Update of the NIOSH Life Table Analysis System: A Person-Years Analysis Program for the Windows Computing Environment

Mary K. Schubauer-Berigan, PhD,[1]* **Misty J. Hein, PhD,**[1] **William M. Raudabaugh, BS,**[2]
Avima M. Ruder, PhD,[1] **Sharon R. Silver, MS,**[1] **Steven Spaeth, BS,**[1] **Kyle Steenland, PhD,**[3]
Martin R. Petersen, PhD,[1] **and Kathleen M. Waters, BS**[1]

Background *Person-years analysis is a fundamental tool of occupational epidemiology. A life table analysis system (LTAS), previously developed by the National Institute for Occupational Safety and Health, was limited by its platform and analysis and reporting capabilities. We describe the updating of LTAS for the Windows operating system (LTAS.NET) with improved properties.*
Software Development Process *A group of epidemiologists, programmers, and statisticians developed software, platform, and computing requirements. Statistical methods include the use of (indirectly) standardized mortality ratios, (directly) standardized rate ratios, confidence intervals, and P values based on the normal approximation and exact Poisson methods, and a trend estimator for linear exposure–response associations.*
Software Features *We show examples using LTAS.NET to stratify and analyze multiple fixed and time-dependent variables. Data import, stratification, and reporting options are highly flexible. Users may export stratified data for Poisson regression modeling.*
Conclusions *LTAS.NET incorporates improvements that will facilitate more complex person-years analysis of occupational cohort data.*   Am. J. Ind. Med. 54:915–924, 2011.   *Published 2011. This article is a U.S. Government work and is in the public domain in the USA.*

KEY WORDS: *epidemiologic methods; cohort analysis; person-years analysis; occupational; statistical methods*

INTRODUCTION

Epidemiologists require specialized methods and software to conduct scientifically valid studies of health effects related to occupational and other exposures. In cohort studies, person-years analyses are often used to apportion person-time and observed events into strata. Standardized event rates are calculated among the strata to produce a standardized event ratio, compared to either a general population [e.g., a standardized mortality ratio (SMR)] or to a group within the cohort [e.g., a standardized rate ratio (SRR)].

Since the 1970s, the National Institute for Occupational Safety and Health (NIOSH) has created and maintained a life table analysis system (LTAS) to conduct

person-years analyses of cohort mortality data [Waxweiler et al., 1983]. LTAS was originally a mainframe-based series of computer programs, with the following features: (1) automated data-editing capabilities; (2) U.S. mortality rates for a large number of underlying cause-of-death categories; (3) the assignment of exposure to specific person-days of follow-up; and (4) the ability to stratify data on exposure level, duration of employment, time since first exposure, age, and calendar time. The program stratified all person-time at risk (from the time of cohort entry until death or censoring) into categories defined by these groups. It used an indirect adjustment, in which expected numbers of deaths were calculated for each sex, race, age, and calendar-year stratum [by multiplying the person-years in the stratum by an external (U.S. or state) rate] and then summed across all strata. Observed numbers of deaths were divided by expected numbers to calculate an SMR, with a confidence interval based on the Poisson distribution or its approximation. Analysis output (person-years at risk, observed and expected deaths, and SMRs and confidence intervals) was displayed by cross-classified duration of employment, exposure level or time since first exposure, or the intrinsic stratifying variables of gender, race, age, and calendar period.

NIOSH-LTAS was updated in the late 1980s to add several new features [Steenland et al., 1990], including: (1) the ability to compute directly standardized SRRs to compare risk between levels of exposure or time since first exposure; (2) addition of the Rothman trend test for standardized rates across categories of exposure duration or level; (3) support for multiple-cause-of-death analysis; (4) capabilities for proportionate mortality ratio (PMR) analyses, which are based not on person-time accrual, but on the distribution of death causes; (5) ability to lag exposures (discounting exposures occurring within a specified window before a given time-at-risk); (6) greater flexibility in analysis; (7) ability to export stratified person-time and deaths for Poisson regression analysis.

These two LTAS programs were utilized in the analyses of numerous landmark occupational studies, including lung cancer among radon-exposed uranium miners [Lundin et al., 1971; Roscoe et al., 1989], hepatic angiosarcoma among vinyl chloride monomer workers [Waxweiler et al., 1976; Wu et al., 1989], leukemia among benzene-exposed pliofilm workers [Infante et al., 1977; Rinsky et al., 1987], lung cancer and pneumoconiosis among chrysotile asbestos-exposed workers [Dement et al., 1983; Brown et al., 1994], lung cancer in workers exposed to sulfuric acid mist [Beaumont et al., 1987], cancer among dioxin-exposed workers [Fingerhut et al., 1991], and non-malignant respiratory disease in silica-exposed workers [Checkoway et al., 1997]. These studies identified excess risks compared to the general U.S. population, as well as (in many cases) SMRs or SRRs that increased with time since first exposure, employment duration, or exposure level.

