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C.S. Lea
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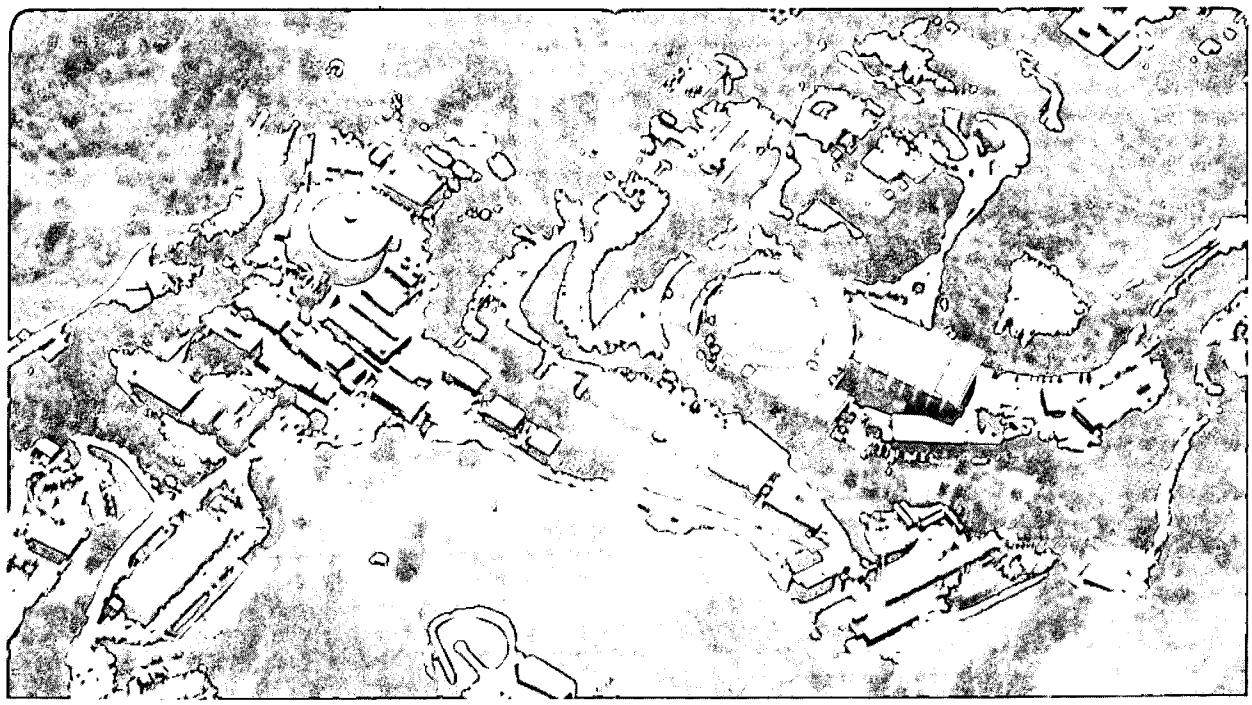

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Abstract

Evaluation of Cancer Mortality in a Cohort of Workers Exposed to Low-Level Radiation

by

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Doctor of Philosophy in Epidemiology

University of California, Berkeley

Professor Patricia A. Buffler, Chair

Workers exposed to low-level radiation at Oak Ridge National Laboratory (ORNL) were found to have higher cancer mortality than workers from other Department of Energy installations exposed to similarly low levels of cumulative radiation (Wing et al., 1991). The purpose of this dissertation was to re-analyze existing data to explore methodologic approaches that may determine whether excess cancer mortality in the ORNL cohort can be explained by time-related factors not previously considered; grouping of cancer outcomes; selection bias due to choice of method selected to incorporate an empirical induction period (EIP); or the type of statistical model chosen.

Cancers have an EIP that is usually quantified as time from first exposure until death. Radiation epidemiology studies have not used consistent approaches to incorporate an EIP. It was determined that removing the first five years of deaths and person-years in the cohort (i.e. adjusting for latency) and lagging dose five years results in the same parameter estimate as lagging dose for 10 years when all person-years and deaths are retained. The deviance difference is greatest at lag=20 for all cancer outcomes evaluated, except lung cancer.

Twelve cancer outcome groups were evaluated. Cumulative radiation exposure was not significantly associated with lung cancers (lag=20, p=0.593), leukemias (lag=10, p=0.18), or leukemias excluding chronic lymphocytic leukemia (lag=10, p=0.629). Cumulative dose was significantly associated with the following cancer outcomes after adjusting for time-related factors:

all cancers (lag=20, p=<0.01), solid cancers (lag=20, p=<0.01), smoking related cancers (p=<0.01), and smoking-related cancers excluding lung cancers (lag=20, p=<0.01).

Two deaths in the highest dose category (one esophageal and one larynx) received doses similar to the Atomic bomb survivor cohort (> 500 mSv). When these two cancers were removed from the cohort, the effect of cumulative dose was no longer significant at lag=20 (p=0.07).

To the memory of Zelia Pocahontas Fontaine

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t_0	time in the past when follow-up began	69
t_1	time in the present or future when follow-up ends	69
y	expected number of deaths	94
g	specifies the link function used in generalized linear models	94
e*	the error distribution assoicated with the Poisson distribution	94
$X\beta$	linear model that says that y increases linearly by β with a unit change in X, where X are covariates	94
log(u)	log-link function for Poisson Regression	94
α	intercept term associated with Poisson model	94
β_k	parameter estimates associated with Poisson model	95
x_k	levels of covariate associated with parameter estimate	95
χ^2, 1 df	chi-square goodness of fit statistic with 1 degree of freedom	96
RR	Relative Risk	98
ERR	Excess Relative Risk	98
βdose	linear parameter for the contribution of dose to excess relative risk	98
s	stratification variables to adjust background mortality	98
r	Pearson correlation coefficient	155

Acknowledgments

Many individuals contributed to the completion of this work. First, many thanks are given to Professor Steve Selvin, who presented the initial idea to re-analyze the Oak Ridge National Laboratory (ORNL) dataset. He was instrumental in encouraging me to proceed with this project and without his support and excellent advice, it would have never been completed.

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Dean Merrill, the Co-Principal Investigator of the Populations at Risk from Environmental Pollutants (PAREP) project, first invited me to attend the weekly PAREP meetings at LBNL. Mark Durst, Project Manager of the Comprehensive Epidemiologic Data Resource (CEDR), introduced me to the UNIX operating system and patiently helped me to plod through my learning curve. The weekly 'PAREP' meetings provided a forum for Steve, Deane, and Mark to provide feedback on my progress. Many of their insightful suggestions are reflected in this volume. I value the opportunity to have benefited from their expertise.

Many interesting issues were discussed at the PAREP meetings in the context of this re-analysis. One of them was the topic of incorporating an empirical induction period. When Sir Richard Doll was visiting the Berkeley campus, I had the opportunity to inquire about construct of the empirical induction period. I am greatly honored and flattered to have been able to meet such a renowned epidemiologist and to correspond with him about this topic. Sir Richard galvanized my interest in pursuing this part of the analysis.

When I first started this dissertation, I knew very little about radiation epidemiology, and the context within which this field has evolved since the bombing of Hiroshima and Nagasaki in 1945. Leif Peterson, Assistant Professor of Epidemiology, Baylor University School of Medicine,

fielded many of my questions regarding analysis of the atomic bomb survivor data. He generously offered guidance and advice as well as provided thorough, specific answers to my questions.

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Whatever value this dissertation has attained owes much to those who have given freely of their time and knowledge. Its flaws reflect, in part, my capacity in taking full advantage of the advice I have received. In the final analysis, I am solely responsible for the contents herein.

CHAPTER 1

INTRODUCTION

I. RATIONALE AND STUDY HYPOTHESES

Of all the etiologic agents which have been shown to cause cancer in cellular organisms, laboratory animals and humans, the effects of ionizing radiation rank among the most demonstrative. Ionizing radiation is a physical agent that has no taste, odor, or feel. In man, our knowledge of radiation exposure and its effects may be considered in three groups: (1) high dose effects (exposure above 0.25 Sv)[1], (2) intermediate dose effects (0.05-0.25 Sv exposures), and (3) low dose effects (exposure below 0.05 Sv)(NIH, 1979, p. 1).

For human populations, there are considerable effects related radiation doses above 50 mSv (0.05 Sv or 5 rem), such as the Atomic Bomb Survivors (ABS) of Hiroshima and Nagasaki, abdominal X-ray of pregnant women, children treated for enlarged thymus, adults treated for ankylosing spondylitis, adult women treated for tuberculosis, adults treated for thyroid condition, individuals with body burdens of radium, and uranium miners exposed to high levels of radiation gases (NIH, 1979). In addition, a vast amount of data from controlled laboratory and experimental conditions investigating effects in bacteria and animals has amassed since the discovery of radiation in 1895.

In order to estimate human health effects due to exposures less than 0.05 Sv, it has been customary to estimate low dose radiation effects on the basis of known high dose effects, primarily using the ABS cohort. However, a variety of worker populations from different countries involved in the production of nuclear weapons have been studied over the past two decades allowing direct estimation of health risks associated with low-level radiation exposure.

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* Scientific terms in *italics* appear in the glossary.

[1]Sievert (Sv) is defined as a unit of radiation measurement that allows combining physical aspects of radiation energy with organ specific dose(s) from different parts of the body to arrive at a dose value applicable to the whole body (see section IV).

One such cohort of workers with low-level radiation exposure has been studied at Oak Ridge National Laboratory (ORNL), a Department of Energy (DoE) research facility (Wing *et al.*, 1991). Results from an investigation of the mortality experience of this cohort suggest a dose-response relationship with low-dose radiation exposure and cancer mortality. The risk estimate for all-cancer mortality was found to be 10-times the estimate based on extrapolation of data from the ABS cohort and departs from findings in similar worker cohorts in other ways. This thesis is a re-analysis of exisiting cohort data to explore possibilities that may help to understand and explain findings published in Wing *et al.* (1991).

The public health implications of exposure to low-level ionizing radiation are important, not the least of which is the need for accurate information to protect workers exposed to radiation. It is the thesis of this research that data analysis methods will yield insight as to whether cancer risks are causally associated with low-level radiation exposure in the ORNL cohort, and, if so, how to reconcile findings from the Wing *et al.* (1991) report with mostly negative findings from other historically similar cohorts.

A. Study Hypotheses

1. Can excess cancer observed in earlier analysis of these data be explained as due to:
(a) confounding due to time-related factors not previously considered;
(b) selection bias that results from the choice of method to incorporate an empirical induction period (EIP); or
(c) grouping of cancer outcomes;
(d) the type of statistical model chosen, such as a log-linear model or linear excess relative risk model.

After choosing the EIP that minimizes bias, the following questions will be answered:

2. Is the excess cancer mortality observed at ORNL due to exposure to low-level ionizing radiation in a cohort of workers hired between 1943 and 1972?
3. Is it feasible to estimate an exposure-response relationship?
4. If so, does an exposure-response relationship exist in this cohort?
5. Is the excess of cancer deaths observed in earlier analysis explained by a few workers who were exposed to large doses (> 500 mSv) during their career?

B. Specific Objectives

These hypotheses will be tested by the following objectives:

- Replicate results as originally published in Wing *et al.*, 1991. This will ensure that the data used in these analysis is comparable with those used by Wing *et al.*, 1991;

- Describe the ORNL cohort (those alive, deceased, all-cancers, all cohort, exposed and unexposed), especially in relation to temporal factors that may influence the exposure-disease relationship (hypothesis 1(a), see Chapter 3: Methods, Section B.).

- Examine the influence of the empirical induction period (EIP) on mortality as quantified by time from first employment until death, lost-to-follow-up, or end of study period (whichever occurs first) using two computational approaches: lagging or a combination of both latency with lagging dose to determine if choice of EIP results in differences in the estimated mortality risk (hypothesis 1(d), see Chapter 3: Methods).

- Determine if mortality risk varies by grouping of cancer and non-cancer outcomes (hypothesis 1(b), see Chapter 3: Methods);

- Examine differences between two statistical modeling approaches: (1) the log-linear model and (2) linear excess relative risk model. Most studies of nuclear worker cohorts emphasize the linear excess relative risk (ERR) model. Wing and colleagues fit a log-linear function to the observed data (hypothesis 1(d), see Chapter 3: Methods).

- Identify if adjustment for time-related variables contributes to the fit of the data, or if these variables act as confounders in the exposure-disease association through their use as covariates in model fitting (hypothesis 1(a), see Chapter 3: Methods).

- Determine if a dose-response relationship exists (hypothesis 4).

II. DEFINITION AND MECHANISM OF ACTION FOR IONIZING RADIATION

A. The Electromagnetic Spectrum

Toward the end of the seventeenth century, Sir Issac Newton held a wedge-shaped piece of glass toward the sun's yellow rays and observed that these rays split into a variegated rainbow when passing through the glass. Newton, an innovator in many avenues of mathematics and science, essentially forged the study of radiant energy (Tievsky, 1962).

