRs for leukemia and cancer of the pleura by 5-year calendar periods. The largest excesses of leukemia mortality occur in the periods 1965-1969, 1985-1989, and 2000-2002. Table V also shows SMRs for cancer of the pleura by 5-year calendar periods. There are no deaths due to cancer of the pleura prior to the 5-year period 1985-1989; in that period, and all subsequent periods, the SMR for cancer of the pleura was above unity. The SMR for cancer of the pleura was 30.29 during the period 2000-2002 (based on one death). Analyses of all cancers and lung cancer by calendar period indicated no notable variation in SMRs (not shown).

DISCUSSION

Workers employed at SRS have fewer deaths due to all causes and all cancers than expected based upon US and SC referent rates. Such observations are typical when the mortality of relatively well-paid workers employed by a large corporation that offers medical and pension benefits is contrasted to the general population [Wilcosky and Wing,1987], and similar to the results obtained via SMR analyses of a number of other nuclear worker cohorts [Geiger et al., 1992: Vrijheid et al., 2007]. However, the analyses in this article illustrate how evidence of relative deficits in all cause and all cancer mortality among male SRS workers differs by pay code (Tables II and III). There is a substantial HWE for monthly-paid men while there is less evidence of a HWE for hourly-paid men. Such differences in mortality may reflect differences between pay code groups in occupational and environmental exposures and living conditions, including regional differences in factors such as diet and tobacco use [Sheridan et al., 1993; Shi, 1998]. Historically, hourly-paid workers tended to be drawn from the local and regional labor pool while many monthly-paid (salaried) workers were drawn from universities and employers outside of the region [Reed et al., 2002].

Despite SMRs that were less than unity for many malignant and non-malignant causes, the SMR for leukemia was greater than unity for monthly- and hourly-paid men; this is particularly notable in the analyses using South Carolina referent rates (Table A2). Subsequent analyses may help to understand whether the leukemia excess is associated with the whole body radiation dose estimates that have been quantified for SRS workers. Examination of calendar period at risk suggests that leukemia excesses were not restricted to the late 1960s, as suggested by previous authors [Wartenberg et al., 2001] but rather excess leukemia mortality was still occurring in the period 2000-2002 (Table V). The peak in the leukemia SMR during the calendar period 1965-1969 follows a peak, several years earlier (in 1960), in the annual collective whole body radiation dose; however, consideration of temporal correlations between collective dose and cause-specific SMRs are less informative than dose-response analyses based upon individual records [Richardson et al., 2006].

Deaths due to cancer of the pleura, a disease strongly related to asbestos exposure, were in excess among male SRS workers. The observation is interesting given the findings of the SRS Former Production Worker Health

TABLE IV. Standardized Mortality Ratios and Approximate 90% Confidence Intervals for Malignant Categories of Cause of Death Based Upon US Mortality Rates (1950-2002) by Duration of Employment

	Duration of employment											
	<10 years			10 to <20 years			20 to <30 years			30+ years		
Cancer cause of death	Ohs	SMR	90%CI	Ohs	SMR	90%Cl	Ohs	SMR	90%C1	Ohs	SMR	90%CI
Lip	0	-	[0.20]a	0	-	[0.11]	0	-	[0.11]	0	-	[0.06]
Tongue	4	1.20	0.41, 2.72	2	1.20	0.21, 3.71	1	0.52	0.03, 2.48	0	-	[1.50]
Other buccal cavity	5	1.34	0.52, 2.78	0		[1.88]	1	0.44	0.02, 2.11	0	-	[1.63]
Pharynx	5	0.67	0.26,1.40	3	0.82	0.22.2.07	1	0.23	0.01,1.11	3	0.86	0.24, 2.30
Esophagus	8	0.44	0.26, 0.86	4	0.50	0.17,1.12	3	0.29	0.03, 0.60	5	0.47	0.19,1.03
Stomach	10	0.53	0.30, 0.85	8	0.84	0.45,1.46	7	0.62	0.31,1.09	3	0.35	0.13, 0.91
Intestine except rectum	47	0.95	0.73,1.21	16	0.70	0.43,1.04	19	0.60	0.42, 0.92	25	0.97	0.66,1.35
Rectum	6	0.54	0.23,1.06	4	0.72	0.24,1.63	3	0.48	0.13,1.24	5	0.99	0.40, 2.14
Biliary	9	0.57	0.36.1.02	3	0.42	0.14,1.00	9	1.00	0.55,1.66	8	0.92	0.44,1.54
Pancreas	31	1.06	0.76,1.37	13	0.95	0.59,1.48	20	1.14	0.76, 1.60	11	0.71	0.45, 122
Peritoneum	2	0.95	0.46, 3.31	2	1.98	0.10, 4.11	0	-	[1.28]	0	-	[0.90]
Larynx	2	0.26	0.06, 0.74	1	0.28	0.03, 1.15	3	0.66	022, 1.55	3	0.76	0.27,1.93
Trachea, bronchus, lung	184	0.85	0.75, 0.95	88	0.93	0.77,1.10	131	1.01	0.86,1.16	94	0.77	0.66, 0.94
Pleura	2	3.26	0.58,10.2	1	3.56	0.18,16.76	1	2.33	0.12,10.9	3	9.23	2.58, 24.5
Oc Breast	2	2.69	0.47, 8.36	1	2.76	0.14,12.87	0	-	[0.43]	1	2.75	0.15.13.51
Prostate	38	0.98	0.73,1.24	20	1.01	0.71,1.49	35	1.00	0.79,1.36	21	0.86	0.57.1.21
Other male genital organs	0	-	[329]	1	0.91	0.10, 4.11	0	-	[0.59]	0	-	[0.34]
Kidney	10	0.64	0.36,1.02	3	0.43	0.23,125	6	0.69	0.25,1.14	4	0.50	021, 1.15
Bladder	9	0.68	0.38.1.14	10	1.54	0.92, 2.61	7	0.75	0.47,1.52	4	0.55	0.17,1.14
Skin	13	0.90	0.56,1.39	3	0.50	0.20, 1.32	6	0.92	0.69, 2.20	5	0.84	0.20,1.37
Mesothelioma	1	1.12	0.06, 5.24	0	-	[0.261	0	-	[0.35]	1	1.47	0.08, 7.25
Eye	1	2.84	0.28,11.3	0	-	[0.17]	1	5.72	0.58, 23.6	0	-	[0.13]
Brain and other CNS	20	1.06	0.66.1.60	12	1.47	0.84, 2.61	3	0.37	0.12.1.15	7	1.00	0.51, 2.22
Thyroid	0	-	[1.10]	0	-	[0.49]	0	-	[0.56]	0	-	[0.52]
Bone	1	0.56	0.06, 2.27	0	-	[0.78]	0	-	[0.70]	0	-	[0.44]
Connective	5	1.38	0.60, 2.68	2	1.31	0.32, 3.78	2	1.20	0.29, 3.41	2	1.32	0.35, 4.02
Other and unspecified	30	0.69	0.51.0.92	18	0.95	0.64,1.39	31	1.22	0.85,1.56	13	0.57	0.38, 0.95
Non-Hodgkin's lymphoma	21	0.89	0.59,1.22	6	0.58	0.35,124	14	1.12	0.64,1.60	10	0.88	0.53,1.53
Hodgkin's disease	2	0.37	0.09,1.02	1	0.46	0.05,1.94	2	1.67	0.42, 4.84	0	-	[0.64]
Leukemia and aleukemia	22	0.93	0.62,1.32	16	1.57	0.98, 2.36	13	1.06	0.62,1.68	17	1.63	1.07, 2.52
Multiple myeloma	5	0.51	0.22,1.00	5	1.18	0.53, 2.37	4	0.66	0.36,1.60	5	0.89	0.30,1.62
All cancers	495	0.82	0.76, 0.88	243	0.89	0.79, 0.98	323	0.90	0.82, 0.99	250	0.79	0.71, 0.88