A third major version of the LTAS program was developed for the personal computer in the late 1990s [Steenland et al., 1998]. This DOS-based version (PC-LTAS) incorporated further new features, including the development of an expanded set of mortality rates and cancer incidence rates, additional reports, and context-specific help screens.

The purposes of this article are: (1) to describe the development, features, independent testing, and applicability of an updated version of LTAS; (2) to provide suggestions to potential or novice users on the optimal methods for using the new program; (3) to provide examples from the recent literature to illustrate some new features of the program.

The following sections of the article describe the software development process, the independent testing, the software's new features, and application examples from the recent literature. We conclude with a discussion of issues related to the software and possible future improvements. More detail about certain aspects of the software is given in the Appendix, and online Supplementary Material gives a series of screen shots exemplifying the use of the software in a published analysis of radon exposures among uranium miners [Schubauer-Berigan et al., 2009].

SOFTWARE DEVELOPMENT PROCESS AND DESCRIPTION

A group of epidemiologists, computer programmers, and statisticians developed software, platform, and computing requirements. Most important was the need for a modern computing platform optimized for use in Windows. We desired to produce a program that would permit greater flexibility in data input and output, and better analysis and reporting capabilities, incorporating new features requested by users. We also aimed to correct a number of small errors and inconsistencies in the allocation of person-days, and in calculation of exact and approximate confidence intervals. We also wanted to more fully document the person-time allocation rules and all statistical calculations, and to thoroughly test the program's new calculation algorithms.

The program, denoted LTAS.NET [NIOSH, 2010], is based on the Microsoft database engine platform. It was developed using Microsoft Visual Studio.NET and Microsoft SQL Server Express. The latest version (LTAS.NET ver. 3.0.3) is compatible with Windows 7, Vista, and XP. LTAS.NET must be installed to the hard drive of a personal computer, although input data files and output reports may reside on a network location. The program permits the flexible import of data and the export of reports and data. LTAS.NET is more interactive and provides more

user options than prior versions, and is self-documenting through extensive, context-sensitive help, as well as a User Manual that is distributed with LTAS.NET. The program is made freely available and may be downloaded at www.cdc.gov/niosh/ltas.

As in previous versions of LTAS, calculations are based on the stratification of events and person-days at risk. The date handling logic was modified for internal consistency (described in Appendix A of the LTAS.NET User Manual and summarized in the Appendix of this article). Statistical methods include the use of SMRs, SRRs, confidence intervals, and P values that are based on the normal approximation and exact Poisson methods, and a trend estimator for linear exposure–response associations. Statistical improvements (described in Appendix B of the User Manual) include the correction of certain confidence intervals, and the addition of optional P values for SMRs and SRRs.

The major methodological improvement in LTAS. NET is the ability for the user to import, stratify on, and analyze any fixed or time-dependent variable of interest. The program allows both fixed and time-dependent categorical and continuous variables (Table I). Statistical adjustment is made, via standardization, for variables that are specified in the rate file (denoted intrinsic stratifiers). For the rate files included by default in LTAS.NET, these include the fixed stratifiers of gender and race, and the time-dependent stratifiers of age and calendar period. LTAS.NET also permits the user to define, stratify, and analyze two or more fixed or time-varying exposures simultaneously (although these will not be adjusted for in

the analysis). The time-dependent variables that are possible include a time-varying categorical variable and a quantitative exposure agent. In addition, the user may specify a global date (or set of dates), upon which all person-time and events are additionally stratified (e.g., see Table I). LTAS.NET also permits the user to stratify on active employment status (with a user-defined lag for inactive status) to allow evaluation of the healthy worker survivor effect [Arrighi and Hertz-Picciotto, 1996].

Typical user-defined time-dependent exposure agents include employment duration and exposure level, which were features of previous versions of LTAS. However, the user may add any others of interest, such as pack-years of cigarette smoking. In addition to such exposure agents, LTAS.NET allows the use of temporal categorical variables. These could include any categorical variable but (for diseases with long latency, such as cancer) are most useful for variables that take on permanent significance with a change, such as highest education level, ever having been monitored for internal radiation exposure, or peak exposure category.