Radiant energies, known as electromagnetic radiations, are transmitted in the form of undulating waves that are of varying lengths and can be measured precisely. Each wavelength oscillates at a different rate, or frequency, and associated with each wavelength is a given amount of energy; the shorter wavelengths contain considerably more energy than the longer wavelengths. Besides the wavelengths of sunlight which Newton described, other electromagnetic radiation comes from outer space. The longest of these are radiowaves emitted by incandescent stars. The shortest are tremendously energetic cosmic rays, whose origins are unknown. The entire electromagnetic spectrum is considered to be encompassed between these two radiations, radio waves and cosmic rays (EPRI, 1989) (Figure 1.1).

Man's senses are in-tune to only a few forms of radiant energy, such as infrared energy perceived as heat, visible light perceived directly through our eyes, and micro- and radio wave energies that are trapped for use by household appliances. Energies beyond our perception include *directly** and *indirectly ionizing radiations.* Directly ionizing radiations exist in the form of electrically charged (positively or negatively) particles having sufficient kinetic (heat) energy to produce ionization by collision (e.g., *alpha* and *beta* particles, *protons*, and *electrons*). *Indirectly ionizing particles* are uncharged discrete packets of energy (*photons*) that travel through air as electromagnetic waves measured in wavelengths (x-ray and gamma radiation energies). The ORNL cohort was monitored to detect exposure to external gamma radiation, a form of uncharged, indirectly ionizing wavelengths.

B. What is Ionization and Radioactivity?

All matter in the universe is made up of elements. Known elements are listed on the Periodic Table of the Elements, some of which are man-made. Gaseous elements on the Periodic Table are life-sustaining, such as carbon, hydrogen, oxygen, and nitrogen, while other elements naturally exist as metals, such as gold, platinum, or uranium.

Elements are made up of atoms. Atoms consist of a small positively charged (+) nucleus around which negatively charged (-) electrons move. Electrons move around the nucleus in orbitals, known as shells. The total number of negatively charged electrons is equal to the number of positive charges carried by the nucleus, so that the atom is electrically neutral. The nucleus contains two particles: the proton and neutron. Inside the nucleus the positive charge is carried by the proton (+), while the neutron is electrically neutral. Moving down the Periodic Table, nuclei contain an increasing number of positively charged protons and electrically neutral neutrons as well as an increasing number of electrons circulating in multiple outer shells. A stable atom will have the same number of protons, neutrons, and electrons.

The concept of an isotope is important to introduce here. Recall that a stable atom will have the same number of protons and neutrons in the nucleus as there are electrons in the outer shells. For example, helium has two electrons in its outer shell, as well as two protons and two neutrons in the nucleus. The number of electrons and protons in an element will be the same. This is a characteristic that makes elements unique (Walter, 1977). When a compound has the same number of electrons and protons, but a different number of neutrons, then the compound is an *isotope* of the element. An isotope of an element is still chemically equivalent to the stable form of an element, since the isotope has the same number of orbital electrons and protons. Isotopes occupy the same place on the Periodic Table as the stable element. The total number of particles in the nucleus - protons plus neutrons -- is thus characteristic of each isotope and is used to designate the isotope (Walter, 1977, p. 48). For example, uranium-235 is an isotope of uranium-238, which is element 92 on the Periodic Table.

Many isotopes in nature are stable. However, elements with many more neutrons than protons are unstable and their nuclei go through a process of readjustment to become more stable elements. In this process of readjustment ionizing radiation is produced. When ionizing radiation is emitted, *radioactivity* occurs. There are naturally occurring radioactive elements, like uranium, that release radiation while in the process of becoming more stable elements. The radiation that is release is capable of removing orbital electrons from materials when contact occurs. The source of gamma radiation at ORNL was from the decay of uranium. Man-made radioactive compounds, such as plutonium, can be created from naturally occurring radioactive elements, such as uranium-238, by bombarding uranium with neutrons in a nuclear reactor.

Early in this century the term radioactivity was coined by Marie and Pierre Curie and during this era radioactivity was found to comprise three kinds of rays: alpha, beta, and gamma.

(1) Gamma Rays: Indirectly Ionizing Radiation

By 1915, it was known that alpha, beta and gamma rays are emitted from the nucleus of an atom, but only gamma radiations were true rays.[2] The so-called alpha and beta rays are streams of particles (Hacker, 1987, p. 19). Gamma rays resulting from radioactive decay consist of energy wavelengths that do not exceed several million electron volts (MeV) in energy, about three-times as much energy as emitted by a dental X-ray (NAS, 1990, p. 10).[3] Often in the literature X-rays and gamma rays are grouped together, since both are streams of photons that have the potential to remove orbital electrons. The major differences between X-ray and gamma radiation are: (1) gamma rays originate from the nuclei of atoms and X-rays are machine made, and (2) gamma rays generally have higher energies per photon than X-rays (Gofman, 1981, p. 24). Even though their energies differ, both X-ray and gamma rays produce indirect ionization most

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[2] Today a fourth type of radiation, the positron, is known to have a positive charge.

[3] The ordinary voltage in electrical power in the US is 120 volts. A bitewing dental X-ray releases about 75,000 volts, or 75 kilovolts (kV) (Shaprio, 1990, p. 94), compared to gamma rays which emit between 124,000 to several million electrons volts.

likely through *ion pair production* and the *photoelectric effect.* Gamma radiation results when the nucleus releases excess energy (Harley, 1991, p. 723).

The same principles of ionization and radioactivity discussed in the previous section apply to gamma rays. When photons interact with tissue medium, such as deoxyribonucleic acid (DNA), the electrons that are set in motion proceed to interact with the atoms and molecules of that medium, such as DNA. The electrons loose energy through collisions and excitations, and are scattered in the process. The result is a complex shower of electrons, the energy distribution of which is continuously degraded as electrons give up their energy at a rate defined by the electron stopping power of the medium, such as the skin surface or DNA (NAS, 1990, p. 11). This results in an electrically unstable atom, and if an electron is lost, the atom becomes deficient by a negative charge. Such a free electron is quickly captured by an adjacent atom, thus producing instability in the atom as a result of one additional negatively charged electron (Tievsky, 1962, p. 20). Therefore, *ionization* can be defined as the ejection of electrons from the atoms with which the radiation interacts.

Gamma radiation, itself, does not have a charge, since these radiations are photons that travel as electromagnetic waves at the speed of light. These waves penetrate through a medium without interacting with electrons, until, by chance, the waves make collisions with electrons, atoms or nuclei, which result in the liberation of energetically charged particles. The charged particles that indirectly ionizing particles liberate are directly ionizing (such as a free, negatively-charged electron), and it is through direct ionization that damage from gamma radiation is produced. This is an important distinction; thus the basic damage is done by charged, directly ionizing particles, the electrons, even though the incident radiation is indirectly ionizing (Shapiro, 1990, p.10). X-rays and gamma rays set electrons in motion; beta particles are negatively charged high-speed electrons (Gofman, 1981, p.24). Once a photon liberates an electron, the subsequent events depend only on the properties of the electron and not on the gamma photon that liberated it. In short, ionization energy sets electrons in motion. The interaction of those electrons with matter, determine the cellular and biological effects.

Ionization occurs when electrons circling around the outside of an atom are rather loosely attached and can be knocked off. Thus, the atom looses a unit of negative electrical charge and is left with an unbalanced surplus of positive charge. The dislodged electron collides with other atoms nearby causing an electrically negative charge on the nearby atom. These positive (due to removal of an electron) and negative (due to gain of an extra electron) fragments are called ions. The cascade effect of knocking out electrons is called ionization. The characteristic of ionizing radiations is that these radiations knock off electrons in their path (Walter, 1977).

(2) Linear Energy Transfer (LET)

The biological effectiveness of particular radiations in causing cell inactivation, mutation, cell transformation, and malignancy in human species depends to a large extent on the energy[4] content of the ionization (Adams, 1989, p. 3). 'Linear Energy Transfer' (LET) describes the amount of energy (ionization plus electron excitation) transferred per unit of path traveled by the ionizing particle (Gofman, 1981, p. 28). The LET of gamma radiation is zero as long as the ray remains a photon, since there would be no interaction with biological material, until and unless the photon sets an electron in motion (Gofman, 1981, p. 28).

Gamma rays have about 1/7360 the mass of alpha particles. Lighter weight gamma ray electrons can move much faster than very heavy alpha particles. Since heavy alpha particles move much slower though the path, the distance between ionizations is much shorter. The ionizations that are much closer together can impart a more severe biological effect than ionizations that are much further apart, such as ionization that results from gamma rays. In general, it is believed that biological effects depend on the density of ionization in tissue (Gofman, 1981, p. 29).

Gamma and X-rays are considered sparsely ionizing radiation with low-LET, whereas, directly ionizing radiation, such as alpha or beta particles are considered dense, high-LET

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[4] energy = 1/2(mass) x (velocity)**2

radiation. Figure 1.2 shows energy of radiation (x-axis) by LET (y-axis), indicating that electrons are a much lower LET than other radiation energies (von Sonntag, 1987, p. 10). For example, alpha particles would produce about 1000 times more ionization per unit distance than gamma rays. Alpha ionizations are packed closely together. Therefore, alpha particles are densely ionizing radiations with high LET. Figure 1.3 provides the spatial representation of high and low LET as related to the deposition of energy across DNA. Both high and low track lines travel through DNA, but the high LET track is a long trail of tightly clustered points representing the energy quantity of this radiation. Slower velocity, due to particle mass, results in many more ionizations per distance of path traveled. Conversely, the low LET track has small packets of clustered points separated by wide spaces, which results in fewer ionizations per distance of path traveled. The distance and quantity of the points along the radiation track demonstrate the energy difference between high and low LET radiation.

III. TEMPORAL STAGES OF RADIATION ACTION

Once an electron has been released and collides with DNA, the potential biological effects of this action are the same no matter the type of radiation. This section summarizes the stages involved for a photon of gamma radiation to act, beginning with the physical lesion taking fractions of a second, up to the manifestation of cancer decades later. Table 1.1 classifies the timing for radiation action after exposure to a photon of gamma radiation.

A. Physical and Chemical Lesions

The amount of time over which energy is imparted to an atom or small molecule during irradiation is extremely short and governed by the velocity of the particle, the dimensions of the molecule impacted, and the amount of energy, lost or transferred in the process. A photon of gamma radiation will pass through a small atom or molecule (e.g., H_2O) and deliver energy to it, in a time between 10^{-18} and 10^{-17} seconds. In human tissue, most of the energy absorption will take place in water, since cells are made up of more than 70% water (NAS, 1990, p. 12). The formation

of physical lesions, when energy degrades and secondary electrons undergo collisions with neighboring atoms, occur within 10^{-16} to 10^{-12} seconds. During this interval ionization occurs (Awwad, 1990).

Next is an intermediate chemical phase of 10^{-12} seconds during which chemical lesions are produced. These lesions are short-lived fragments: hydrated electrons (e^-_{aq}), the hydrogen radical (H•), and the hydroxyl free radical (OH•). Water molecules break apart rapidly following absorption of radiation. Overall, the radiation-induced dissociation of water,

$$H_20 \rightarrow (H\bullet + e^-_{aq}) + OH\bullet$$

gives rise to both an oxidizing species (OH•) which is looking to abstract a hydrogen (von Sonntag, 1987, p. 4) and a highly reactive reducing species ($H\bullet + e^-_{aq}$) which is looking to attach to a molecule (von Sonntag, 1987). A proportion of radicals react together to produce molecular hydrogen (H_2) and hydrogen peroxide (H_2O_2). Reactive radicals diffuse away from regions of the radiation tracks where they are formed and react with neighboring molecules. Eventually the spatial distribution of free radicals becomes homogeneous in about 10^{-7} seconds. Free radical reactions are largely complete in times of milli-seconds or less (Adam, 1989, p. 4).

OH• radicals are of special importance since they are produced at high density in close proximity to the biological target, such as DNA (Awwad, 1990). The biological lesion produced may have a high probability of evolution into an irreparable lesion (Awwad, 1990). It has been estimated that about 65% of the lethal cellular effects of ionizing radiation are due to OH• radicals (Awwad, 1990). The is because the local energy that a free radical generates is greatly in excess of the normal bond energies of all the affected molecules (Adams and Cox, 1991, p. 198). The cascade of free radical formation in water surrounding DNA can also contribute to loss or change in cellular function other than immediate damage to DNA. The combination of free radical attack and direct damage to DNA increases the probability of irreparable lesions that go unrepaired (Awwad, 1990, p. 6). The fundamental problem that remains to be solved is the identification of

the specific types of free radical chemical damage critical to the onset of the multistage process of carcinogenesis (Adams and Cox, 1991, p. 198).

B. Biological Lesions and Mathematical Representation

The evidence that damage to the genomic material of the cell is the principal cause of radiation-induced cell death and various sub-cellular changes, such as mutation, chromosomal exchanges, and malignant transformation, is now overwhelming (Adams, 1989). It is believed that radiation must pass through the nucleus of the cell to cause mutation or cell death (Figure 1.4). An absorbed dose of 1 Sv (100 rem) will cause an average of about 2×10^5 ionizations in a mammalian cell, of which approximately 1% will occur in genomic material.