Male SRS workers who were hired by DuPont prior 10 1987 and who worked at least 90 days.

Obs, observed deaths; SMR, standardized mortality ratio; Cl, confidence interval; CNS, central nervous system.

[a]fhe bracketed value is the expected number of deaths. SMRs and associated confidence intervals were not calculated if the observed number of events was zero

TABLE V. Standardized Mortality Ratios (and Approximate 90% Confidence Intervals) for Leukemia and Cancer of the Pleura Based Upon US Mortality Rates (1950-2002) by 5-Year Calendar Periods of Observation

	Leukemia			Cancer of the pleura		
	Ohs	SMR	90%CI	Obs	SMR	90%CI
1950-1954	0	—	[0.28]a	0	—	[0.00]
1955-1959	0	—	[1.35]	0	—	[0.00]
1960-1964	1	0.59	0.03,2.82	0	—	[0.00]
1965-1969	6	2.69	1.17, 5.31	0	—	[0.03]
1970-1974	3	1.06	0.29, 275	0	—	[0.09]
1975-1979	4	1.03	0.35,2.35	0	—	[0.15]
1980-1984	6	1.09	0.48, 2.16	0	—	[0.22]
1985-1989	11	1.46	0.82, 2.41	4	12.55	4.29, 28.72
1990-1994	11	1.09	0.61,1.80	1	2.37	0.12,11.25
1995-1999	12	0.96	0.55,1.55	1	2.64	0.14,12.55
2000-2002	14	1.64	0.99, 2.56	1	30.29	1.55,143.76

Male SRS workers who were hired by DuPont prior to 1987 and who worked at least 90 days.
Obs, observed deaths; SMR, standardized mortality ratio; CI, confidence interval.
[a]The bracketed value is the expected number of deaths. SMRs and associated confidence intervals were not calculated if the observed number of events was zero.

Project, which conducted medical evaluations of 1,368 former SRS workers [Makie et al., 2005]. That study found that pleural abnormalities were more common among male SRS workers than in the general population (OR = 2.4), and were associated with occupational asbestos exposure. In our analyses, the largest excess of cancer of the pleura was among workers with 30+ years employment at the site, although elevated SMRs for pleural cancer were also observed among workers with shorter terms of employment. Industrial hygiene reports from the early 1970s indicate that occupational asbestos exposure was a problem at SRS, particularly in the Maintenance Department [Du Pont de Nemours and Co. Savannah River Plant, 1969]. During this period, air samples for asbestos indicated personnel exposures during some sawing operations, for example, exceeded the Threshold Limit Value of 5 fibers/ml (air). Among the seven SRS workers who died of pleural cancer, four were mechanics, one was an engineer, one was a technician, and one was a power plant operator; all were hired prior to 1955 with a median age at hire of 28 years. Excesses of cancer of the pleura have been observed in other nuclear worker cohorts, including studies of workers in Australia [Habib et al., 2005, 2006], the United Kingdom [Muirhead et al., 1999; Omar et al., 1999; McGeoghegan and Binks, 2000, 2001], and France [Telle-Lamberton et al., 2004]. Asbestos exposure is also associated with cancer of the peritoneum. Evidence of excess cancer of the peritoneum in this cohort is less clear: in comparisons to SC death rates SMRs are slightly above unity for each of the pay code groups while SMRs are below unity for each of these groups when calculations are based upon US referent rates. Previous studies have found that deaths due to malignant mesothelioma often accounted for the majority of deaths classified as pleural cancer [Robinson et al., 2006]. Prior to the tenth revision of the ICD there was not a separate code for malignant mesothelioma; mesothelioma deaths were coded to the site specified on the death certificate. Consequently, our SMR analyses for that cause of death are based upon deaths in the period 1999-2002. An excess of deaths due to mesothelioma was observed among hourly-paid workers (based upon two observed deaths) while fewer deaths than expected due to mesothelioma were observed among monthly- and weekly-paid workers. It is interesting to note that prior mortality studies of this cohort did not observe an excess of cancer of the pleura. Examination of the SMR for cancer of the pleura by year of death (i.e., calendar period) reveals that no deaths due to cancer of the pleura were observed prior to the period 1985-1989 and the most notable excesses have been observed in the most recent follow-up period (2000-2002).

More deaths than expected due to breast cancer were observed among hourly-paid males (four deaths observed 0.99 expected). However, given the relatively small number of cases of male breast cancer in this cohort we have little ability to explore associations with duration of employment or other indicators of exposure. Other categories of cancer mortality for which we noted excesses that were based upon small numbers (i.e., less than five deaths) include cancer of the eye among males, and cancer of the tongue, buccal cavity, esophagus, and Hodgkin's disease among females.

In analyses based upon US referent rates, lung cancer mortality was in excess among hourly-paid males and in substantial deficit among monthly-paid males. Differences in cigarette smoking offer a plausible explanation for this gradient in lung cancer SMRs [Sheridan et al., 1993; Shi, 19981, although given the evidence of excess pleural cancer and the potential occupational exposure to a number of lung carcinogens, variation in occupational exposures by pay code could also contribute to the gradient in lung cancer. Cigarette smoking was regulated at SRS; however, regulations were not specific to pay code groups but rather to work areas or locations at the site. Consequently, statistical adjustment for pay code in analyses of exposure-mortality associations may control, in part, for confounding by cigarette smoking; however, residual confounding by cigarette smoking is likely in such analyses.