Any accumulating exposure variable may be lagged for any specified time period, and the Rothman test of trend for the standardized rates is supported, as in previous versions of LTAS [Rothman, 1986]. SRRs may be calculated for temporal categorical variables; however, LTAS. NET does not support the lagging of temporal categorical variables, and no trend test is conducted. Stratified data may be exported for Poisson regression analyses in other software analysis packages.

INDEPENDENT TESTING OF SOFTWARE

To ensure that all modifications to the earlier versions of LTAS were based on robust computations, the core algorithms of LTAS.NET (to import, stratify, and analyze data using SMRs, SRRs, and trend tests) were tested independently using SAS Software (SAS Institute, Inc., Cary, NC). We found these algorithms to be reliable: stratification of person-time and events and calculation of SMRs, SRRs, and the trend test for standardized rates matched LTAS.NET exactly for the large test cohorts evaluated.

NEW SOFTWARE FEATURES

LTAS.NET is operated using a series of pull-down menus in which options for running the program are selected step-by-step. There are three main modules associated with the program: Import data, Stratify data, and Analyze data. A fourth module relates to the handling of rate files (described further below). The different file types associated with LTAS.NET are illustrated in Figure 1. The Import data module creates a project file that saves the

TABLE I. Definitions and Examples of Study Variables Employed by the NIOSH Life Table Analysis System for Windows (LTAS.NET)

Study variables	Fixed[a]	Temporal[b]
Intrinsic[c]	Gender	Age (5 year)
	Race	Calendar period (5 year)
Extrinsic[d]	Fixed stratifiers	Exposure agents
	Birth country	Cumulative exposure
	Ethnicity	Employment duration
	Hire age	
		Temporal categoricals
		Smoking status
		Highest education level
		Peak exposure
		Global categoricals
		Time after 9/11/2001
		Calendar period (10 year)

[a]Do not change over time.
[b]Can change over time.
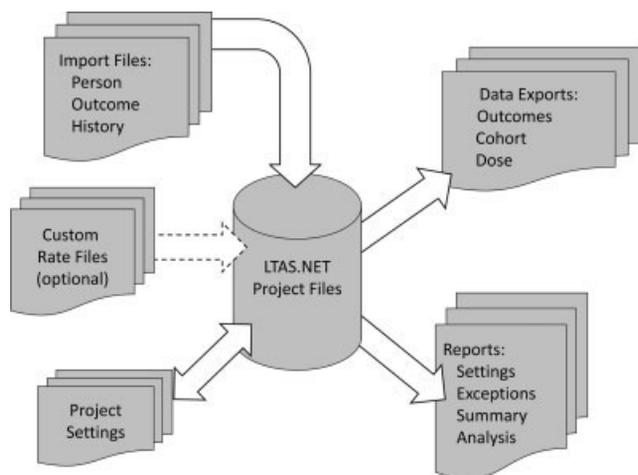[c]Built-in (defined by rate file).
[d]User-defined.

FIGURE 1. LTAS.NET program input and output structure.

settings and processed data associated with each computer run. Project settings files can be exported to a file that can be copied and used to create new projects with the same settings.

The user is required to input three data files to carry out analyses in LTAS.NET: the "Person" file (which contains demographic and any fixed stratifier data), "Outcome" file (which contains causes and dates of death or disease), and "History" file (which contains any time-dependent covariate data). The specifications for these files are detailed in Appendix C of the User Manual and in the Appendix of this article.

LTAS.NET provides numerous reports to document the selected settings and describe any problems that are encountered. In addition, the program offers reports that give the "personal cumulative dose" values for each cohort member. Data that may be exported for use in other programs include all records with exceptions (errors) identified during Import, observed deaths and diagnoses, records rejected during Stratify, the stratified cohort, and the personal cumulative dose files.

The default rate files provided with LTAS.NET include U.S. underlying cause rates and proportions beginning in 1940 for 92 cause categories, and U.S. underlying and multiple-cause rates and proportions beginning in 1960 for an expanded set of 119 cause categories [Steenland et al., 1992; Robinson et al., 2006]. These rate files are stratified by gender, race (white and all other races), age (15 to ≥85 in 5-year intervals), and calendar period (currently, 1940 or 1960 to 2009 in 5-year intervals). Annual updates for these rate files may be downloaded from the NIOSH website. Other rate files currently available include underlying and multiple-cause rate and proportion files for each U.S. state, and underlying and multiple-cause rate files for neurodegenerative diseases [Steenland et al., 2006], all beginning in 1960, and cancer

incidence rate files beginning in 1973, based on data from the Surveillance, Epidemiology, and End Results program.