The theory of the formation of the biological lesion is diagrammatically shown in Figure 1.5. The left side of the figure shows two sublesions are initially produced by one ionization event (e.g., the traverse of a single electron through two targets) produced simultaneously or in rapid succession (Awwad, 1990, p. 6). Mathematically, small doses or low dose rates would be linear where the cellular response is proportional to dose. A linear (L) dose response (αD) would result from the production of both sublesions by one activation event, assuming no repair.

The right side of Figure 1.5 represents the formation of two separate sublesions from two different ionization tracks. In the absence of repair, a quadratic term represents the production of two sublesions by two separate events (αD^2). The squared term represents the probability that the event is proportional to the square of the radiation dose. The probability of producing both sublesions by separate events is low with low LET radiation or when the dose rate is low, where there is a greater chance of repair of the first before induction of the second sublesion occurs (Awwad, 1990, p. 6).

Once damage occurs, there are several pathways to initiate cellular response. One possibility is cell death. If the damage is not immediately lethal, then fate of the lesion has several possibilities: (a) complete and correct repair, (b) incorporation of the lesion as part of DNA that

may occur during progression of the cell through the cell cycle but does not disrupt normal cellular function, and (c) misrepair of the lesion, which may be transformed into a lethal lesion, or into a mutated or malignant cell (Awwad, 1990).

C. DNA Changes and DNA Repair

Loss of cellular function cannot be observed immediately after radiation exposure. Loss of reproductive capacity or cell death can only be observed and measured quantitatively when the cell fails to divide. Cellular changes in chromosome content, configuration, and morphology or development of mutations, only appear evident after sufficient numbers of cell divisions have taken place in order to allow the analyses of aberrant cells in the total cell population (Adam, 1989, p. 5). Changes are usually visible in metaphase (Adams and Cox, 1991, p. 191). Human cells in metaphase possess two thickened daughter chromatids tied together at the centromere. This is the stage of cell division just before the chromatids separate.

Mammalian cells are usually most susceptible to radiation damage during somatic cell division. Specifically cells are most sensitive during early Interphase, the G_1-phase of cell division, a stage that precedes DNA and chromosome replication and is a major point for regulating cell division (Adams and Cox, 1991, p. 180). Cells are usually most resistant in the early S-phase, when the DNA begins replication. Variation in sensitivity between the different parts of the cell cycle is highly dependent on radiation quality. Cellular sensitivity to low LET gamma radiation is usually much more variable than to more densely ionizing radiation. Thus, it appears that 'when' exposure occurs in relation to cell division is important as well as the energy content of radiation.

The rate of repair in cellular damage is crucial for understanding the consequence of exposure. The primary types of damage in cells exposed to ionizing radiation are: direct strand breaks, base damage, and cross-links. There are two types of direct strand breaks: single strand breaks (ssb) and double strand breaks (dsb). The most important precursor to strand breakage is the OH free radical (von Sonntag, 1987, p. 240), which was discussed in section III.A.

(1) Single Strand Breaks

Ssb affect one strand of the double helix and dsb affect both strands of DNA. Ssb are the most frequent lesions occurring in DNA from radiation exposure, at approximately 1000 ssb per diploid genome per Sievert of exposure (Bryant, 1989, p. 16). Ssb are induced with a linear function of radiation dose, meaning that there is a linear relationship between the frequency of breaks and cumulative dose. Besides direct strand breakage, it is hypothesized that ssb results when DNA base-damage is converted into a ssb during repair of a damaged base (Bryant, 1989, p. 21). DNA undergoing transcription (the process of making RNA from DNA) is likely to suffer more breakage than DNA not undergoing transcription (Bryant, 1989, p. 16). It is hypothesized that ssb can result in deletion of a gene or chromosome. Loss of a gene could be the primary carcinogenic event of radiation exposure.

However, it is believed that repair of ssb is more likely to occur than not and is estimated to occur within 10 minutes of damage (Bryant, 1989, p. 23). The repair mechanisms of ssb are unknown, but involve *excision repair* of damaged bases (Hagen, 1994, p. 51). Of the 2000 or so breaks that occur out of 2×10^5 from an absorbed dose of 1 Sv, almost all will be repaired by cellular defense mechanisms and are of no consequence. More study in the area of mammalian cell ssb repair has been suggested (Hagen, 1994, p. 54).

(2) Double Strand Breaks

Some strand breaks are not repaired, however, and lead to cell death or irreversible changes (Adams, 1989, p.8). Dsbs are essentially two ssbs occurring exactly opposite to one another (straight across both strands of DNA), referred to a "blunt dsb", or in close proximity (probably not more than four base-pairs apart), referred to as "sticky end dsb". As both strands are broken in a dsb, there is less chance of restoring the original nucleotide sequence. Bryant (1985) found that "blunt dsbs" lead to chromosome aberrations and cell inactivation, whereas dsb with "sticky ends" were easily repaired (Hagan, 1994, p. 54).

Dsbs have been found to be induced linearly with dose, and probably arise from single ionizing events (like ssb), but resulting from much higher energy. Dsbs are less frequent than ssb. It is estimated that 40 dsb occur per Sv of exposure when the nucleus is not undergoing division (Blocher, 1982, p. 17).

Dsbs are thought to be the most important group of lesions that cause biological damage (Goodhead *et al.*, 1993, p. 552; Hagen, 1994). When enzymatic repair of dsb occurs, it is usually complete within 6-18 hours (Goodhead *et al.*, 1993, p. 551), which is slower than repair of ssb (Hagan, 1994, p. 52). The repair of dsbs with or without loss of nucleotides requires a complex of several enzymes working together at the damaged site. Insight into possible mechanisms of dsb DNA damage has been gained by Thacker and coworkers (North *et al.*, 1990; Fairman *et al.*, 1992; Thacker, 1992; Thacker *et al.*, 1992)(Hagan, 1994, p. 54). Possible mechanisms include enzymatic activity of DNA ligases and recombinational repair. In general the more complex the induced damage, the more protracted the repair process. This means that a higher fraction of unjoined dsb would potentially result in genetic information being lost at either end of the dsb, or result in a deletion around the dsb (Hagan, 1994, p. 56).

(3) Other Types of Damage

DNA base-pair damage is defined as chemical alteration of the bases of DNA without breakage of one of the two strands of DNA. The damage, which can involve removal of a side-group off the backbone chain or damage to the side-group structure (Bryant, 1989, p. 17), is believed to be more common than dsb (Frankenberg-Schwager, 1990, p. 276), and three times more frequently induced when DNA is replicating. Repair of damage to the DNA base pairs is usually complete within one-hour (Frankenberg-Schwager, 1990, p. 278). Repair is thought to involve removal of the damaged base from the sugar side-group, prior to induction of a ssb by an endonuclease repair enzyme. Thus, base damage is removed via excision repair (Frankenberg-Schwager, 1990, p. 278).

The last type of cellular damage involves two types of cross-links that are known to occur. The first is inter-strand cross-links and the second is protein cross-links. These are much less common than other types of damage, occurring no more than 1 cross-link per nucleus per Sievert (Bryant, 1989, p. 17) and will not be discussed further.

In summary, cellular damage leads to induction of mutations or cellular transformations when a lesion is not repaired. Evidence suggests that ssb and base damage are not critical lesions for cellular and genetic damage, possibly because of efficient and accurate repair (Bryant, 1989, p. 23). Dsb, while also subject to repair, are thought to be the critical lesion leading to permanent genetic damage via chromosomal aberrations and mutation (Bryant, 1989, p. 25). In the low dose region transformations and mutations can be expressed, since a large proportion of cells survives. At high doses (> 2.0 Sv) cell killing predominates.

D. The Tissue Stage

With the correlation between radiosensitivity and phase within the cell cycle, it is not surprising that damage to biological tissue *in vivo* also depends on the rate of cell turn-over. Tissues with rapid turn-over exhibit damage early after radiation, such as effects on the blood-forming tissues, gut, testes, and skin. Tissue with a very low rate of cellular turnover exhibit damage much later, such as connective tissue, brain cells, liver, kidney, endocrine glands, and lung (Awwad, 1990, p. 8). For example, damage to the intestine becomes apparent after 2 weeks of irradiation, damage to the lung appears after 3 to 4 months, and damage to cells of the central nervous system appears even later (Gofman, 1981, p. 364]

In humans, the rate at which cell division occurs is inversely related to age. Children exposed to high doses of radiation are at much higher risk of developing cancer than adults exposed at the same level (Shimizu *et al.*, 1990). This may be due to the much higher rate of cell turnover in children, resulting in the potential for rapid clonal expansion of a mutated cell. The

interval from first exposure until diagnosis of disease (or death)[5] varies widely depending on the dose, radiation quality, the site of irradiation, and also the age of the individual. In the low dose range, low LET radiation is less effective per unit dose in inducing cancer than high LET radiation (Adam, 1989). The aforementioned discussion suggests that mutations and carcinogenesis result due to the timing of exposure in relation to cell division, the amount of energy which the radiation source releases to cellular targets, and cell-turnover of the organ-specific location where exposure is presumably absorbed. Major modifying factors are the presence of complete and correct repair, and the age of the exposed individual. Efficient and correct repair probabilities decrease with increasing age. DNA double strand breaks produced by free radical formation which go unrepaired may be the initiation event, assuming no repair. Advances in molecular biology in recent years have rapidly expanded the scope of knowledge about radiation-induced damage and excision repair. For example it is now known that certain hereditary disorders, such as xeroderma pigmentosum, are deficient in excision repair (Sancar, 1994, p. 1956). Xeroderma pigmentosum patients are also very sensitive to sunlight exposure and develop multiple skin cancers at younger ages than the general population. New understanding is also emerging regarding the role of tumor suppressor genes and oncogene activation in radiation-induced cancers, as well as sources of cell damage that may not directly involve DNA (Trosko, 1995).

E. Cancer Development

There is evidence that gamma radiation exposure can cause cancer. Children treated for tinea capitis received an estimated 75 mSv resulting in a significant excess of thyroid cancer.

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[5]Latency is definded as the time between first exposure and disease diagnosis or death, since it is rarely known when disease acutally begins. Disease or death occuring during this interval is not assumed to be due to exposure.

Breast cancer developed in women who were enrolled and treated for tuberculosis using x-ray fluoroscopy. These women received about 10.5 mSv with each fluoroscopy (Gofman, 1981, p.410). Children of pregnant women who received between 0.025 mSv and 10.5 mSv total dose in-utero exposure developed leukemia and other cancers in childhood. Levels experienced by women and children for medical therapy were on average higher than levels encountered by predominantly male worker populations that have been the subject of cohort studies.

IV. MEASUREMENT OF X-RAYS AND GAMMA RAYS

Various measurement techniques for determining the intensity of a beam of radiation energy have been used since x-rays were identified by William Roentgen in 1895. The problem of determining the precise definition of a particular term used in radiation measurement has been exacerbated by apparently slight but often significant changes in the official definitions of radiological units over the years (Kathren and Petersen, 1989). Changes in measurement units over the years have obvious implications to epidemiologists conducting retrospective studies. In 1977 a new system of scientific units, the Systeme International (SI), was accepted by all signatories of the Meter Convention, including the United States (US). The new measurement system was supposed to be used beginning in 1989, but much of the radiation epidemiology literature after 1989 used the pre-1977 radiation units. The following units of measurement were used prior to 1989 to quantify radiation *exposure*: Roentgen (R), Radiation Absorbed Dose (rad), and Roentgen Equivalent for Man (rem). After 1989, the terms Gray (Gy), and Sievert (Sv) should be used exclusively to replace the terms 'rad' as a measure of absorbed dose and 'rem' as a measure of dose equivalent. All the aforementioned units of exposure and dose are distinct from units of measurement that quantify radioactivity of a substance, such as the Curie (Ci) and Becquerel (Bq). For reference, Table 1.2 provides interconversions of some units commonly used in radiation research.

A. The Roentgen

Early in this century, the fundamental unit of x-ray measurement was the Roentgen (R). With development of a standard measurement instrument, an ionization chamber, it became possible to define an objective and readily reproducible unit of radiation. R measures radiation in air, and therefore crudely measures exposure. It does not quantify how much radiation is absorbed by an individual's tissue or what happens after radiation enters the body tissue (Kathren and Petersen, 1989), therefore, the R is not relevant in studies of human population exposures.

B. Units of Absorbed Dose: Gray (Rad)

The basic quantity that characterizes the amount of energy imparted to matter is the absorbed dose. The average absorbed dose in a region of the body is determined by dividing the energy imparted in that region by the mass of the matter in that region (Shapiro, 1990, p. 44). Absorbed dose could be different in different parts of the body.