There are a number of obstacles to the ability to detect adverse effects of occupational exposures via SMR analyses. The strong evidence of a healthy worker effect suggests that SMRs below unity don't necessarily imply the absence of occupational exposure effects; rather, relying on comparisons of observed deaths to expected deaths derived using national or state referent rates may spuriously mask the health effects of occupational exposures. Further, masking of adverse effects of occupational exposures may be exacerbated if a substantial proportion of the study cohort has little or no exposure to the hazards of interest. SMRs that don't discriminate between subgroups based upon exposure level, or simply consider being employed as an indication of exposure, may dilute evidence of any adverse exposure effect by mixing exposed and unexposed members of the study cohort. Despite these obstacles, the findings of this study provide evidence of excess mortality due to leukemia among hourly- and monthly-paid workers, and excess mortality due to pleural cancer among all workers. The evidence of excess cancer of the pleura has not been noted before in this cohort, but is consistent with recent evidence (derived from medical screening) of excesses of pleural abnormalities among former SRS workers. The leukemia excess also is notable in recent years.

The National Academies of Sciences recently reviewed the epidemiological research program on US Department of Energy workers, concluding that this research program should continue, albeit with greater communication, and collaboration between the Departments of Health and Human Services and Energy [National Research Council of the National Academies and Committe to Review the Worker and Public Health Activities Program Administered by the Department of Energy and the Department of Health and Human Services, 2006]. The findings of this study underscore the importance of continued follow-up of former nuclear workers in order to understand the range of potential occupational health effects associated with production activities in the nuclear weapons complex and particularlyto identify occupational diseases that have long induction and latency periods. Such studies may help to inform medical screening programs, occupational health services, compensation programs, and worker protection efforts.

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REFERENCES

Arrighi HM, Hertz-Picciotto I. 1994. The evolving concept of the healthy worker survivor effect. Epidemiology 5:189-196.

Cassinelli R, Kock KJ, Steenland K, Spaeth S, Laber P. 1998. User documentation: PC LTAS life table analysis system for use on the PC Cincinnati, OH: US Department of Health and Human. Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

Cragle DL, McLain RW, Qualters JR, Hickey JL, Wilkinson GS, Tankersley WG, Lushbaugh CC. 1988. Mortality among workers at a nuclear fuels production facility. Am J Ind Med 14:379-401,

Cragle DL, Watkins JP, Robertson-DeMers K. 1998. Mortality among workers at the Savannah River nuclear production facility. American Statistical Association: Section on Statistics in Epidemiology. Dallas, TX: American Statistical Association.

Du Pont de Nemours and Co. Savannah River Plant 1969. SRS industrial hygiene 1969-1986: Monthly reports. Aiken, SC: SRP.

Geiger HJ, Rush D, Michaels D. 1992. Dead reckoning: A critical review of the Department of Energy's Epidemiologic Research. Washington, DC: Physicians for Social Responsibility.

Habib RR, Abdallah SM, Law M, Kaldor J. 2005. Mortality rates among nuclear industry workers at Lucas Heights Science and Technology Centre. Aust N Z J Public Health 29:229-237.

Habib RR, Abdallah SM, Law M, Kaldor J. 2006. Cancer incidence among Australian nuclear industry workers. J Occup Health 48:358-365.

Hickey JLS, Cragle D. 1985. Occupational exposures of workers to chemicals at the Savannah River Plant1952-1984 Oak Ridge, TN: Oak Ridge Associated Universities. p 69.

Makie T, Adcock D, Lackland DT, Hoel DG. 2005. Pulmonary abnormalities associated with occupational exposures at the Savannah River Site. Am J Ind Med 48:365-372.

McGeoghegan D, Binks K. 2(X)0. The mortality and cancer morbidity experience of workers at the Capenhurst uranium enrichment facility 1946-95. J Radiol Prot 20:381-401.

McGeoghegan D, Binks K. 2001. The mortality and cancer morbidity experience of employees at the Chapelcross plant of British Nuclear Fuels plc, 1955-95. J Radiol Prot 21.221-250.

McMichael AJ. 1976. Standardized mortality ratios and the "healthy worker effect": Scratching beneath the surface. J Occup Med 18:165–168.

Muirhead CR, Goodill AA, Haylock RG, Vokes J, Little MP, Jackson DA, JA OH, Thomas JM, Kendall GM, Silk TJ, Bingham D, Berridge GL. 1999. Occupational radiation exposure and mortality: Second analysis of the National Registry for Radiation Workers. J Radiol Prot 19:3-26.

National Research Council of the National Academies, Committe to Review the Worker and Public Health Activities Program Administered by the Department of Energy and the Department of Health and Human Services. 2006. Review of the worker and public health activities program administered by the Department of Energy and the Department of Health and Human Services.

Omar RZ, Barber JA, Smith PG. 1999. Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. Br J Cancer 79:1288-1301.

Reed MB, Swanson MT, Gather S, Joseph IW, Henry WR. 2002. Savannah River Site at fifty. Washington, DC: US Government Printing Office.

Richardson DB, Wing S, Daniels RD. 2006. Evaluation of external radiation dosimetry records at the Savannah River Site. J Expo Sci Environ Epidemiol 1951-1989.

Robinson CF, Schnorr TM, Cassinelli RT 2nd, Calvert GM, Steenland NK, Gersic CM, Schubauer-Berigan MK. 2006. Tenth revision U.S. mortality rates for use with the NIOSH Life Table Analysis System. J Occup Environ Med 48:662-667.

Shi L. 1998. Sociodemographic characteristics and individual health behaviors. South Med J 91:933-941.

Sheridan DP, Hornung CA, McCutcheon EP, Wheeler FC. 1993. Demographic and educational differences in smoking in a tobacco-growing state. Am J Prev Med 9:155-159.

Steenland K, Beaumont J, Spaeth S. Brown D, Okun A, Jurcenko L, Ryan B, Phillips S, Roscoe R, Stayner L., et al. 1990. New developments in the Life Table Analysis System of the National Institute for Occupational Safety and Health. J Occup Med 32:1091 - 1098.

Telle-Lamberton M, Bergot D, Gagneau M, Samson E, Giraud JM, Naeron MO, Hubert P. 2004. Cancer mortality among French Atomic Energy Commission workers. Am J Ind Med 45(1):34-44.