User-created rate files are easily generated, using the instructions provided in Appendix E of the User Manual. For example, disease mortality or incidence rates for countries outside the U.S. may be created (provided that the user can access the raw rate data of interest; e.g., Dimich-Ward et al. [2007]). Users may also create different intrinsic stratifier categories from those in the default rate files (e.g., to revise or expand upon the race groupings).

Custom analysis reports are easily generated in the Analyze step. The user selects the type of report (person-year distribution, SMR, or SRR). Any number of variables, stratifier levels for each variable, and outcome categories can be selected for analysis. For SRR reports, the user must specify a variable for the vertical axis (i.e., the rows) and a second variable for the horizontal axis (i.e., the columns) of the report. SRRs will be calculated for the horizontal axis variable within each level of the vertical axis variable. The user may also select whether confidence intervals (90%, 95%, or 99%) or *P* values are reported.

A powerful new feature of LTAS.NET is that different combinations of stratifier levels may be selected. If stratifier categories are deselected, the "total" category, if selected, will include only the selected categories. For example, if the user decides to exclude all workers employed less than 1 year, deselecting the 0–1 year employment category while selecting the total duration category will produce results for all groups other than those employed less than 1 year [e.g., Schubauer-Berigan et al., 2011].

APPLICATION EXAMPLES

Radon and Smoking Among Uranium Miners

LTAS.NET was recently used to update the mortality experience of the Colorado Plateau uranium miner cohort (Table II) [Schubauer-Berigan et al., 2009]. Exposures of interest included quantitative radon daughters, and qualitative last smoking status for nearly all cohort members. Of interest were: whether there was confounding by smoking of the association between radon and lung cancer, the form of interaction between smoking and radon exposure in causing lung cancer, and whether observed differences in lung cancer rates between white and American Indian miners were explained by the different smoking patterns in the two groups. LTAS.NET output was used to address all these questions.

Screenshots for the Import, Stratify, and Analyze steps, and the main Analysis results for radon exposure, stratified by smoking category, are given in the online

TABLE II. Examples of Recent Studies Using the NIOSH Life Table Analysis System for Windows (LTAS.NET)

Reference	Main exposure of interest	Outcome	User-defined stratifiers used in LTAS.NET
Kang and Bullman [2008]	Military service in Iraq or Afghanistan	Suicide	Branch of service, active status (SMRs only)
Dement et al. [2009]	Former construction workers at DOE sites	Cancer, non-malignant respiratory disease	DOE facility, usual trade, year and age of entry (SMRs only)
Loomis et al. [2009]	Asbestos	Lung and pleura cancer, mesothelioma, non-malignant respiratory disease	Employment duration (SMRs only)
Schubauer-Berigan et al. [2009]	Radon	Lung cancer, non-malignant respiratory, and urinary tract disease mortality; end-stage renal disease incidence	Cumulative radon exposure, smoking category (SMRs, SIRs, and SRRs)
Birdsey et al. [2010]	Truck driving	Overall mortality	None (SMRs only)
Carreón et al. [2010]	o-Toluidine	Bladder cancer incidence	Employment duration among the exposed; highest exposure group (SIRs and SRRs)
Calvert et al. [2010]	Dry cleaning	Bladder, esophageal, oral cavity, and digestive tract cancer mortality; end-stage renal disease incidence	Employment duration; time since first employment (SMRs, SIRs, and SRRs)
Chan et al. [2010]	Radiation and metals	Overall and lympho-hematopoietic cancer mortality	Job title, cumulative external and internal radiation (SMRs and SRRs)
Schubauer-Berigan et al. [2011]	Beryllium	Cancer and non-malignant respiratory and urinary tract disease mortality	Peak and cumulative beryllium exposure, plant, employment duration, exposure to other lung carcinogens (SMRs and SRRs)
Waggoner et al. [2011]	Agricultural health study	All-cause mortality	None (SMRs only)

DOE, Department of Energy; SMR, standardized mortality ratio; SRR, standardized rate ratio; SIR, standardized incidence ratio.

Supplementary Materials. Table III shows the standardized rate trend slope and standard errors for radon exposure and lung cancer for each smoking category and for all categories combined. This slope, a measure of change in absolute risk, differed substantially across many of the exposure groups, and suggested a super-additive interaction between smoking and radon. However, there did not appear to be confounding by smoking of the radon-lung cancer association: using an inverse-variance-weighted pooled estimate of the standardized rate trend across the smoking categories yielded an estimate that differed by only 2.7% from the unadjusted total across smoking categories in Table III.