The physical basis for measurement of energy absorption depends on the minute increase in temperature when matter is irradiated; the unit of measurement is known as the radiation absorbed dose, or rad. One gram of tissue which has absorbed 100 ergs of energy during the process of irradiation is said to have received one rad of the given radiation. The rad has also been defined as 0.01 Joule per kilogram (J/kg). The rad can be used for exposures for any radiation in any absorbing medium (Kathren and Petersen, 1989, p. 1081). For x-ray tissue dosage in the diagnostic range and occupational exposure range, one rad is approximately equivalent to one R. A Roentgen of gamma radiation in the energy range 0.1-3 MeV produces 0.96 rad in tissue, a typical energy range of radioactive decay for uranium. The millirad (mrad) has been used in specifying levels for radiation protection.

Since 1977, the fundamental dosimetric quantity in radiological protection is still the absorbed dose, but radiation is measured in units referred as the Gray (Gy). Therefore, simple correspondence exists between the old and new units:

100 rad =1 Gy.

C. Roentgen Equivalent for Man (Rem): Sievert

Thus far, the discussion has been concerned with only the physical aspects of radiation. Neither R nor Gy expresses the varying biological effects of radiation types. Certain radiations require a smaller dose to effect biological change than other types. This is known as the biological effectiveness of the radiation. As stated earlier, the higher the LET of the radiation, the greater the injury produced for a given absorbed dose. The factor expressing the relative effectiveness of a given particle based on its LET is known as the quality factor, 'Q' (Shapiro, 1990, p. 46). The

quality factor (Q) takes into account the type and rate of radiation dose (ICRP 1992, p. 5) by weighting the absorbed dose (Gy) by a factor related to the quality of the radiation (Q). The International Commission on Radiation Protection (ICRP) now refers to Q as the 'radiation weighting factor', because it is assumed that the absorbed dose is averaged over a tissue organ and then weighted for the quality of the radiation (ICRP, 1992, p.5). Gamma radiation and all photon energies have a Q of 1.0. The dose equivalent is designed to express different radiations on the same scale; that is, it is intended to correlate with the injury produced as a result of radiation exposure (Shapiro, 1990, p. 46).

When the absorbed dose in rads is multiplied by Q, the result is the 'dose equivalent' expressed in units of Roentgen Equivalent for Man, or rem. Rem was devised to combine both physical as well as biological aspects of radiation exposure. By arbitrarily assigning x-rays in the commonly used medical range as the standard with a quality factor of 1 unit, quality factors for other types of radiation were developed. In common usage of the past, rem was applied to whole body irradiation, unless an organ was specified. Since the quality factor equals 1 for gamma radiation, 1 Gy = 1 Sv.

The Sievert (Sv) has the same relationship to the gray in SI units (Shapiro, 1990, p. 46), as the rem does to the rad: (1) rems = rads * QF and (2) sieverts = grays * QF.

Standards for radiation protection are given in terms of the rem unit. Doses expressed in the older units, rads, may be compared to regulatory limits given in terms of rem, when dealing with x-ray and gamma photons. The 1:1 correspondence does not exist for high LET particles. Table 1.3 summarizes correspondence in the measurement units for gamma radiation. A rem can be converted to Sv by dividing by 100 and a rad can be converted to a Gy by dividing by 100. Personnel records of cumulative dose at ORNL were kept in units of millirem (mrem).

V. ACUTE, HIGH DOSE EXPOSURE VERSUS CHRONIC, LOW DOSE EXPOSURE: FITTING THE THEORETICAL DOSE-RESPONSE CURVE

A. Non-Stochastic Processes

The integrity of normal tissue or organs depends on the maintenance of a certain number of normally functioning mature cells. High doses (above 0.1 Sv or 10 rem) of radiation received at once preferentially kill and deplete the functioning cell population (Awwad, 1990, p. 8). When this depletion reaches a certain level, a clinically detectable effect, such as failure of an organ, becomes apparent. Such reactions are termed "non-stochastic" (non-random) effects. Since organ failure requires high dose levels necessary to reduce a mature cell population to a critical level, a threshold dose exists below which cell killing is not expressed in a clinical response. Between induction of radiation damage and the time of appearance of the radiation effect, the cell population may begin to regenerate, repair and restore tissue (Awwad, 1990, p. 8). Above the appropriate threshold, the severity of the harm will increase with dose, reflecting the number of cells damaged or killed. The dose rate is usually reflected in the threshold as well, because a protracted dose will cause cell damage to be spread out in time, allowing for more effective repair or repopulation (ICRP, 1992, p. 15). The term non-stochastic is applied to this phenomenon because the large number of cells that are killed for the initiation of a clinical outcome are not considered random (ICRP, 1992, p. 15). For non-stochastic processes, both the probability of cell death and severity of damage increase with dose, because full repair capacity is unlikely in the range where cell killing predominates (Awwad, 1990, p. 8).

B. Stochastic Processes

Effects resulting from transformation of individual cells are called 'stochastic' effects. Since these effects occur in individual cells, they are also called 'single-cell' effects. Mutations and carcinogenesis are two expressions of cellular transformation that are considered single cell effects. The expression of single cell effects are considered to have no threshold dose, meaning that there is

no dose below which it can be assumed no damage will occur. The probability of a cancer resulting from radiation will be at least partly dependent on the number of modified cells initially created, since this number will influence the probability of at least one modified cell surviving (ICRP, 1992). It is then the probability of malignancy that is related to dose, while the severity of a particular cancer is influenced only by the type and location of the malignant condition (ICRP, 1992, p.16). The process of single cell effects resulting in malignancy appears to be random, due to genetic and physiological variation between individuals. Thus, the process is considered 'stochastic'.

As the dose increases the observed effect will be a balance between mutation and transformations or cell death. Like cell killing, the biological lesion that evolves into a transformation may be produced by a single track or may result from the interaction of two 'sublesions' each produced by a single track (see Figure 1.5 and section III.B.). Thus the probability of occurrence of a stochastic effect (e.g. random mutation) can be expressed as a sum of a linear (αD) and quadratic term (αD^2). Stochastic effects are considered all or none since there are only two discrete severity states: effect or no effect (Awwad, 1990, p. 10). Figure 1.6 gives a typical response curve for a stochastic process where the frequency of effect (e.g. mutation) is plotted against dose. The plot has three distinct parts. At first the frequency increases linearly with dose, since in the low dose region the linear term predominates (αD). The second segment is more steep due to predominance of the quadratic term (αD^2). This is followed by segment three, a drop in frequency of mutations due to the occurrence of a significant amount of cell killing, so that the number of cells expressing transformation is low (Awwad, 1990, p. 16).

This curve fits a linear-quadratic (L-Q) ($\alpha D + \alpha D^2$) model. The L-Q formulation has its origins in the 1930's when it was used to fit data for radiation induced chromosome aberrations. Thus the interpretation of the model is that the characteristic shape of the dose response curve reflects a predominance of single-track events (a single electron passing through two targets), which are proportional to dose at low doses and low dose rates, and of two-track events (two lesions from two different ionization tracks), which are proportional to the square of the dose and

result in a upward bending of the cancer induction curve at high doses received at high dose rates (NAS, 1990, p. 21).

C. For Radiation Protection: No-Threshold at Low Doses

According to the ICRP, cancer is the only 'stochastic' effect induced by radiation in an exposed individual (ICRP, 1992, p. 16). If, as seems likely, some types of cancer result from the damage originating in a single cell, there can be a real threshold in the dose-response relationship for those types of cancer, only if the defense mechanisms are totally successful at small doses. However, ICRP assumes that defense mechanisms are not totally successful at small doses. The balance of damage and repair in the cell and the existence of subsequent defense mechanisms can influence the shape of the dose-response relationship. The ICRP does not assume these factors result in some safe level of radiation exposure below which there is no damage occurring, i.e. there is no real threshold (ICRP, 1992, p. 17). That is why international committees charged with determining the health effects of low dose radiation assume a no-threshold approach. The probability of repair is not integrated into statistical models that quantify risk in human population studies.

Stochastic effects are relevant to low dose radiation levels experienced by occupational exposure to DoE radiation workers. There are two important implications to this assumption. First, since stochastic effects are assumed to have no threshold, it cannot be assumed that mutagenesis and carcinogenesis are entirely prevented by observing dose limits recommended by the ICRP.

Secondly, with regard to carcinogenesis, low dose exposures are considered additive. Experimental studies have shown that in the low dose region where the linear term predominates, the induction of mutation per unit dose was independent of the dose rate (Awwad, 1990, p. 11). Accordingly, the mutagenic potential of small, repeated doses between 0.05 and 0.1 Sv (5 and 10 rem) are expected to have an additive effect, particularly if separated by a few days or more. Such exposures are of the same magnitude as those involved in radiodiagnostic examinations, while much smaller doses are delivered during occupational exposure (Awwad, 1990, p. 11). This has

been interpreted to mean that the overall risk of mutation is proportional to the total dose and independent of whether exposures are separated in time.

Based on experimental conditions, carcinogenesis risk tends to diminish as the dose rate is reduced, but the dose-response curve for the low dose region is uncertain in human populations. As more becomes known about the process of carcinogenesis, it is apparent that cancer may not be totally explicable in terms of a 'single cell effect'. Interaction and communication between intercellular enzymes and proteins are likely to be involved. Moreover, susceptibility to cell transformation differs with cell age, cell type, stage of the cell cycle, and the type of DNA damage rendered (Adam, 1989). Hence equal repeated doses spread over time, as occurs in many occupational settings, may not have equal effects. However, in the interest of worker health and safety, the risk of carcinogenesis is considered to be linearly related to dose, as has been shown for mutagenesis where small repeated doses have additive effects (Awwad, 1990, p. 13).

Current radiation protection standards allow up to 50 mSv (5 rem) of exposure per year or 100 mSv over 5 years. There is no standard in effect for cumulative lifetime or working lifetime exposure in occupational settings. However, the National Commission on Radiological Protection in the US provides informal guidance that a worker's cumulative exposure should not exceed 10 mSv * his/her age in years (Shapiro, 1990, p. 338).

D. Fitting the Dose-Response Curve to Atomic Bomb Survivor Data: Why Choose the Linear Excess Relative Risk Model

Under experimental conditions and with cell lethality as the end-point, the dose-response relationship for low-LET is represented in Figure 1.6. In human populations the dose-response relationship of exposure and cancer mortality is more uncertain. For this reason, data collected from the survivors of the atomic bomb explosion in Japan has been fit to a variety of statistical model structures to determine which best represents the observed data: (1) the linear excess relative risk model (ERR), (2) L-Q, and (3) purely quadratic (Q) models (Schull *et al.*, 1990, p. 72). Figure 1.7 shows the shapes of dose-repsonse curves derived from in vitro studies of mutations

and chromosome aberration. Curve A is linear depicting the occurance of mutations in the fruit fly, *drosophila melanogaster*. Curve B depicts that chromosome aberrations are induced following a quadratic dose-response. Curve C shows that mutations arise in a linear-quadratic fashion with dose in neurospora. Finally, curve D shows that mutations and cell-killing occur in Tradescania, reflecting a linear-quadratic dose-response with cell killing at higher doses. It is cautioned that all these models are merely convenient descriptors of what is observed and may have no deep biological meaning for humans (Schull *et al.*, 1990). Cellular and molecular events may suggest a dose-response relationship under experimental conditions, but it does not follow that the same dose-response would be seen when measured in terms of case occurrence or relative risk of mortality (Schull *et al.*, 1990, p. 72).

In follow-up of the Life Span Study[6] of the ABS through 1985, there was some discussion about which model type (the linear or linear-quadratic model[7]) best fits exposure below 2 Sv (200 rem), where 2 Sv is considered low exposure in the ABS cohort. Table 1.4 indicates that for solid cancers below 2 Sv total dose, the linear and linear-quadratic models fit equally well, since the deviance values are similar (see column labeled 'deviance'). For leukemias the linear-quadratic model fits slightly better than the linear model, though not significantly so. This can be assessed by evaluating the column labeled 'deviance' (Shimizu *et al.*, 1990, p. 131). Since the linear ERR model provides the best goodness-of-fit for solid tumors, this model has emerged as the preferred model to use in studies of nuclear cohort workers. In analysis of Wing *et al.* (1991), a log-linear model was used to fit the data. It was not viewed as incorrect to use a log-linear model, and there is no biological reason against this model. It was simply not a model form comparable to those referenced above that have been employed to analyze nuclear cohort data.

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[6]The Life LSS of the ABS is the largest and most detailed source of human dose-response data on both male and female cancers (Land, 1980, p. 1200), with approximately 75,991 subjects and over 2 million person-years of follow-up since 1950. The exposure of interest is high energy gamma radiation released in large quantities at the time of explosion.

[7] Models used in recent mortality analysis of ABS cohort. L: $RR= 1+ \beta D * \exp(\alpha 1 age\ ATB + \alpha 2 sex)$; L-Q: $RR= 1+ (\beta 1 D + \beta 2 D^2)* \exp(\alpha 1 age\ ATB + \alpha 2 sex)$

Analysis of the ABS cohort data seems complex. Teams of physicians, epidemiologists, and statisticians have been studying this cohort for forty-years, first via the Atomic Bomb Casualty Commission and then through the Radiation Effects Research Foundation (RERF). The statistical models that appear in footnote 7 have evolved over the past two decades due to developments in statistical methodology and collection of empirical data from follow-up of the ABS cohort.