Vrijheid M, Cardis E, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Ahn YO, Ashmore P, Auvinen A, Bae JM, Engels H, Gulis G, Habib R, Hosada Y, Kurtinaitis J, Malker H, Moser M, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, Turai 1, Usel M, Veress K. 2007. The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: Design, epidemiological methods, and descriptive results. Radiation Res 167:361-379.

Wartenberg D, Brown S, Mohr S, Cragle D, Friedlander B. 2001. Are African-American nuclear workers at lower mortality risk than Caucasians? J Occup Environ Med 43:861-871.

Wilcosky T. Wing S. 1987. The healthy worker effect. Selection of workers and work forces. Scand J Work Environ Health 13: 70-72.

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Original Contribution

Leukemia Mortality among Workers at the Savannah River Site

David B. Richardson and Steve Wing

From the Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC.

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The authors investigated associations between ionizing radiation and leukemia mortality among workers at the Savannah River Site (South Carolina). A total of 18,883 workers hired between 1950 and 1986 were followed through 2002 to ascertain causes of death. Estimates of radiation doses from external sources and internal tritium uptakes were derived from dosimetry records through 1999. Radiation dose–mortality trends were evaluated for leukemia, leukemia excluding chronic lymphocytic leukemia, and myeloid leukemia. A positive association was observed between leukemia mortality and radiation dose under a 3-year lag assumption (excess relative rate/10 mSv = 0.04, 90% confidence interval: –0.00, 0.12). The association was of larger magnitude for leukemia excluding chronic lymphocytic leukemia (excess relative rate/1 0 mSv = 0.08, 90% confidence interval: 0.01, 0.20) and myeloid leukemia (excess relative rate/10 mSv = 0.12, 90% confidence interval: 0.02, 0.35). Compared with males, females had less complete dosimetry information; when analyses were restricted to males, the estimated association for each cause of death increased slightly in magnitude and goodness of fit. Exposures accrued 3-15 years prior were more strongly related to leukemia than exposures in the more distant past. This study provides evidence of positive associations between radiation dose and leukemia mortality among Savannah River Site workers. The temporal patterns of association appear consistent with those in studies of populations exposed at higher dose rates.

leukemia; mortality; nuclear energy; radiation, ionizing; South Carolina

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; ERR, excess relative rate; ICD, *International Classification of Diseases.*

To our knowledge, the largest study to date of cancer in workers in the nuclear industry assessed mortality among workers in 155 nuclear facilities in 15 countries (1). In that study, the estimated association between leukemia mortality and cumulative radiation dose under a 2-year exposure lag assumption was smaller in magnitude than an estimate obtained by fitting a linear dose-response model to male atomic bomb survivors exposed between the ages of 20 and 60 years; 90 percent confidence limits ranged from less than zero to more than twice the linear estimate for A-bomb survivors (excess relative rate (ERR)/10 mSv = 0.02, 90 percent confidence interval (CI): <0, 0.07). The temporal pattern of the radiation dose–leukemia association in the15-country study is noteworthy, because the nuclear workers' data showed evidence of an increase in the magnitude of the radiation-leukemia association with increasing lag assumptions (1); in contrast, evidence of radiation effects diminished with time since exposure in many studies of leukemia among people who have received high dose-rate exposures (2).

Although pooling nuclear worker data affords the opportunity for statistical precision, a potential disadvantage of such an approach is that it increases the possibility of heterogeneity in exposure effects between cohorts and/or heterogeneity in selection or confounding factors and measurement of exposure and outcome. From this perspective,

Correspondence to Dr. David B. Richardson, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-8050 (e-mail: david.richardson@unc.edu).

analyses of a single cohort of workers may be useful if such analyses suffer less bias than pooled analyses yet still encompass adequate numbers of cases to draw valid statistical inferences. In this paper, we assess radiation dose–leukemia associations in a large cohort of US nuclear weapons workers that is independent of the 15-country study. Although our study includes only about one third the number of leukemias included in the 15-country study, the number of cases exceeds the number contributed by any single cohort in the collaborative study and is comparable to the number of leukemia cases contributed by the United Kingdom, by the 13 countries other than the United States and the United Kingdom, or by the combined Hanford, Oak Ridge National Laboratory, and US commercial nuclear power cohorts included in the 15-country study (1).

In this paper, we evaluate associations between ionizing radiation and mortality due to leukemia among workers employed at the Savannah River Site. We focus on ionizing radiation doses from external sources and internal doses from tritium intakes. We examine modification of radiation dose–leukemia associations by subtype of leukemia and time since exposure.

MATERIALS AND METHODS

The Savannah River Site, located near Aiken, South Carolina, was constructed in 1950 by E. 1. du Pont de Nemours and Company (DuPont) to produce materials for the US nuclear weapons program. Activities at the Savannah River Site have included operation of five large reactors, two chemical separation areas, a heavy-water extraction plant, and nuclear fuel and target fabrication plants, as well as test reactors, power plants, and laboratories.

Between 1950 and 1986, 21,204 people were known to have been hired by DuPont to work at the Savannah River Site. We excluded from these analyses workers for whom date of birth (n = 57), sex (n = 10), or date of hire (n = 184) was unknown. People employed less than 90 days (n = 1,355) were excluded since short-term workers often differ from those with longer employment tenures with respect to mortality risk and cumulative occupational exposures (3). Workers known to be employed at other US Department of Energy facilities (n = 715) also were excluded because we did not collect information on occupational radiation exposures that occurred outside of employment at the Savannah River Site. Vital status and cause of death were ascertained through December 31, 2002, via records of the Social Security Administration and the National Death Index. We obtained underlying and contributing causes of death for deceased workers. For deaths occurring prior to 1979, cause-of-death information was coded according to the Eighth Revision of the *International Classification of Diseases* (ICD); for deaths occurring in 1979 or later, cause of death information was coded to the ICD revision in effect at the time of death. If there was no death indication for a worker and he or she was confirmed to be alive on January 1, 1979, or later by the Social Security Administration or the Savannah River Site's employment records, then that worker was assumed to be alive as of December 31, 2002.

We conducted dose-response analyses for leukemia (ICD-8 codes 204-207, ICD-9 (Ninth Revision) codes 204-208, ICD-10 (Tenth Revision) codes C91-95), leukemia excluding chronic lymphocytic leukemia (CLL; ICD-8 and ICD-9 code 204.1, ICD-10 codes C91.1 and C91.4), and myeloid leukemia (ICD-8 and ICD-9 code 205, ICD-10 code C92). We used information on all listed causes of death (underlying and contributory) to define the outcome categories. The use of multiple-cause-of-death information may be particularly valuable as a way to increase the sensitivity and specificity of case classifications for studies of diseases, such as adult leukemia, that tend to occur at older ages in patients with multiple morbid conditions at death (4).