One useful new feature in the SRR report is that the absolute standardized rate is printed for the baseline category in the SRR calculation (see Supplementary Materials Fig. S22). This permits the graphing of standardized rates, using the baseline value and either the SRRs or the trend estimate (the latter is shown in Fig. 2). The graph suggests that the super-additive relation observed in the trend estimate is sub-multiplicative, which is confirmed by examination of the SRRs, which are higher for never-smokers than for smokers (Table 5 of Schubauer-Berigan et al. [2009] and Supplementary Materials Fig. S22). Lastly, by calculating SRRs for race within strata defined by

smoking, race was determined not to be an important risk predictor, after accounting for the fact that white miners smoked more frequently and heavily than American Indian miners [Schubauer-Berigan et al., 2009].

Confounding by Plant in a Multisite Beryllium Cohort

LTAS.NET was also used to evaluate lung cancer risk in an update of a beryllium processing cohort (Table II) [Schubauer-Berigan et al., 2011]. Quantitative beryllium exposure estimates were available for three plants, which were pooled for analyses. Previous studies of the processing plants found that baseline lung cancer risks were much lower in the county where one of the plants was located, while the plant's beryllium exposures tended to be much higher. Therefore, potential confounding by plant was of concern. In LTAS.NET, trend estimates for lung cancer related to beryllium exposure were stratified by plant (Table IV). Each individual plant produced a higher standardized rate trend than the pooled (unadjusted) trend estimate, suggesting substantial confounding by plant. Using the inverse-variance-weighted pooled estimate across plants produced an estimate that was double the unadjusted estimate.

TABLE III. Lung Cancer Standardized Rate Trend Estimates With Cumulative Radon Progeny by Smoking Status Among Male Colorado Plateau Uranium Miners, 1960–2005 [Data From Schubauer-Berigan et al., 2009]

Smoking category	N	SR trend slope (cases per WLM-person-year)	Trend standard error
Never smoker	76	4.5×10^{-6}	4.5×10^{-7}
Former smoker	234	7.7×10^{-6}	1.2×10^{-6}
Current smoker			
<1 pack/day	52	4.2×10^{-6}	2.2×10^{-6}
1 pack/day	150	9.5×10^{-6}	4.4×10^{-7}
>1 pack/day	100	9.4×10^{-6}	3.1×10^{-6}
All workers combined	612		
Estimate unadjusted for smoking		7.3×10^{-6}	5.9×10^{-7}
Pooled estimate, adjusted for smoking[a]		7.1×10^{-6}	—

N, number of lung cancer deaths; WLM, working level months (cumulative radon exposure measure); SR, standardized rate (standardized on the intrinsic stratifiers of age, race, and calendar period, but not gender, because all were male).
[a]Inverse-variance-weighted pooled estimate among smoking categories, standardized on race, age, and calendar period.

Use of Temporal Categorical Variables

A re-analysis of bladder cancer incidence among workers exposed to *o*-toluidine and aniline at a chemical manufacturing plant used LTAS.NET to estimate standardized incidence ratios (Table II) [Carreón et al., 2010]. Detailed work history records available for each worker included begin and end dates, department code, and job code. Each record was classified based on department code as probably not exposed (PNE), possibly exposed (PE), or definitely exposed (DE) to *o*-toluidine and aniline. Since workers could move from an exposed job to a non-exposed job, and vice versa, a temporal categorical variable (MaxGrp) was created to reflect each worker's highest exposure category (Fig. 3). Workers were considered to be DE on the date of their first DE employment; otherwise, workers were considered to be PE on the date of their first PE employment prior to any DE employment. Workers who were always employed in PNE departments were considered to be PNE. For example, while workers 0001 and 0004 did not have any variation in their exposure group, workers 0002 and 0003 became PE on the date of their first PE exposure, and worker 0003 remained PE even though his exposure group returned to PNE (Fig. 3). Worker 0005 became DE on the date of his first DE employment and remained DE through subsequent employment. Using the temporal categorical variable MaxGrp defined in this manner resulted in the correct classification of person-time and events. To estimate duration of DE employment, an accumulating exposure agent, DEEmp (defined to be 1 for DE records, 0 otherwise) was included in the history file. The study found that duration of DE employment was associated with increased bladder cancer risk with standardized incidence rate ratios of 1, 2.0 (95%CI: 0.13–32), and 6.1 (95%CI: 0.77–48) for <5, 5 to <10, and ≥10 years of DE employment, respectively (trend *P*-value < 0.0001) [Carreón et al., 2010].