RERF researchers prefer use of the ERR model for three primary reasons. The linear excess relative risk model is considered a suitable descriptor of the survival data based on tests of goodness-of-fit to the observed data (Schull *et al.*, 1990). Secondly, the ERR model assumes there is no threshold below which radiation exposure is safe, and finally, the risk of cancer increases linearly with dose.

E. Results of Recent Follow-up of Atomic Bomb Survivors

The most recent follow-up of the ABS cohort through 1985 shows a significant dose response for mortality from all malignant neoplasms, leukemia, solid cancers, cancers of the esophagus, stomach, colon, lung, urinary bladder, and multiple myeloma, as previously observed in earlier mortality follow-up of this cohort. No significant increase was demonstrated for cancers of the rectum, gall bladder, pancreas, prostate, and malignant lymphoma, which were evaluated in earlier follow-up studies of the ABS. Cancers of the bone, pharynx, nose, and larynx were also examined for the first time in this follow-up interval but did not show a significant increase with dose (Shimizu *et al.*, 1990, abstract). Mortality did not increase for brain tumors but tended to increase with dose insofar as central nervous system (CNS) tumors other than brain were concerned ($0.05 < P < 0.10$). There were important differences between male and female mortality due to smoking related deaths.

In a recent study of cancer incidence (as opposed to mortality) in the ABS cohort, significant associations were found for radiation exposure and the following cancers: stomach, colon, lung, urinary bladder, and thyroid in males. There was no significant effect from radiation

exposure for cancers at the following sites: oral cavity, larynx, esophagus, rectum, pancreas, kidney and renal pelvis, or prostate (Thompson *et al.*, 1994). Table 1.5 compares the excess relative risk estimates of mortality and incidence rates in the ABS cohort.

Based on mortality studies in the ABS, it was determined that age at time of bombing (ATB) and sex are important modifiers. The highest values for relative mortality risk occurred in survivors exposed under age 10 (Shimizu *et al.*, 1990, p. 124). Consistent with this observation, those exposed to greater than 1 Gy (1 Sv) who were less than 10 years of age at the time of bombing had a shorter interval between exposure and death compared to those exposed to < 1 Gy under age 10 (Shimizu *et al.*, 1990, p. 125). This is consistent with the occurrence of cell death at high doses under experimental conditions and increased risk associated with exposure for younger children (<10 yrs) who have rapid cell turnover.

Thyroid and prostate cancers were conspicuously absent as related to dose. Previous analysis of the cohort showed that leukemia mortality peaked within 6-8 years after bombing and has declined steadily. There is evidence that radiation-induced cancers appear earlier than other cancers of the same sites among survivors exposed prenatally or within the first 10 years of life. Among the adult exposed population, evidence is lacking that radiation-induced cancers appear earlier than other cancers. Therefore, since cancers induced by radiation are indistinguishable from those occurring as background mortality, the existence of excess cancer can only be inferred on the basis of statistical excess above background between comparable age cohorts. This excess appears to be present in the ABS cohort based on mortality obtained from death certificate for the following cancers: leukemia, colon, esophagus, lung, urinary bladder, and multiple myeloma when grouping both men and women.

F. Review of Worker Populations

There has been considerable discussion about the appropriateness of applying extrapolation and lifetime risk projection procedures to populations exposed at high doses in order to determine estimates of mortality in worker populations and in subgroups of the general population. In the nuclear cohort workers, the exposure experience is very different from the the ABS cohort. In the ABS cohort the exposure was acute and very high, while in the worker cohorts exposure is over intervals of months and years and the levels are fairly low (usually less than the annual occupational limit for cumulative lifetime dose). There is still uncertainty about extrapolating from high doses to low-doses in order to set public health standards. Figure 1.8 shows that the shape of the dose-response curve at low doses can take at least two forms: linear or linear-quadratic. The same model structures to estimate mortality risk in the ABS may be used to estimate risk to low-level radiation exposure. Prior to conduct of follow-up studies of nuclear worker cohorts, effects in the low-dose region were determined by statistical assumptions and data available from high dose exposure groups like the ABS cohort to estimate exposures at low-doses.

Given uncertainties with estimating low-dose risk, numerous studies have implemented a direct assessment of mortality risk based on cohorts of workers exposed to actual exposure levels of interest. Some worker cohorts have been collapsed together for analysis in order to increase the number of person-years and deaths so that better precision of the estimated dose effect can be achieved. Another major objective for study of these cohorts is to evaluate the adequacy of risk estimates that provide the basis for radiation protection standards (Gilbert *et al.*, 1989). This review is limited to worker populations that are assumed to have had exposure to low-LET radiation, principally X-and gamma radiation and does not address populations exposed to radon gas, particles emitted from radioactive decay, or populations exposed to radiation used in medical diagnosis and treatment.

A number of groups occupationally exposed to low dose, low-LET radiation have been studied in recent years. Findings from these studies have naturally been compared to risk estimates

obtained from study of ABS. A summary of studies conducted in worker populations exposed to X- and gamma radiation are found in Table 1.5. The Hanford cohort (Gilbert *et al.*, 1993) has the largest number of male workers (n=31,500), followed by workers from the United Kingdom (UK) Atomic Energy Authority (AEA) (n=29,173) (Beral *et al.*, 1985). The smallest worker cohort is ORNL with 8318 members.

Several of the cohorts listed in Table 1.6 have been combined in order to increase precision and statistical power, and to understand the similarities and differences between earlier studies (Kendall *et al.*, 1992; IARC, 1994; Cardis *et al.*, 1995). Kendall *et al.* (1992) combined five groups from the UK into a registry of radiation workers (n= 87,522). The International Agency for Research on Cancer (IARC) recently published a combined analysis of worker cohorts in the US and UK including 95,673 workers and 2,124,256 person-years of follow-up (IARC, 1994). The registry cohort is larger than the ABS cohort which has 75,000 men and women and over 2 million person-years of follow-up. In general, many of these cohorts have similar eligibility criteria and follow-up periods (mid-1940's through mid-1980's), although total cancer deaths and person-years of observation differ between each study.

Many of these worker studies (both individual and combined analyses) follow the same methodology used to analyze data from the ABS. Similarities are: (1) the empirical induction period, (2) variables and levels of stratification, (3) statistical model to fit observed data, and (4) use of an internal comparison group.

The EIP used in the ABS cohort studies are 2-years for blood cancers, since mortality from leukemia in this cohort peaked by the late 1950's. Cancers that occur as solid tumors have an induction period of 10 years or more. Because of the differing EIPs, analysis of total cancers are usually grouped as 'solid cancers of all types' and 'solid cancers of all types excluding leukemia'. In analysis of the ORNL cohort, Wing *et al.* (1991) provide an EIP of 0, 10, and 20 years for solid tumors as well as leukemias.

Secondly, many results were stratified by age, calendar year, sex, and paycode. Studies by Gilbert *et al.* (1993(a)(b)) generally stratify by both 5-year and single year intervals for age (in the

same analysis), as well as 5-year intervals for calendar year, number of years monitored and a measure of socio-economic status. Kendall *et al.* (1992) stratified by age and calendar year intervals, gender, facility, and social class. Beral *et al.* (1988) also stratified by agerisk and social class, and yearrisk singly and in seven 5-year intervals. For some analyses stratification by duration of employment and years since recruitment were performed (Beral *et al.*, 1988, p. 760). Beral et al. (1985) stratified by age, sex, social class, calendar year and facility but did not specify the intervals. Smith and Douglas (1986) stratified by agerisk and yearrisk in 5-year intervals, and industrial code. Gribbin *et al.* (1993) used agerisk, yearrisk, and length of follow-up in five year intervals for stratification.

Third, many studies use a statistical model to fit the observed data that is the same as the model used to fit data from the ABS cohort, namely the linear ERR model (Gribbin *et al.*, 1993; Kendall *et al.*, 1992; Gilbert *et al.*, 1989; Gilbert *et al.*, 1993; and Smith and Douglas, 1986). This approach attempts to identify whether risk estimates from low dose worker exposure correspond to mortality risks estimated from high dose exposure, such as risk estimates obtained from the ABS. Table 1.5 summarizes findings reported for excess relative risk. Not all studies use the preferred analytic approach, but nevertheless, an estimate for excess relative risk of mortality can be obtained.

Upon examination of the percent increase per 10 mSv, a strong increase in mortality risk is not observed when grouping all cancers. Results of this type model structure are interpreted as the percentage increase (or decrease) in 'excess relative risk' per 10 mSv for all cancer sites. (It should be noted that the relative risk of mortality per Sv is the same as the percentage risk per 10 mSv). Wing *et al.* (1991) used a purely log-linear model structure. While some studies employ the linear ERR model structure and Wing *et al.* employs a log-linear model, Gilbert *et al.* (1993) has argued that the two structures should yield similar results due to low exposure in the worker cohorts. While Gilbert *et al.* (1993) have not elaborated on the reasoning for this statement, it would be plausible, since divergence in estimates would occur at higher doses.

Assume for the sake of this review that model structure does not make a difference in mortality risk. Beral (1988) shows the highest ERR estimate from mortality for cancers of all types (8.1%; 95% CI=4.0, 20.2), which deviates from mortality estimates in other worker populations. The trend was almost entirely confined to workers who were monitored for exposure to radionuclides, the main contribution coming from lung and prostate cancers. Wing *et al.* (1991) exhibits the second highest estimates of mortality risk, a 3.27% excess relative risk per 10 mSv increase in exposure. Smoking has been suggested to explain the excess found in Wing *et al.*, 1991 (Gilbert, 1992, p. 260).

While all cancers as a group generally show no increase in mortality risk, evaluation of specific cancers shows much greater cancer mortality risk. In the Hanford cohort with follow-up through 1981 (Gilbert *et al.*, 1989), a worker had a 55% (90% CI=14, 250) ERR of dying from multiple myeloma per 10 mSv increase in exposure compared to workers who were considered unexposed. Kendall *et al.*, 1992 reports a 6.9% (90% CI= -0.03, 46.0) increase in ERR for multiple myeloma, while the other worker populations previously studied demonstrate ERR estimates that are less than 1%. There was only one death from multiple myeloma in the ORNL cohort.

For leukemia, Wing (1991) and Kendall (1992) show an increase in ERR of 6.9% (no 95% CI provided) and 4.3% (90% CI= 0.4,13.6; lag=2), respectively, per 10 mSv increase in exposure. In a recent IARC study, the ERR for leukemia excluding chronic lymphocytic leukemia was 2.2% per 10 mSv (90% CI=0.1, 5.7; p=0.05)(IARC, 1994). In general, results for specific cancer outcomes using ERR expressed as a percentage change per 10 mSv increase in exposure are not consistent across studies. Given the differences in cohort size, person-years, and exposure levels (as well as potential for misclassification) this is not surprising.

Analysis of observed to expected deaths with an increase in cumulative exposure using a test for trend reveals some similarities between studies with certain outcomes. Gilbert (1989) and Smith (1986) reported a statistically significant trend from multiple myeloma using a 10- and 15 year EIP, respectively. Kendall (1992) and Smith (1986) reported a significant dose-response

trend for leukemia using a 2- and 15-year EIP, respectively. In summary, multiple myeloma and leukemia are elevated in two cohorts, Hanford and UK Radiation Workers as a group.

G. Limitations of Existing Data

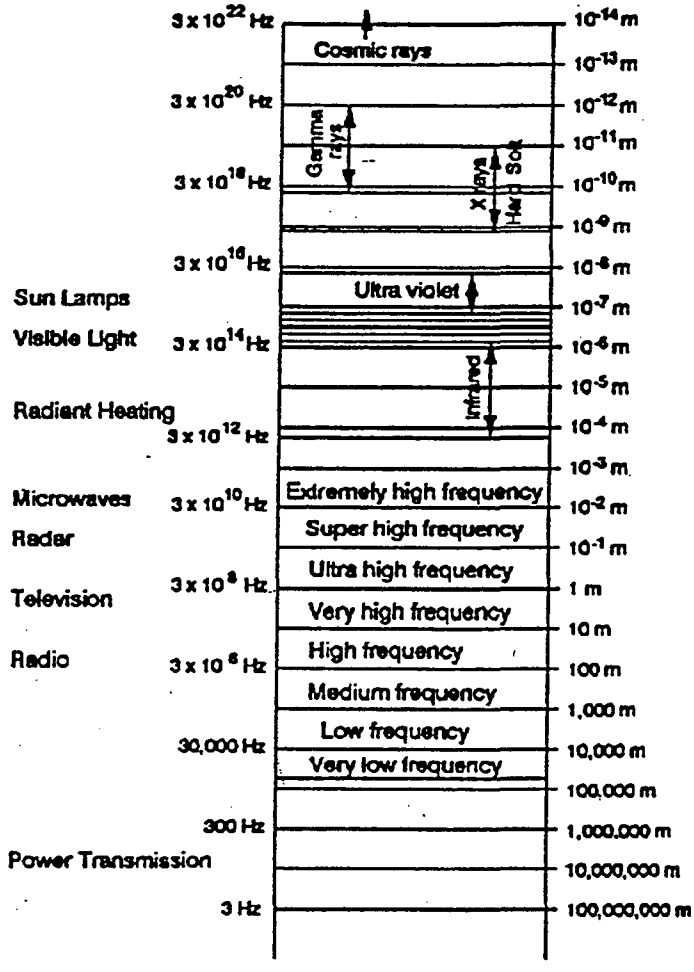
A number of limitations can be found in the epidemiologic data from ABS studies and occupational studies. The radiation effects of human populations exposed to less than 50 mSv (5 rem) are difficult to demonstrate and quantify primarily due to: (1) uncertainty in dosimetry, especially as related to early recorded doses; (2) misclassification of disease status on death certificate; (3) separating effects of external gamma radiation from effects due to chemical agents in the workplace; (4) making assumptions about the correct EIP for different organ sites; (5) absence of incorporating mechanisms for cellular repair in estimating risk; (6) lack of ability to detect effect due to small sample size coupled with low exposure; (7) unknown individual susceptibilities such as immune status, genetic characteristics, or hormonal influences; and (8) difficulty differentiating cancers induced by external radiation from those that occur from other causes in these worker populations. Bias introduced by the limitations listed in one through seven may be distributed randomly in both the exposed and unexposed groups. However, if the healthy worker effect was operating in this cohort, bias could operate toward the null, underestimating mortality risk from exposure.