The exposure of interest was defined as cumulative whole-body radiation dose equivalent in milliSieverts (mSv) from external sources and tritium received during employment at the Savannah River Site. Personal monitoring data were available for the period 1950-1999 from Savannah River Site records. Monitoring of external ionizing radiation exposure began with film badge dosimeters as well as neutron nuclear track emulsion dosimeters; beginning in 1970, external exposures were monitored via thermoluminescent dosimeters. Radiation dose estimates from tritium depositions were derived via bioassay monitoring. Details about the Savannah River Site's dosimetry program, including the quality factors used to calculate dose equivalents, have been reported previously (5-7). Whole-body radiation doses were estimated for work-years in which dose data were missing by using dose estimates in adjacent time periods and average values for similar workers. Estimated annual doses constituted 4 percent of employment years for males and 17 percent of employment years for females (7).

Analyses were conducted by using a nested case-control approach. Risk sets were formed by incidence density matching of cases (leukemia deaths) to noncases. Risk sets were matched on the following factors: attained age; sex; race (Black vs. other); year of birth (born before 1915; in 1915–<1925, 1925–<1930, 1930–<1935, or 1935–<1950; or after 1950); pay code (used to control for socioeconomic differences in mortality and classified on the basis of the worker's pay schedule when hired as paid monthly, weekly, or hourly); and employment status (used to control for the healthy worker survivor effect and to indicate whether a worker was employed) (8-10). All eligible controls were selected for each case. Index dates for cases and controls were defined as their date of death (for a case) or date of selection (for a control). Cumulative radiation dose was examined under a fixed 3-year lag and in time windows defined by the periods 3–< *15,* 15–<30, and >30 years prior to the index date. Since exposure data were available for the period 1950-1999 while follow-up spanned the period 1950-2002, a 3-year lag was the minimal lag assumption evaluated in these analyses. The statistical program PECAN was used to fit conditional logistic regression models of the form RR - OR = e^{a} (1 + (3x), where a; indexes the stratum-specific risk sets and x represents cumulative dose (in 10-mSv units) (11). This approach is equivalent to a Cox proportional hazards regression analysis with age as the time scale and stratification on sex, race, birth cohort, pay code, and employment status (12, 13). The value 13 provides

an estimate of the ERR per 10-mSv dose and is discussed as such in this paper. Confidence intervals were estimated via the likelihood method. Goodness of fit was evaluated by a likelihood ratio test comparing nested models.

Because radiation monitoring records were less complete for female than for male workers (suggesting greater potential for exposure misclassification for female than for male workers) and the majority of the dose was accrued by male workers, we also conducted analyses by using data for the subcohort of 15,264 male workers. Given the low doses and small number of leukemia deaths among female workers, we did not estimate separate dose-response trends for females.

RESULTS

With follow-up through 2002, we found that 27 percent of the study cohort was deceased (5,098 workers), 72 percent of the cohort was alive at the end of follow-up (13,590 workers), and 1 percent of the cohort was lost to follow-up (195 workers). Information on cause of death was collected for 99 percent of decedents (5,047 workers). In total, 84 leukemia deaths were observed, of which 73 were cases for whom leukemia was listed as the underlying cause of death. Acute myeloid leukemia accounted for 29 cases, chronic myeloid leukemia for 10 cases, acute lymphocytic leukemia for four cases, and CLL for 22 cases; the remainder consisted of monocytic leukemia (n = 2) and other and unspecified leukemias (n = 17).

The analyses involved risk sets formed by density sampling; the average risk set included 480 controls, the median number of controls per risk set was 451, and the smallest risk set included one case and four controls. The distributions of cases by study factors are shown in table 1. The average age of leukemia cases was 63.7 years, with the majority born prior to 1930 (table 1). Consistent with the relatively old age of cases, 72 of the 84 leukemia cases were hired prior to 1960. The mean cumulative dose under a 3-year lag accrued by males was 43.7 mSv (standard deviation, 73.4), and the mean dose accrued by females was 4.9 mSv (standard deviation, 14.9).

Under the minimal 3-year lag assumption, the estimated ERR of leukemia was 0.041 per 10 mSv (90 percent CI: –0.001, 0.116). The estimate of association between ionizing radiation dose and leukemia excluding CLL was of larger magnitude than the estimated association for all leukemias (ERR/10 mSv = 0.077, 90 percent CI: 0.014, 0.198). When analyses were restricted to myeloid leukemias, the magnitude and fit of the model were greater (ERR/10 mSv = 0.123, 90 percent CI: 0.021, 0.354), although the analyses of myeloid leukemia deaths were based on smaller numbers of cases.

Table 2 also shows the results of analyses restricted to male workers. For each leukemia category, there was a modest increase in the magnitude of association and goodness of model fit upon exclusion of female workers. For example, among male Savannah River Site workers, the association between radiation dose and mortality due to leukemia excluding CLL was ERR/10 mSv = 0.082 (90 percent CI: 0.016, 0.211).

TABLE 1. Distribution of cases with respect to attained age, sex, race, pay code, birth cohort, employment status, and subtypes of leukemia at the Savannah River Site, South Carolina, 1950-2002

	Leukemia	Leukemia (excluding CLL*)	Myeloid leukemia
Mean age in years	63.7 (11.7)t	**63.7** (12.2)	**64.0** (11.5)
Sex			
Male	79	58	37
Female	5	4	3
Race			
White/other	79	60	39
Black	5	**2**	**1**
Pay code			
Monthly	**22**	18	15
Weekly	16	11	7
Hourly	46	**33**	18
Birth cohort			
<1915	7	5	4
1915–<1925	35	27	19
1925–<1930	24	18	9
1930–<1935	8	**5**	**3**
1935–<1950	6	3	2
>1950	4	4	3
Employment status			
Employed	13	10	7
Terminated	71	52	**33**
Total	84	62	40

* *CLL,* chronic lymphocytic leukemia.

t Values in parentheses, standard deviation.

ERRs for three time windows are shown in table 3. Associations between radiation and leukemia mortality under the 3-year lag were largely due to doses accrued in the period 3–<15 years prior to the index date. A positive association of lower magnitude was observed in the period 15–<30 years prior, and essentially no association with radiation doses accrued in the period >_30 years prior (table 3). For leukemia excluding CLL and myeloid leukemia, a positive but highly imprecise association was observed with doses accrued >_30 years in the past. In analyses restricted to males (table 3), similar patterns were observed, with some improvement in the precision of estimates when contrasted to analyses that included males and females. Exposures accrued in the time window 3–<15 years prior to the index date were positively associated with mortality due to leukemia (ERR/10 mSv = 0.280, 90 percent CI: 0.021, 0.728), leukemia excluding CLL (ERRI10 mSv = 0.369, 90 percent CI: 0.003, 1.046), and myeloid leukemia (ERR/10 mSv = 0.437, 90 percent CI: <0, 1.598).