DISCUSSION

LTAS.NET incorporates a number of improvements that should facilitate more complex person-years analyses of occupational cohort data. The modern computing platform, streamlined method of inputting data, large numbers of edit checks conducted on the complex data involved in cohort studies, and capabilities of defining, stratifying, and analyzing any number of user-defined fixed and temporal covariates, including active employment status, are some of the most useful features of the new program. These features allow the user to correctly calculate SMRs, PMRs, and SRRs (all of which are difficult to conduct using standard statistical software), adjust for confounding and to evaluate effect modification, as shown in these examples, and may be particularly useful when modeling analyses are not required. The ability to evaluate additive
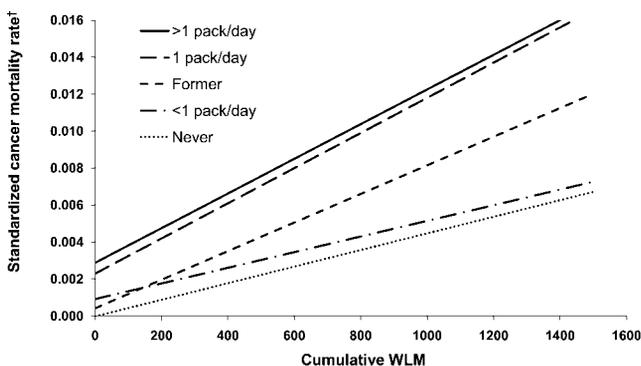
†Standardized on race, age, and calendar year; units are lung cancer deaths per person-year.

FIGURE 2. Trend in standardized lung cancer rates per working level month·per-person-year of radon exposure, for different smoking categories, among male uranium miners [data from Schubauer-Berigan et al., 2009].

TABLE IV. Lung Cancer Standardized Rate Trends for 10-year Lagged Cumulative Beryllium Exposure (Based on Underlying Cause of Death Analysis, 1940–2005), Excluding Short-Term Workers (Employed < 1 year), From Schubauer-Berigan et al. [2011]

Beryllium processing plant number	N lung cancer deaths	Trend slope[a]	Trend standard error
Plant 2	84	7.0×10^{-8}	6.6×10^{-9}
Plant 6	35	3.5×10^{-7}	2.7×10^{-8}
Plant 7	27	1.1×10^{-7}	7.3×10^{-8}
All plants combined	146		
Unadjusted for plant		4.3×10^{-8}	1.7×10^{-8}
Pooled estimate, adjusted for plant[b]		8.6×10^{-8}	—

[a]Lung cancer deaths per $\mu g/m^3$-day · person-year, standardized on race, age, and calendar period (not on gender, because all are male).
[b]Inverse-variance-weighted pooled estimate among plants, standardized on race, age, and calendar period.

risk (e.g., as shown in Fig. 2) is another strength of LTAS.NET.