One aspect of investigation that seems apparently absent in analysis of the ORNL cohort study is consideration of time-related factors unique to each worker. Since there is a historical context which dictated how many workers were hired or terminated, and their levels of exposures (degree of protection provided), it would seem prudent to consider these factors as covariates in analysis. In a combined analysis of three DoE facilities, Gilbert and colleagues (1993) note that mortality risk estimates at ORNL differ by subgroups and that these differences are related to age in a manner that is not well understood. Gilbert *et al.* (1993) suggest analyses addressing the modifying effect of factors such as age at exposure, time since exposure, calendar period of

exposure, age at risk, birth cohort, and calendar year at risk (p. 418). Thus, the emphasis is on time-related factors in the current analysis.

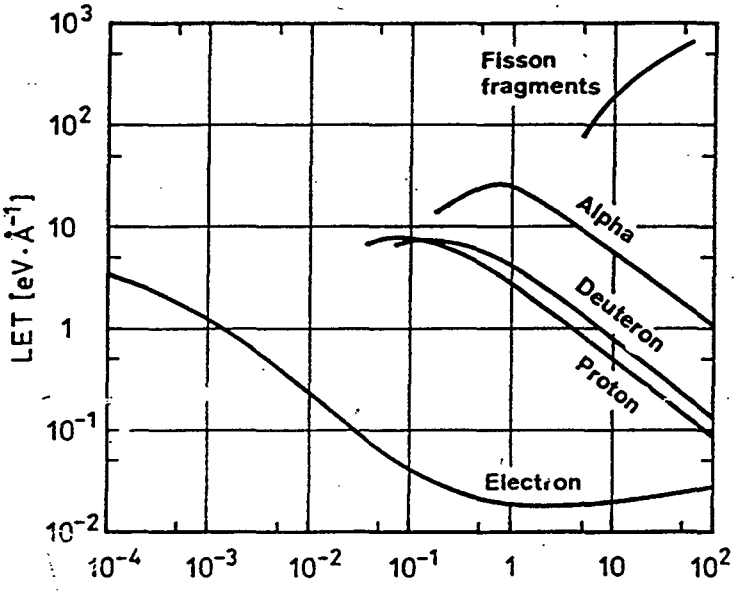
Figure 1.1

The Electromagnetic Spectrum and Commerical Uses of Wavelengths



(Adapted from: EPRI, 1989)

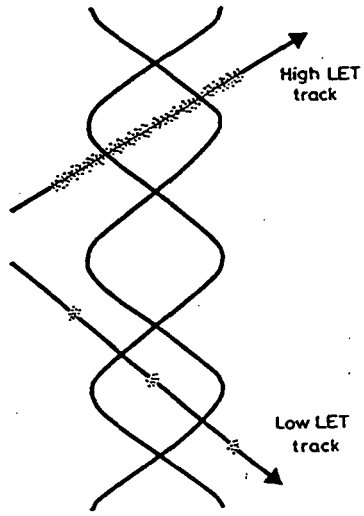
Figure 1.2



LET Values as a Function of Photon Energy

(Adapted from: von Sonntag, 1989, p. 10)

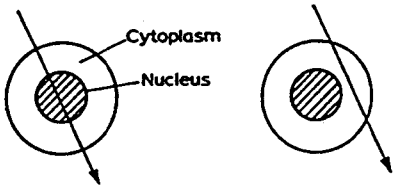
Figure 1.3



Spatial representation of low and high LET radiation traversing a section of the DNA helix.

(Adapted from: Adams, 1989; In: The Biological Basis of Radiotherapy. GG Steel, GE Adams, and A Horwich, editors; 1989, p. 9).

Figure 1.4



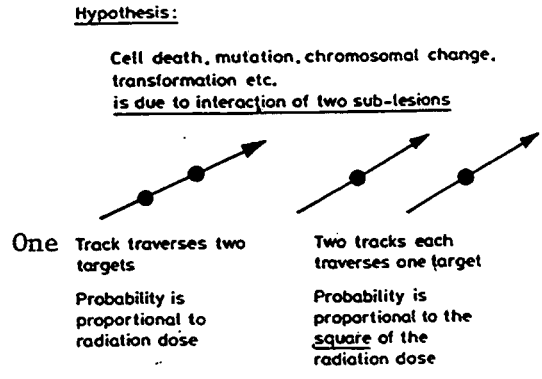
Radiation must pass through the nucleus of the cell to cause

mutation, cell death, cancer

Importance of the cell nucleus as a radiation target.

(Adapted from: Adams, 1989; In: The Biological Basis of Radiotherapy. GG Steel, GE Adams, and A Horwich, editors; 1989, p. 6).

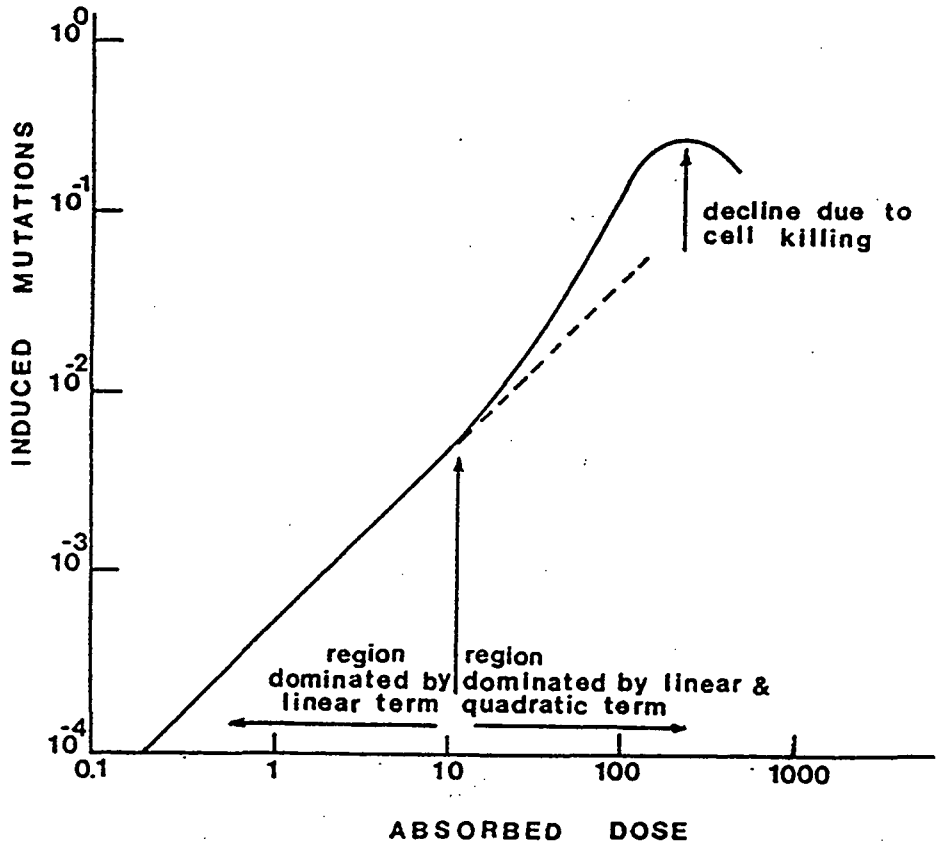
Figure 1.5



Illustrating the theory of dual radiation action.

(Adapted from: Adams, 1989; In: The Biological Basis of Radiotherapy. GG Steel, GE Adams, and A Horwich, editors; 1989, p. 11).

Figure 1.6

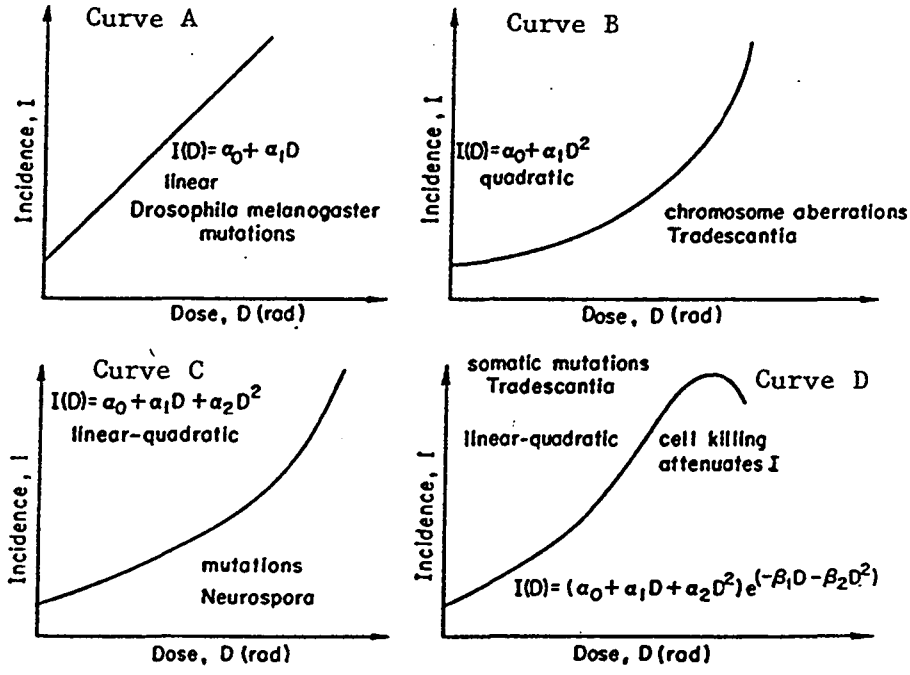


A typical dose-response curve for induction of mutations (a stochastic effect). The initial part of the curve from 0-10 rem is dominated by the linear component of αD. The quadratic component αD^2 dominates between 10 and 200 rem where the curve becomes steeper (bending upward). After 200 rem cell killing is significant with decline of mutation induction since the number of surviving cells capable of expressing mutations is reduced.