Table 4 shows the distribution of observed leukemia deaths and estimates of relative rates by categories of cumulative dose under a 3-year lag assumption derived via a model that included eight indicator terms for these nine dose categories (results tabulated by categories of

TABLE 2. Estimated association between cumulative radiation dose (under a 3-year lag assumption) and mortality due to leukemia among workers at the Savannah River Site, South Carolina, 1950-2002

Leukemia excluding CLL*		Leukemia	Myeloid leukemia
Males and females			
ERR*/10 mSv	0.041	0.077	0.123
90% CI*	-0.001, 0.116	0.014, 0.198	0.021, 0.354
Likelihood ratio test (X^2, 1 df)	2.50	4.92	5.14
Males only			
ERR/10 mSv	0.044	0.082	0.136
90% CI	0.000, 0.123	0.016, 0.211	0.025, 0.395
Likelihood ratio test (X^2, 1 df)	2.72	5.22	5.54

* CLL, chronic lymphocytic leukemia; ERR, excess relative rate; CI, confidence interval.

cumulative dose accrued in the period 3-< 15 years prior are presented in Appendix table 1). In analyses of all leukemias, the estimated rate ratios increased monotonically across nearly all categories of dose with the exception of the dose category 5-< 10 mSv (for which the estimated rate ratio was similar to that for the category >0-<5 mSv) and the

TABLE 3. Estimated association between mortality due to leukemia and cumulative radiation dose accrued by workers In three exposure time windows, Savannah River Site, South Carolina, 1950-2002

Time since exposure	Leukemia	Leukemia CLL* excluding CLL	Myeloid leukemia
Males and females			
3-<15 years			
ERR*/10 mSv	0.265	0.344	0.403
90% CI*	0.015, 0.694	-0.004, 0.980	<0, 1.441
Likelihood ratio test	3.18	2.61	1.65
15-<30 years			
ERR/10 mSv	0.011	0.008	0.007
90% CI	<0, 0.105	<0, 0.1595	<0, 0.327
Likelihood ratio test	0.07	0.01	0.00
>30 years			
ERR/10 mSv	-0.004	0.100	0.209
90% CI	<0, 0.145	<0, 0.440	<0, 1.147
Likelihood ratio test	0.00	0.94	0.87
Males only			
3-<15 years			
ERR/10 mSv	0.280	0.369	0.437
90% CI	0.021, 0.728	0.003, 1.046	<0, 1.598
Likelihood ratio test	3.34	2.78	1.74
15-<30 years			
ERR/10 mSv	0.012	0.009	0.013
90% CI	<0, 0.109	<0, 0.167	<0, 0.364
Likelihood ratio test	0.07	0.02	0.01
>30 years			
ERR/10 mSv	-0.003	0.104	0.211
90% CI	<0, 0.151	<0, 0.458	<0, 1.192
Likelihood ratio test	0.00	**0.98**	0.86

* CLL, chronic lymphocytic leukemia; ERR, excess relative rate; CI, confidence interval.

TABLE 4. Observed deaths of workers and estimated rate ratios by category of cumulative dose under a 3-year exposure lag assumption, Savannah River Site, South Carolina, 1950-2002

Cause of death	Dose category (mSv)								
	0	>0-<5	5-<10	10-<20	[illegible]	[illegible]	80-<160	160-<320	>320
Leukemia									
Observed no. of deaths	5	26	9	8	8	9	13	4	2
Rate ratio	1	1.39	1.39	1.55	1.74	2.08	3.49	1.34	4.91
Leukemia excluding CLL*									
Observed no. of deaths	4	19	7	6	4	5	11	4	2
Rate ratio	1	1.25	1.38	1.59	1.10	1.59	4.03	1.87	**6.61**
Myeloid leukemia									
Observed no. of deaths	4	11	3	5	3	4	6	2	2
Rate ratio	1	0.62	0.49	1.05	0.67	1.15	2.21	1.06	8.09
Mean dose (mSv)	0	1.9	7.2	14.3	28.9	56.7	115.2	219.4	360.2

* CLL, chronic lymphocytic leukemia

penultimate category (for which the estimated rate ratio was 1.34). In analyses of leukemia excluding CLL, there was less evidence of a monotonic trend in estimated rate ratios across dose categories; however, the estimated rate ratios for leukemia excluding CLL for the highest three dose categories were substantially larger than the values derived from analyses that included CLL. In analyses of myeloid leukemia, rate ratios were less than unity for the categories >0-<5, 5-<10, 10-<20, and 20-<40 mSv but were greater than unity for the higher dose groups.

The results in table 4 suggest a substantial increase in observed relative rates with increasing dose; we contrasted the goodness-of-model fit of an exponential rate model to the fit of the additive ERR model. For analyses of the association between cumulative dose under a 3-year lag and each category of cause of death, we found that the exponential rate model fitted the data slightly worse than the additive ERR model; for example, for analyses of leukemia excluding CLL, the residual model deviance under the exponential rate model was 732.81, whereas, under the additive ERR model, the residual deviance was 731.84.

DISCUSSION

We observed positive associations between leukemia mortality and ionizing radiation doses from external sources and internal tritium depositions. The association between leukemia excluding CLL and cumulative radiation dose under a 3-year lag (ERR/10 mSv = 0.077) was larger than, but not incompatible with, the risk estimate (under a 2-year lag) for non-CLL leukemia in the 15-country study (ERR/10 mSv = 0.019, 95 percent CI: <0, 0.085) and analyses of mortality among A-bomb survivors (ERR/10 mSv = 0.032, 95 percent CI: 0.016, 0.057) (1). There is no overlap between the workers included in this analysis and the workers included in the 15-country study.

Via exposure time windows we observed that the ERR estimate for leukemia was 0.265 per 10 mSv for exposures accrued 3-<15 years prior, 0.011 per 10 mSv for exposures accrued 15-<30 years prior, and essentially null for exposures accrued >30 years prior. Such a temporal pattern of diminishing radiation dose-leukemia mortality associations with time since exposure differs from the pattern observed in the 15-country study but is consistent with observations derived from some studies of leukemia risk following acute exposure to ionizing radiation, including patients who received radiotherapy for ankylosing spondylitis (14). Among survivors of the atomic bombings of Hiroshima and Nagasaki, Japan, leukemia mortality is positively associated with ionizing radiation dose, with the preferred model allowing for diminishing effect of irradiation on leukemia risk with increasing time since exposure (2).