The program's flexibility can, however, lead to unanticipated complexities in the analyses. For example, the risk begin date for each cohort member is the latest of several candidate dates: the rate begin date, the qualifying birthday (i.e., date at which person achieves the youngest age in the selected rates), and any of the following optional dates—first exposed date, study begin date, a date that may be specified in the Person file for each cohort member, and a global date that may be specified in the Import step. Selecting "first exposed date" will cause all imported exposures to be considered, even if they are not included later in the Stratify step. The user is strongly encouraged to give advance thought to the time-at-risk options. The precise cohort definition and consideration of prior exposures should determine the selections.

```
ID    BeginDate  EndDate    Dept  Job  Emp  ExpGrp  MaxGrp  DEEmp
0001  08/01/1968 02/15/1970  14   26   1    PNE*    PNE     0
0001  02/16/1970 04/08/1978  14   32   1    PNE     PNE     0

0002  07/13/1954 12/31/1960  14   26   1    PNE     PNE     0
0002  01/01/1961 09/15/1978  14   26   1    PNE     PNE     0
0002  09/16/1978 12/31/1979  21   56   1    PE*     PE      0
0002  01/01/1980 06/18/1981  21   56   1    PE      PE      0
0002  06/19/1981 04/15/1984  21   55   1    PE      PE      0

0003  01/10/1957 03/05/1959  14   26   1    PNE     PNE     0
0003  03/06/1959 06/15/1960  21   56   1    PE      PE      0
0003  08/15/1960 10/20/1960  21   56   1    PE      PE      0
0003  10/21/1960 12/31/1960  14   26   1    PNE     PE      0
0003  01/01/1961 04/03/1964  14   26   1    PNE     PE      0

0004  01/01/1969 10/26/1969  24   26   1    DE*     DE      1

0005  06/05/1965 08/15/1967  14   26   1    PNE     PNE     0
0005  08/16/1967 10/17/1967  24   26   1    DE      DE      1
0005  10/18/1967 05/15/1969  14   26   1    PNE     DE      0
0005  05/16/1969 12/31/1979  19   50   1    PE      DE      0
0005  01/01/1980 04/10/1986  19   50   1    PE      DE      0
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*Abbreviations: DE—definitely exposed; PE—possibly exposed; PNE—probably not exposed.
The exposure agent Emp (1 for all) was used to evaluate duration of employment.
The variable ExpGrp, assigned based on department codes, reflects the exposure group for each work history record, but was not useful for analysis because all person-time at risk from the end date of the last history record through date last observed is assigned to the most recent category.
The temporal categorical MaxGrp was used to stratify person-time and events according to each worker's highest exposure group.
The exposure agent DEEmp (1 for DE employment, 0 otherwise) was used to evaluate duration of DE employment.

FIGURE 3. Example creation of an LTAS.NET History file that includes a temporal categorical variable.

Previous versions of LTAS limited the SRR report to evaluation of time since first exposure by duration or cumulative exposure. A powerful new feature of LTAS.NET is the ability of the user to specify any combination of intrinsic or extrinsic stratifiers in the grid report; however, users are cautioned that using an intrinsic stratifier (e.g., gender, race, age, or calendar year) for the vertical variable (or as a page stratifier), will cause the variable not to be adjusted for via standardization in the "total" row of an SRR report. For this reason, it is useful to include at least two extrinsic stratifiers for each analysis, if SRR computations are of interest. Other suggestions to optimize the use of the software are provided in the Appendix.

To date, a number of studies have been conducted using LTAS.NET (Table II). Notably, not all of the studies appeared to make use of the most unique features of the program (e.g., the use of fixed and temporal categorical variables). We note that some authors publish only SMRs, even when stratifying on and comparing risk among levels of user-defined covariates. We encourage users to incorporate internally adjusted, directly standardized SRRs into person-years analyses, if direct comparisons among exposure categories are desired. It is well understood that direct comparisons of SMRs are generally less appropriate, because distributions of the standardizing variables that differ substantially among the groups may give ratio estimates that are quite misleading. It is perhaps less well appreciated that confidence interval estimates are appropriately wider when properly incorporating variance for both groups in the comparison, when directly standardized SRRs are used for internal comparisons.

Future improvements that may be useful for LTAS.NET include the addition of a different trend test [Breslow and Day, 1987, p. 114], expansion of the race groups in the default rate files, and the translation of LTAS.NET into Spanish and Chinese (the native languages most common among non-US users). We welcome suggestions for additional improvements to LTAS.NET.

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APPENDIX

This appendix summarizes some of the most important details about LTAS.NET software functionality for the potential or new user. However, users are strongly encouraged to consult the LTAS.NET User Manual for complete information on how to use the software.

Summary of Input File Requirements

Three files are required for inputting data into LTAS. NET: the Person, History, and Outcome files. All must be either fixed or delimited ASCII files. The Person file must contain for each cohort member a unique identifier, gender, race, date of birth, vital status, date last observed (required for deceased persons and for living persons if used to account for loss-to-follow-up), and the optional variables name, person-year begin date, and any fixed stratifier of interest. The Outcome file contains one or more events (deaths or diagnoses) for each person who experienced an event during the follow-up period. The file requires the unique identifier for each cohort member, the event date, and a code [typically, an International Classification of Diseases (ICD) code] to identify the outcome. It optionally contains flags to identify whether the outcome is underlying and whether it is terminal (i.e., fatal), as well as a revision number for the event code (e.g., ICD revision number). Terminal and underlying flags of T T are used for underlying cause of death analyses, T F are used for multiple cause of death analyses, and F T are used for morbidity analyses.