(Adapted from: Awwad HK, 1990, p. 12)

Figure 1.7

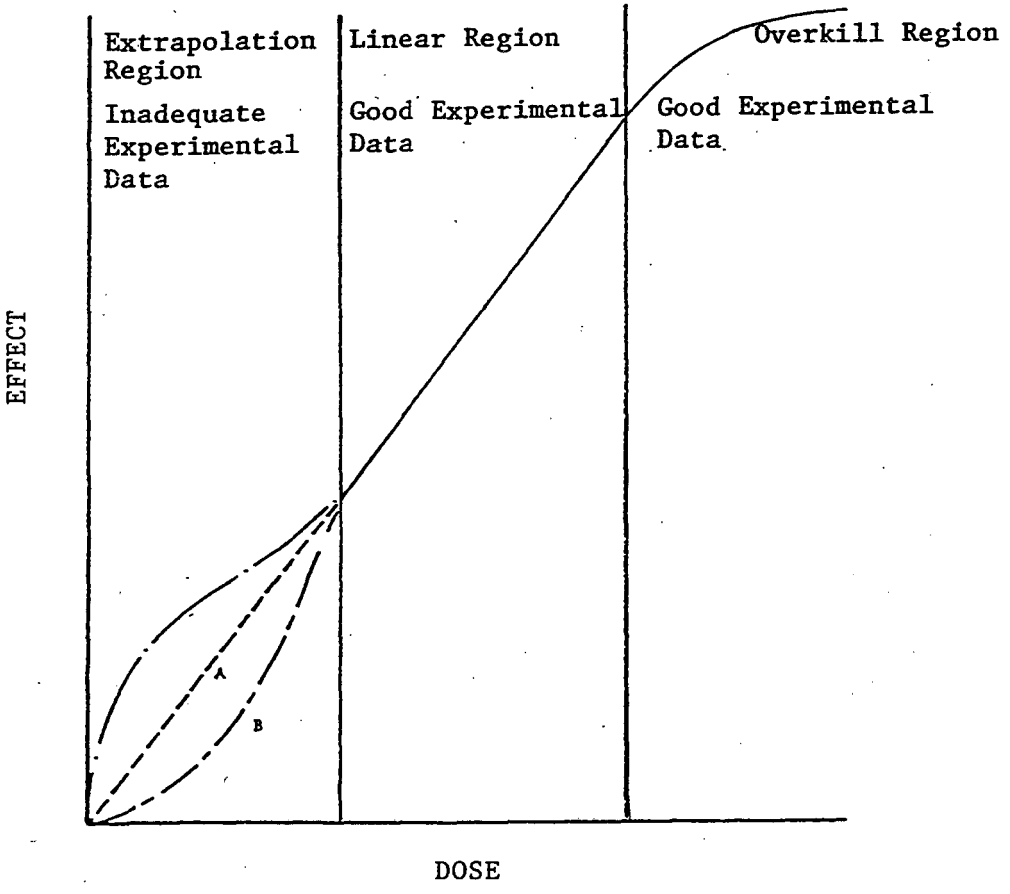
Shapes of Dose-Reponse Curves from Experimental Studies



(Adapted from: NIH, 1979)

Figure 1.8

Dose-Response Curve for Radiation Exposure Indicating Possible Extrapolation Curves for Low-Dose Region



(Adapted from: NIH, 1979)

Table 1.1

Time Domains of Radiation Action in Biological Systems as Related to Gamma Radiation Exposure

Physical stage:	
10^{-18} to 10^{-17} s	Fast particle traverses small atom or molecule
10^{-16}	Ionization $H_2O \rightarrow H_2O^+ + e^-$
10^{-15}	Electronic excitation $H_2O \rightarrow H_2O^*$
10^{-13}	Molecular vibrations and dissociation
10^{-12}	Rotation, relaxation and solvation of the electron in water
Chemical stage:	
10^{-10} to 10^{-7} s	Reactions of e^-_{aq} and other free radicals with solutes in radiation tracks and spurs
10^{-7}	Homogeneous distribution of free radicals
10^{-3}	Free-radical reactions largely complete
Seconds, minutes, hours	Biochemical changes (enzyme reactions)
Cellular and tissue stages:	
Hours	Cell division inhibited in microorganisms and mammalian cells; reproductive death
Days	Damage to gastrointestinal tract (and central nervous system at high doses)
Months	Haemopoietic death; acute damage to skin and other organs; late normal-tissue morbidity
Years	Carcinogenesis and expression of genetic damage in offspring.

(Adapted from: Adams, 1989; In: The Biological Basis of Radiotherapy. GG Steel, GS Adams, and A Horwich, editors; 1989, p. 2)

Table 1.2

Interconversions of Some Commonly Used Units in Radiation Research

Radiation-physical quantities	*Unit*			*Conversion to other systems*
Activity	bequerel	Bq	(s^{-1})	1 curie (Ci) = $3{\cdot}7 \times 10^{10}$ Bq
Absorbed dose	gray	Gy	($J\ kg^{-1}$)	1 rad = 0·01 Gy
Dose equivalent	sievert	Sv	($J\ kg^{-1}$)	1 rem = 0·01 Sv
Energy	joule	J	(N m)	1 eV = $1{\cdot}60 \times 10^{-19}$ J
				1 cal = 4·18 J
Power	watt	W	($J\ s^{-1}$)	
Electric charge	coulomb	C		
Radiation-chemical yield	*G* value		($mol\ J^{-1}$)	1 molecule $(100\ eV)^{-1} \triangleq 1{\cdot}036 \times 10^{-7}$ mol J^{-1}
Exposure			($C\ kg^{-1}$)	1 röntgen = $2{\cdot}58 \times 10^{-4}$ C kg^{-1}
Dose rate			($Gy\ s^{-1}$)	

(Adapted from: von Sonntag, 1987, p. 18)

Table 1.3

Summary of Dosimetry Measurements for Gamma Radiation Exposure*

Quantity:	**Units:**	**Comment:**
Absorbed Dose	100 rad= 1 Gray (Gy) 10 rad=0.1 Gy 1 rad=0.01 Gy 1 rad=10 mGy 1 millirad=1/1000 rad	'rad' means Radiation Absorbed Dose Absorbed dose is multiplied by a quality factor to produce dose equivalent. Quality factor (Q) for gamma radiation is 1.0
Dose Equivalent		
	1 rad=1rem 1Gy = 1 Sievert (Sv) 100 rem=1 Sv 10 rem=0.1 Sv 1rem=0.01 Sv 1rem=10mSv 1rem=1 centiSievert (cSv) 1rem= 1/100 Sv 1 millirem= 1/1000rem 1000 millirem= 1 rem	'rem' means Roentgen Equivalent in Man Dose equivalent takes into account absorbed dose plus effect of radiation to produce biologic damage. 'rem' is recoded to Sv in current analysis 'mrem' is recoded to 'rem' in current analysis 'mrem' is historical unit to record dose at ORNL

* For Gamma radiation 1 Gray x Q = 1 Seivert, where Q=1.0

Table 1.4

Comparing Goodness-of-Fit between Models,
Results of Linear (L) and Linear-Quadratic (LQ) Model-Fitting
for Mortality in Atomic Bomb Survivors

Dose 0-2 Sv	Model(a)	Dose Coefficient beta1	beta2	Goodness-of-Fit deviance	*df*
Solid Cancers					
	L	2.79	na(b)	917.5	1005
	LQ	2.42	0.00042	917.3	1004
Leukemias					
	L	16.27	na	396.8	1005
	LQ	8.16	0.0084	394.5	1004

(a) see foonote 7: linear model (L) is RR = 1 + b1D*exp(a1ageATB + a2sex)
linear quadratic (L-Q) model is RR = 1 + (b1D + b2D2) * exp(a1ageATB + a2sex).
'ageATB' means age at time of bombing.
(b) 'na' means 'b2' term is not applicable and not in model.

Table 1.5

Comparison of Atomic Bomb Survivor's (ABS) Cancer Incidence and Mortality Risk Estimates with Other Radiation Exposed Populations*

Cancer Site	ABS(a) Incidence ERR/Sv 95% CI	ABS (b) Mortality ERR/Sv 90% CI	Other Studies
Oral cavity	-0.09-0.93	NR	RR=1.7 for exposed cervical cancer patients
Salivary gland	0.15-6.04	NR	Increased risk in patients receiving head and neck radiotherapy or dental X-rays
Esophagus	-0.21-1.04	0.13-1.24	Increased risk in spondylitis patients
Stomach	0.16-0.50	0.14-0.43	Increased risk in peptic ulcer patients
Colon	0.29-1.28	0.39-1.45	Increased risk in some studies of women with benign gynecological disorders and ovarian cancer patients
Rectum	-0.17-0.75	NE-0.27	Not increased in most major studies
Liver	0.16-0.92	-0.13-0.70	Large excess risk after thorotrast exposure
Gallbladder	-0.27-0.72	-0.02-0.96	Not increased in most major studies
Pancreas	-0.25-0.82	NE-0.23	Not increased in most major studies
Lung	0.60-1.36	0.25-0.72	Increased in cervical cancer patients, spondylitis patients and uranium miners
Nonmelanoma skin	0.41-1.89	NE-2.47	Increased in children receiving head and neck radiotherapy
Breast	1.09-2.19	1.56-3.09	Increased risk in most studies
Uterus	< -0.29-0.10	0.01-0.50	Not increased in most major studies
Ovary	0.12-2.34	0.37-2.86	Increased risk in some studies of women with benign gynecological disorders
Prostate	-0.21-1.16	NE-0.73	Not increased in most studies
Bladder	0.27-2.08	0.40-2.28	Increased risk in most studies of women treated with large doses of pelvic radiation
Nervous system	< -0.23-1.27	NR	Increased risk in most studies of irradiated children
Thyroid	0.48-2.14	NR	Increased risk in most studies of external radiation in childhood
Total Solid tumor	0.52-0.74	0.23-0.36	

* Adapted from Thompson et al., 1994, p. S30

NR= not reported; NE= not estimable

(a) Thompson et al., 1994, p. S30

(b) Shimizu et al., 1990

Table 1.6: Occupational Cohort Studies of Workers Monitored for External Radiation

Study Site	Operation	Eligibility	End of Follow-up	Number Enrolled (m)ale/(f)emale	Number Monitored	Mean Dose (mSv)	Number Cancer Deaths	Number Person-Years	Percent (a) Increase Per 10 mSv
Oak Ridge National Lab (Ch85)	Reactor research, Plutonium Production	1943-1972	1977	8,375 m	6,213(c)	17.3	194	164,004	0.1(j)
Oak Ridge National Lab (Wi91)	Reactor research, Plutonium Production	1943-1972	1984	8,318 m	6,189(c)	17.3	346	215,680	3.27 1.26, 5.28 (i)
Hanford Site (Gi89)	Reactor research and development	1944-1978	1981	31,500 m 12,600 f	36,235 (b)(c)	NA	1603	413,394	-0.4 -1.9, 1.6
Hanford Site (Gi93)	Reactor research and development	1944-1978	1985	31,486 m 12,668 f	32,643 (b)(c)	26.2	2195	633,511	-0.15 <0, 1.0
UK Atomic Energy Authority (AEA)(Be85)	Reactor research and development	1946-1979	1979	21,173 m 10,373 f	20,382(d)	32.4 (g)	827	638,834	1.25
British Nuclear Fuels, UK (Sm86)	Plutonium production, fuel reprocessing	1947-1975	1983	11,402 m 2,598 f	10,157(d)	124(e)	572	303,547	1.7 -3.0, 7.0 (h)
UK Atomic Weapons Establishment (AWE)(Be88)	Atomic weapons defense research	1951-1982	1982	17,178 m 5,374 f	9,389(d)	7.8(g)	865	145,715	8.1 -4.0, 20.2
UK National Registry of Radiation Workers (Ke92)	Combination nuclear energy, defense research	variable	1988	87,522 m 7,695 f	36,272(b)	33.6 (g)	1,828	NA	0.47 -0.12, 1.2 (l)
Atomic Energy of Canada, Ltd. (AECL)(Gr93)	Reactor research non-defense	1956-1980	1985	8,977m	4,260	15	227	157,101	0.36 -0.46, 2.45

Table 1.6 (continued)

Study Site	Operation	Eligibility	End of Follow-up	Number Enrolled (m)ale/(f)emale	Number Monitored	Mean Dose (mSv)	Number Cancer Deaths	Number Person-Years	Percent (a) Increase Per 10 mSv
IARC(Ca95)(k)	Combination	variable	variable	81,745 m 13,928 f	95,673	40.2	3,976	2,124,526	-0.02 -0.34, 0.35) (l)

Notes to Table 1.5 : Occupational Cohort Studies of Workers Monitored for External Radiation

(a) Percent increase in all cancer mortality per 10 mSv increase in external penetrating dose using an internal comparison groups and various EIP assumptions;
95% Confidence Intervals where provided by the authors.
(b) number of workers monitored for external radiation for 6 months or more;
(c)cannot separate those unmonitored from those monitored with zero dose.
(d) workers with a radiation record.
(e) demonminator includes only exposed workers
(f) letter 'f' omitted so not to confuse with 'f' for female.
(g) includes neutron exposure
(h) Based on national mortality rates; no internal comparison group
(i) calculated as cited in Gribbin et al., 1993
(j) Confidence Interval and standard error not provided.
(k) Seven cohorts in the IARC combined analysis include: Hanford, Rocky Flats, ORNL Sellafield Plant of British Nuclear Fuels, UK Atomic Energy Authority, UK Atomic Weapons Establishment, and Atomic Energy of Canada, Ltd.
(l) 90% Confidence Interval
NA= not available

CHAPTER 2

DESCRIPTION OF THE OAK RIDGE COHORT

I. BACKGROUND AND HISTORY OF OAK RIDGE NATIONAL LABORATORY

A. Motivation for ORNL Construction

The drama of the World War II era invites one to gain an appreciation of the context of ORNL in 1943. In 1939 two German chemists discovered nuclear *fission* in *uranium* (U), opening the way for production of weapons of mass destruction (Johnson and Schaffer, 1994, p. 7). Subsequently, US government activity in nuclear weapons research began in 1939. At Columbia University, in March 1940, it was demonstrated that fission occurs more readily in the isotope U-235 than in U-238, but only in 1 out of 140 U atoms was the 235 isotope present. Using cyclotrons at the University of California, Berkeley (UCB) in 1940, Edwin McMillian and Philip Abelson discovered the first transuranium element, number 93 on the Periodic Table. They named it Neptunium. A year later Glenn Seaborg and colleagues, also at UCB, discovered element 94 (the decay product of the newly synthesized number 93) naming it plutonium (Pu) (in the planetary sequence Uranus, Neptune, Pluto), and demonstrated its fissionability (Johnson and Schaffer, 1994, p. 9).