Although the 15-country study includes more leukemia cases than our study of Savannah River Site workers, an important consideration is the distribution of cases with respect to cumulative dose. The average dose accrued by workers in the 15-country study (19.4 mSv) is less than half the average dose accrued by males employed at the Savannah River Site. Crucially, this study of Savannah River Site workers and the 15-country study include the same number of non-CLL leukemia deaths among workers who accrued a >50-mSv dose (19 deaths), and this study includes more non-CLL leukemia deaths among workers who accrued ≥100 mSv than the 15-country study does (the latter includes 10 deaths in the ?100-mSv range, whereas this study includes 13 deaths in that range) (15).

At the Savannah River Site, film badge dosimeters were exchanged on a weekly schedule until October 1957, on a biweekly schedule from October 1957 to 1964, on a 4-week cycle in 1965, and on a monthly schedule beginning in 1966 (6). Thermoluminescent dosimeters were exchanged on a quarterly cycle for personnel judged to have low-exposure potential and on a monthly cycle for other employees.

Frequent reading of dosimeters could lead to cumulative dose underestimation if dosimeters were not sufficiently exposed to reach a minimum detectable dose. However, analyses based on simulations and dose estimation procedures suggest that the impact on estimates of radiation dose-response trends of this source of exposure measurement error is modest (16-18). Recent work on radiation dosimetry for occupational cohort studies suggests that the errors that may be most important for dose estimates are those that result from the fact that dosimeters used in the earliest years of the nuclear era were limited in their ability to respond accurately for some energies and geometries of radiation exposures (19, 20). Biases resulting from these limitations may differ between facilities with different exposure conditions and will tend to be greater in analyses that include larger numbers of workers employed in the earliest year of the nuclear era. The Savannah River Site, however, started operations in the 1950s and therefore began operations in a period that benefited from experience with radiation protection and the advances in monitoring practices developed during the first decade of the Manhattan Project (17).

For nuclear worker studies of associations between radiation and leukemia mortality, the potential for confounding by nonradiologic leukemogens, such as benzene, must be considered as well. Potential confounding by benzene exposure was not assessed in the 15-country study because detailed assessments of such exposures for all facilities included in the collaborative study were not possible, although assessments for some cohorts included in the study noted a potential for occupational benzene exposures (21). In contrast, in a study that focuses on a single cohort, there is substantial opportunity for detailed evaluation of historical information on process activities and potential for significant occupational exposures to hazards other than ionizing radiation. Several assessments of nonradiologic exposures have been conducted for workers employed at the Savannah River Site indicating that benzene exposure was not a significant hazard at the site. For this study, we reviewed monthly industrial hygiene reports, two prior assessments of chemical and physical hazards (22, 23), and hazard assessments conducted as part of the Savannah River Site building database (24) to assess the potential for confounding by nonradiologic hazards that are known leukemogens. These documents show little evidence of exposure to established leukemogens other than ionizing radiation. For example, reviews of industrial hygiene reports spanning the period 1952-1986 provide little indication of benzene exposure potential. For more recent years, computerized records of industrial hygiene monitoring at the Savannah River Site were reviewed; the only monitoring for benzene exposure that occurred was limited to the laboratory areas where benzene was used in small (reagent) quantities.

Aside from the external exposures to ionizing radiation and internal depositions of tritium (which were quantified as the exposure of interest in these analyses), plutonium-239 is the primary radiologic hazard at the Savannah River Site. Plutonium delivers alpha radiation to the lung, liver, and bone surface; a very small proportion of the delivered dose is to the hematopoietic red bone marrow. While annual dose estimates for intakes of plutonium and other radionuclideshave not been computerized for all intakes over this study period, dose estimates have been derived for some leukemia cases at the Savannah River Site. These analyses suggest that plutonium contributes only about 3 percent of the total biologically equivalent dose to the red bone marrow, with the remainder due to gamma radiation and tritium (17, 25, 26). Without direct estimates of doses from all internal depositions, however, the joint effects of these exposures cannot be evaluated.

Our prior work suggests that information on cigarette smoking is incomplete in the available records from the site's medical division and is difficult to evaluate for workers prior to the middle 1960s and for all workers after termination of employment (27). However, this limitation is minor in the context of these analyses of leukemia mortality, since, given the small magnitude of association between smoking and leukemia mortality, high levels of correlation between occupational radiation exposure and smoking would be necessary to account for even modest dose-response trends for leukemia (28, 29).

Although considerations about heterogeneity in radiation dose-response analyses for different subtypes of leukemia are of interest, because of small numbers we did not conduct subtype-specific dose-response analyses. A thorough consideration of the topic would include evaluations of heterogeneity by disease subtype in the temporal pattern of radiation dose–mortality associations (30); such analyses demand relatively large numbers of cases.

In addition to the cohorts of nuclear workers aggregated for analyses in the 15-country study (1), there are several other cohorts of US nuclear workers in which associations between occupational exposure to ionizing radiation and leukemia have been examined. Two studies that included relatively large numbers of leukemias are those by Yiin et al. (31) on radiation dose–leukemia mortality association among 13,468 radiation-monitored workers employed at the Portsmouth Naval Shipyard (Maine) and by SchubauerBerigan et al. (32) on leukemia among workers at five US nuclear facilities. Both studies are consistent with a positive association between low-level occupational exposure to ionizing radiation and non-CLL leukemia mortality characterized by a relatively short empirical induction period.

This study provides evidence of positive associations between radiation dose and leukemia mortality among workers at the Savannah River Site. The temporal patterns of association appear consistent with the temporal patterns in studies of populations exposed at higher dose rates. Associations appeared stronger for leukemia excluding CLL than for all leukemias and were of the largest magnitude for the myeloid forms of leukemia. We found relatively little evidence to support hypotheses of potential confounding by known nonradiologic leukemogens. The findings illustrate the importance of continued follow-up and analyses of these historical US Department of Energy cohorts because the evidence obtained from these studies continues to grow as the cohorts are followed over time. Persistence of dose-response associations at magnitudes observed in this analysis would be inconsistent with previous arguments that chronic low-level doses of ionizing radiation are less leukemogenic than acute

exposures to the same doses.