The History file is used to input data for all extrinsic temporal variables for each cohort member. Because of the flexibility allowed in specifying these variables, the file structure is different from that used in previous versions of LTAS. The History file must contain one record for each worker-exposure period (i.e., a period over which every exposure is constant). Conceptually, the file may contain daily exposure agent values and values at given dates for temporal categorical variables. Required

fields include the unique identifier for each cohort member, an exposure begin date, an exposure end date, and one or more exposure agents or temporal categorical variables. For occupational studies, the most common exposure "agent" for each cohort member is an indicator (value = 1) to represent active employment periods. Other examples of variables that we have used in our studies include: quantitative occupational exposures such as daily values for radon daughter, external ionizing radiation, and beryllium exposure; semi-quantitative exposures such as employment in an "exposed" occupation; and temporal categorical variables such as maximum beryllium exposure category, and internal radiation monitoring status. Any or all of the following can be selected for each exposure agent: level (i.e., cumulative exposure), duration, time since first exposure, time since last exposure, and active status. Including more agents and variables requires more space in the database and more processing time. A hypothetical example of the development and layout of a History file for a study with several quantitative exposures is shown in Figure A1.

Data Processing Details

In the Import Step, the user selects the rate file to be used, whether a global categorical variable is needed, the set of dates to be considered to start and stop person-time for each cohort member, and maps all the fields in the three imported files. During Import processing, LTAS.NET performs extensive data validation by verifying that the input data satisfies requirements detailed in Appendix C of the User Manual. Persons or records that do not satisfy the requirements may be excluded, rejected, or redeemed, as necessary. All exclusions, rejections, redemptions, and warnings identified during Import are detailed in Exceptions reports. Serious errors may result in program termination.

After data are imported, the Stratify step is used to select options for person-time and event stratification. Steps include selecting the stratifiers (the more selected, the longer the run time), assigning the lag period (if any) to be used for each exposure agent, and providing category cutpoints for any user-defined exposure agents. For exposure agents with a positive assigned lag period, the user has the option to treat the lagged-out events and person-time as a separate category or to group them with the lowest exposure category.

Details About Date Handling

In LTAS.NET, the smallest unit of time is a day. Calculations are based on the actual number of days between events using a calendar function (e.g., leap years are handled correctly). Some events are assumed to occur

1. One employed period for each worker, no exposure data or temporal categoricals (simplest case)

ID	Begin date	End date	Employment (Emp)
0001	07/01/1953	06/30/1958	1
0002	11/15/1960	05/14/1962	1

2. One or more employed periods for each worker, with differing daily average levels of asbestos exposure (fibers/cc)

ID	Begin date	End date	Emp	Asbestos (Asb)
0001	07/01/1953	12/31/1953	1	0.01
0001	01/01/1954	12/31/1957	1	0.10
0001	01/01/1958	06/30/1958	1	0
0002	11/15/1960	05/14/1962	1	0

3. One or more employed periods for each worker, with daily packs of cigarettes smoked over time
   - Worker 0001 (DOB 05/17/1916) started smoking 2 packs/day on his 20th birthday, dropped to 1 pack/day on his 40th birthday, and quit on his 50th birthday
   - Worker 0002 (DOB 03/10/1924) never smoked

ID	Begin date	End date	Emp	Smoking (Smk)
0001	05/17/1936	06/30/1953	0	2
0001	07/01/1953	05/16/1956	1	2
0001	05/17/1956	06/30/1958	1	1
0001	07/01/1958	05/16/1966	0	1
0002	03/10/1944	11/14/1960	0	0
0002	11/15/1960	05/14/1962	1	0

4. One or more employed periods for each worker, with differing daily levels of asbestos exposure (fibers/cc) and smoking (packs/day)
   - Three separate time-dependent exposure agents integrated

ID	Begin date	End date	Emp	Asb	Smk
0001	05/17/1936	06/30/1953	0	0	2
0001	07/01/1953	12/31/1953	1	0.01	2
0001	01/01/1954	05/16/1956	1	0.10	2
0001	05/17/1956	12/31/1957	1	0.10	1
0001	01/01/1958	06/30/1958	1	0	1
0001	07/01/1958	05/16/1966	0	0	1
0002	03/10/1944	11/14/1960	0	0	0
0002	11/15/1960	05/14/1962	1	0	0

FIGURE A1. Example creation of an LTAS.NET History file for workers with employment, asbestos exposure, and quantitative smoking data.

at the beginning of the day (e.g., date of birth, risk begin date, history begin dates), and others are assumed to occur at the end of the day (e.g., risk end date, date of death, study end date, history end dates).

Details About Analysis Step in LTAS.NET

Depending on the "rate" file selected during Import, requesting an "SMR" provides PMRs if a proportion file is specified and standardized incidence ratios if an incidence rate file is specified. For list reports, the user must specify a variable for each "row" of the report. All other selected stratifiers will appear in the header with a separate page of output for each unique combination of the stratifier(s) values selected in the previous step.

Suggestions to Optimize Disease or Death Specifications in LTAS.NET

In the Outcome file specifications, omitting Terminal and Underlying flags could have unintended consequences. Omitting the terminal flag causes all outcomes to be treated as deaths for deceased persons and diagnoses for living persons. Omitting the underlying flag causes all outcomes to be treated as underlying.

LTAS.NET explicitly attempts to map each outcome code to an outcome category. If a code is not recognized, then it will be "redeemed" to the residual category and mentioned in the exceptions report. Users must check the exceptions report for codes that were not intended to be mapped to the residual category and correct them, if necessary, before proceeding to the next step.