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REFERENCES

1. Cardis E, Vrijheid M, Blettner M, et al. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. BMJ 2005;331:77.
2. National Research Council, Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation. Health risks from exposure to low levels of ionizing radiation: BEIR VII phase 2. Washington, DC: The National Academies Press, 2006.
3. Cardis E, Gilbert E, Carpenter L, et al. Combined analyses of cancer mortality among nuclear industry workers in Canada, the United Kingdom and the United States of America. Lyon, France: World Health Organization, International Agency for Research on Cancer, 1995.
4. Richardson DB. Use of multiple cause of death data in cancer mortality analyses. Am J Ind Med 2006;49:683-9.
5. Taylor GA, Crase KW, La Bone TR, et al. A history of personnel radiation dosimetry at the Savannah River Site. Springfield, VA: US Department of Energy, 1995.
6. Scalsky ED. Technical basis document for the Savannah River Site: to be used for EEOICPA dose reconstructions. In: Neton JW, ed. ORAU Team Dose Reconstruction Project for NIOSH. Cincinnati, OH: National Institute for Occupational Safety and Health, 2004.
7. Richardson DB, Wing S, Daniels RD. Evaluation of external radiation dosimetry records at the Savannah River Site, 1951-1989. J Expo Sci Environ Epidemiol 2006;17: 13-24.
8. Arrighi HM, Hertz-Picciotto I. The evolving concept of the healthy worker survivor effect. Epidemiology 1994;5: 189-96.
9. Steenland K, Stayner L. The importance of employment status in occupational cohort mortality studies. Epidemiology 1991; 2:418-23.
10. Steenland K, Deddens J, Salvan A, et al. Negative bias in exposure-response trends in occupational studies: modeling the healthy workers survivor effect. Am J Epidemiol 1996; 143:202-10.
11. Preston DL, Lubin JH, Pierce DA, et al. Epicure: user's guide. Seattle, WA: Hirosoft International Corporation, 1993.
12. Langholz B, Thomas D, Xiang A, et al. Latency analysis in epidemiologic studies of occupational exposures: application to the Colorado Plateau uranium miners cohort. Am J Ind Med 1999;35:246-56.
13. Langholz B, Goldstein L. Risk set sampling in epidemiologic cohort studies. Stat Sci 1996;11:35-53.
14. Weiss HA, Darby SC, Fearn T, et al. Leukemia mortality after X-ray treatment for ankylosing spondylitis. Radiat Res 1995; 142:1-11.
15. Cardis E, Vrijheid M, Blettner M, et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation related cancer risks. Radiat Res 2007;167:396-416.
16. Daniels RD, Yiin JH. A comparison of statistical methods for estimation of less than detectable ionising radiation exposures. Radiat Prot Dosimetry 2006;121: 240-51.
17. Daniels RD, Schubauer-Berigan MK. Bias and uncertainty of penetrating photon dose measured by film dosimeters in an epidemiological study of US nuclear workers. Radiat Prot Dosimetry 2005;113:275-89.
18. Shin H, Ramsay T, Krewski D, et al. The effect of censoring on cancer risk estimates based on the Canadian National Dose Registry of occupational radiation exposure. J Expo Anal Environ Epidemiol 2005;15:398-406.
19. Thierry-Chef I, Pernicka F, Marshall M, et al. Study of a selection of 10 historical types of dosimeter: variation of the response to Hp(10) with photon energy and geometry of exposure. Radiat Prot Dosimetry 2002;102: 101-13.
20. Gilbert ES, Thierry-Chef I, Cardis E, et al. External dose estimation for nuclear worker studies. Radiat Res 2006; 166:168-73.
21. Baysson H, Laurier D, Tirmarche M, et al. Epidemiological response to a suspected excess of cancer among a group of workers exposed to multiple radiological and chemical hazards. Occup Environ Med 2000;57: 188-94.
22. Hickey JLS, Cragle D. Occupational exposures of workers to chemicals at the Savannah River plant 1952-1984, Oak Ridge, TN: Oak Ridge Associated Universities, 1985:69.
23. Makie T, Adcock D, Lackland DT, et al. Pulmonary abnormalities associated with occupational exposures at the Savannah River Site, Am J Ind Med 2005;48: 365-72.
24. Bingham E, Rice C. Savannah River Site building database. Cincinnati, OH: University of Cincinnati, 1999.
25. Daniels RD, Lodwick CJ, Schubauer-Berigan MK, et al. Assessment of plutonium exposures for an epidemiological study of US nuclear workers. Radiat Prot Dosimetry 2006; 118: 43-55.
26. Cragle DL, Watkins JP, Robertson-DeMers K. Mortality among workers at the Savannah River nuclear production facility. American Statistical Association: Section on Statistics in Epidemiology. Dallas, TX: American Statistical Association, 1998.
27. Wing S, Richardson DB, Wolf S, et al. A case control study of multiple myeloma at four nuclear facilities. Ann Epidemiol 2000;10:144-53.
28. Axelson 0, Steenland K. Indirect methods of assessing the effects of tobacco use in occupational studies. Am J Ind Med 1988;13:105-18.
29. Siemiatycki J, Wacholder S, Dewar R, et al. Smoking and degree of occupational exposure: are internal analyses in cohort studies likely to be confounded by smoking status? Am J Ind Med 1988;13:59-69.
30. Richardson DB, Wing S, Schroeder J, et al. Ionizing radiation and chronic lymphocytic leukemia. Environ Health Perspect 2005;113:1-5.

31. Yiin JH, Schubauer-Berigan MK, Silver SR, et al. Risk of lung cancer and leukemia from exposure to ionizing radiation and potential confounders among workers at the Portsmouth Naval Shipyard. Radiat Res 2005;163: 603-13.

32. Schubauer-Berigan M, Daniels RD, Fleming DA, et al. Risk of chronic myeloid and acute leukemia mortality after exposure to ionizing radiation among workers at four U.S. nuclear weapons facilities and a nuclear naval shipyard. Radiat Res 2007;167:222-32.

APPENDIX TABLE 1. **Observed deaths of** workers and **estimated rate ratios** by **category** of cumulative dose accrued **in the period** 3–<15 years **prior to** case **occurrence, Savannah River Site, South Carolina, 1950-2002**

Cause of death	Dose category						
	0	>0—<5	5—<10	10—<20	20—<40	40—<80	>80
Leukemia							
Observed no. of deaths	39	20	2	3	4	9	2
Rate ratio	1	**1.36**	0.94	1.55	2.05	5.50	**1.86**
Leukemia excluding CLL*							
Observed no. of deaths	29	14	1	2	3	8	1
Rate ratio	1	1.32	0.64	1.47	2.26	7.12	1.22
Myeloid leukemia							
Observed no. of deaths	13	9	1	1	2	5	1
Rate ratio	1	2.17	1.57	**1.83**	**3.85**	10.88	2.55

* CLL, chronic lymphocytic leukemia.