The implications of this were that the less common U-235 could be separated from the more common U-238 for weapons use, and U-238 could be bombarded with neutrons - in a nuclear reactor - to produce plutonium (Pu) that could be chemically extracted for weapons production. Pu is chiefly an alpha emitter. Massive and highly charged, alpha particles present little threat outside the body; even a sheet of paper will block them. However, inside the body Pu deposits in the bone.

B. ORNL Within the Oak Ridge Reservation Complex

Shortly after the Japanese attack on Pearl Harbor on December 7, 1941, century-old family farms and cross-road communities in rural Tennessee became the Oak Ridge reservation. In early 1942, the Army Corp of Engineers identified a fifty-nine thousand-acre swatch of land in eastern Tennessee between Black Oak Ridge to the north, the Clinch River to the south, and 25-miles west of Knoxville, TN to serve as one of the three sites nationwide for development of pilot-testing facilities for the production and separation of Pu to produce the atomic bomb (Figure 2.1). President Roosevelt had assigned the US Army responsibility for managing plant construction for the separation of U and Pu.

Back in California, by mid-1942, Glenn Seaborg's chemical research group had developed a process to separate micrograms of Pu from U irradiated in cyclotrons. Producing sufficient amounts of Pu necessitated construction of large reactors that operated at high power levels, thus releasing a great deal of heat and radiation (Johnson and Schaffer, 1994, p. 14).

Thousands of scientists, engineers, and workers swarmed into Oak Ridge, TN to build and operate three huge facilities that would change the history of the world forever (Johnson and Schaffer, 1994, p.2). On the reservation's western edge rose K-25, the gaseous diffusion plant. The purpose of K-25 was to separate U-235 from U-238 using a gaseous diffusion process. U-235 is an isotope suited for achieving continuous nuclear fission. On its northern borders, near the town of Oak Ridge, the Y-12 plant used an electromagnetic method to separate U-235 from U-238. Near the reservation's southwest corner, about 10 miles from Y-12, the third plant, X-10, was located (Johnson and Schaffer, 1994, p.3). Workers from X-10, a code name for the Oak Ridge National Laboratory, are the subject of this cohort analysis.

Built between February 1, 1943 and November 1943, X-10 was much smaller than K-25 or Y-12. As a pilot plant for the larger Pu plant built at Hanford, Washington, X-10 used neutrons emitted in the fission of U-235 to convert U-238 into Pu-239. Originally, X-10 was referred to as

Clinton Laboratories, named after a nearby county seat. In 1948 Clinton Laboratories was renamed Oak Ridge National Laboratory (ORNL), just one facility in the Oak Ridge reservation (Johnson and Schaffer, 1994, p. 5).

To speed up construction during the war effort, in January 1943, DuPont was contracted to build and operate ORNL and the full scale reactors to be built later at Hanford. In March 1943, construction began on the six hot cells composed of thick concrete walls, for Pu and fission-product separation. Because DuPont was also constructing Y-12 and K-25 plants, there was some difficulty recruiting enough workers to each of the facilities. Just at the X-10 plant, during the summer of 1943, about 3,000 workers completed 150 buildings at a cost of $12 million dollars using 4,500 gallons of paint and 30,000 cubic yards of concrete among other materials (Johnson and Schaffer, 1994, p.19). Wartime employment leveled off at 1,513 in 1944. Some workers were DuPont personnel relocated from DuPont ordinance plants across the US.

By October 31, 1943, the industrial-scale graphite reactor at ORNL was completed. Thousands of U slugs were inserted into the reactor. The sequence involved loading a ton or two of U, withdrawing control rods to measure the increase in neutron flux, reinserting the rods into the reactor, loading another batch of U, then stopping again to assess the neutron activity levels, each time attempting to estimate when the reactor would achieve a self-sustaining chain reaction. Some 30 tons of aluminum-coated U slugs were continually added to the reactor until fission occurred, a process that took less than 24 hours. Near the end of November 1943, the graphite reactor at ORNL discharged the first U slugs for chemical separation. By the end of 1943, chemists had extracted 1.54 milligrams of Pu from the slugs. Subsequent production was made more efficient so that 90% of the Pu in the slugs was recovered and shipped to Los Alamos, NM (Johnson and Schaffer, 1994 p. 23). The major exposures were to high energy gamma radiation and some neutrons. The graphite reactor eventually provided an abundant supply of neutrons for physics research, and produced radioactive isotopes for medicine.

C. Reactor Research

By early 1945, when Pu separation ceased at X-10, the graphite reactor had produced a total of 326.4 grams of Pu. One month before the bomb was dropped in 1945, Monsanto became the contractor operating the ORNL, replacing DuPont. After the war the Army transferred government oversight and management of the national laboratories to the Atomic Energy Commission (AEC) (Johnson and Schaffer, 1994, p.29). In late 1947 operation of ORNL was transferred to Union Carbide (Johnson and Schaffer, p.54). In order to diversify and strengthen ORNL's research efforts, the Y-12 Research Division was merged with ORNL in February 1950. In the early 1950's, metal experts were employed to design ways to fabricate reactor components to withstand high temperature and radiation stress (Johnson and Schaffer, p. 37). By 1952 ORNL had three reactors operating, two nearing completion and several others in various stages of planning (Johnson and Schaffer, p. 75). New reactor types were designed, such as a high neutron flux reactor. The proto-type reactors built at ORNL served as the proto-type for light-water reactors that would propel naval craft and generate commercial power (Johnson and Schaffer, p. 33). For example, planes were anticipated to fly 12,000 miles at 450 miles per hour without refueling (Johnson and Schaffer, p.60). Nuclear reactor development reached a pinnacle in 1956 and began a slow descent in 1957 with cancellation of the Navy's aircraft reactor program.

After successful completion of the first aqueous homogeneous reactor in 1954, ORNL had troubles with its second experimental homogeneous reactor, which was the site of an accident in 1956. The reactor was intended to convert thorium into U-233 to supplement a dwindling supply of U-235 (Johnson and Schaffer, 1994 p. 98). By 1953, laboratory personnel numbered more than 3,600, which was more than double the wartime peak. In 1956 the ORNL staff reached 4,369. With the aircraft reactor cancellation in 1957 (Johnson and Schaffer, 1944, p.76), staffing was cut to 3,943. The 1957 reduction would have been deeper if the laboratory had not absorbed some people into the molten-salt reactor, gas-cooled reactor, and Sherwood fusion programs (Johnson and Schaffer, 1944, p. 96).

D. Other Research Activities During the 1950's

Accelerator research also began to isolate sub-atomic particles and research heavy particle reactions involving protons. This was the era of hydrogen bomb development (Johnson and Schaffer, 1994, p. 68). A cyclotron became operational in 1952 to study if a hydrogen bomb would ignite nitrogen in the atmosphere. Efforts were also underway to construct a plant to reprocess nuclear fuel using a solvent-extraction process, eventually the standard model worldwide for reprocessing spent nuclear fuel (Johnson and Schaffer, 1994, p. 33). Recovery, separation, and extraction - the primary components of fuel purification of U and Pu - were big business at ORNL during the 1950's, which included the technology to recover U from waste tanks.

Radioisotopes produced by the graphic reactor for biological and industrial research became the most publicized activity of the Lab in the post-war era. Today radioactive isotopes for medical diagnosis and therapy are still produced at ORNL. Health physics and genetic research activities related to radiation damage expanded or began in the post-war era (Johnson and Schaffer, 1994, p. 73).

E. Research Activities During the 1960's

In the 1960's the laboratory became involved in nuclear-powered studies for the national space program, even though nuclear-powered transportation research essentially ended when the Navy canceled its contract in 1957.

By the 1960's, ORNL broadened its scope beyond nuclear reactor and fission research into environmental restoration, disposal of radioactive material and information science, a desalination project and studies of radioactivity on ecology, soil, and water. In 1967 small plots of land at the laboratory were intentionally treated with cesium-137, to observe the environmental effects of weapons fallout. The grounds on which the cesium was released are still contaminated today (Johnson and Schaffer, 1994, p. 117). By the late 1960's the Biology Division had become the largest division at ORNL employing 450 people.

During this era, X-10 became the premier place for separating and producing transuranic elements (Johnson and Schaffer, 1994, p. 129). In 1965 a new transuranium reactor was completed at X-10 to produce elements heavier than U at the open end of the Periodic Table (Johnson and Schaffer, 1994, p.131). This reactor replaced the high-flux isotope reactor which had produced isotopes for medical use and industry research for 25 years (Johnson and Schaffer, 1994, p. 132).

F. ORNL in the 1970's, 1980's and 1990s

During the 1970's and 1980's, ORNL continued to expand research in the area of life sciences and environmental toxicology. Methods for reclaiming contaminated land were being developed. In the 1980's mathematics and computer science became another area of importance for research and application.

Currently, Martin-Marietta is the operating contractor at ORNL. ORNL still produces radioisotopes for medical use. A large research effort is underway to restore the environment around ORNL and safely dispose of radioactive waste and other hazardous materials. ORNL also has been active in the Human Genome Initiative to sequence human DNA. Finally, ORNL has been active in developing new and stronger materials for use in industry, defense, and space exploration. In short, ORNL continues to build on its old strengths to undertake large scale, complicated projects that address broad national concern.

II. MEASUREMENT AND SUMMARY OF RADIATION DATA AT ORNL

A. Dose Aggregation: Inclusion, Exclusion, and Summarization

The primary exposures in the ORNL (X-10) cohort were from gamma radiation emitted from the decay of U released in the reactor and some to the atmosphere during the fission process[4] Radiation records were first reviewed and summarized for a human health study of the worker population in 1964, hereafter called the Mancuso study (Mancuso, AEC Contract No. At-(30-1)-3394). Radiation data were accumulated for persons who were employees of ORNL as determined from payroll number assignments. Two types of dose data were excluded: (1) dose data for non-ORNL employees, and (2) dose data for ORNL employees who were not on the ORNL payroll (Hart, 1966, p. 1). It is unknown how many exclusions there are based on these criteria. The absence of monitoring data in a personnel folder during the time when the employee was on the ORNL payroll was construed to mean that the individual was not monitored and that he was not subject to radiation exposure. Before 1951, only employees working in areas where exposure was known to occur were monitored.

Individual daily or weekly readings taken from a card file were summarized on an adding machine into an annual total for each worker. Mancuso first summarized these annual totals on an "External Radiation Dose Summary Worksheet", hereafter referred to as the Mancuso worksheet, as part of the DoE health effects program. The worksheet included (a) the badge number assigned to the employee, (b) the initials and the name of the person monitored, (c) dates of hire and termination, (d) dose data summarized for each year monitored in terms of a "superficial dose" (DS) and a "whole body" dose (DC). Dose data collected after 1960 were not aggregated and manually recorded on the Mancuso worksheet, but summarized by computer.

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[4] Discussion of dosimetry does not include two other sites at the Oak Ridge reservation, K-25 or Y-12, since both had different types of exposures and dates for start of monitoring than X-10.

Instruments for dosimetry changed several times between 1943 and 1975 when the thermoluminescent dosimeter (TLD) was introduced. The next sections summarize dosimetry practices at ORNL.

B. Data for the Year 1943: Pocket-Chamber

Recording of monitoring data during 1943 began in October and ended on December 25, 1943. The only meter issued (or available in sizable quantities) during 1943 was a pencil-type ionization chamber, also called a pocket meter (PC). PCs were read and recorded daily and issued in sets of two for each worker. Two were issued since the PC required an electrical charge to work, had to be read from a separate device and was sensitive to shock and moisture (Hacker, 1987, p. 36). The PC was calibrated with a *radium* (Ra) gamma source and had a range of 0 to 200 mrad or 2 mSv (0.2 rem), readable in increments of 5 mrad. Threshold sensitivity on the early ionization chamber was not available, but could be compared to a later model, where specifications were known. The later Model 352 was known to be sensitive to beta radiation above 1 MeV. Gamma radiation between 0.08 and 0.2 MeV could be detected with about 10% error. Above 0.2 MeV the device measured gamma radiation of mixed energies equally well and would not differentiate between beta radiation above 1 MeV and/or gamma radiation (Hart, 1966, p. 4).

Where PC entries were the basis for a value appearing in the yearly total, the lower reading was considered the more significant reading and it was the lower reading in a pair that was computed in the dose. In a book about the history of radiation protection, Hacker (1987, p. 36) stated that personnel in the health division at ORNL considered the lower reading as correct "since all errors increased apparent exposure." The PC was prone to error in readings because it was sensitive to moisture and shock required electrical charging (Hacker, 1987, p. 36). Where off-scale readings (high exposure scale) were recorded, the off-scale entry was incorporated in the computation of dose only when an estimated dose could be derived from explanatory memoranda included in a worker's file (Hart, 1966, p. 4). In all other cases, the off-scale readings was assumed

to represent a "bogus" reading (Hart, 1966, p. 4). Hart does not say what exposure value was assigned if the dose could not be estimated.

C. Data for the Years 1944 Through 1960

The pocket chamber meter was used the first half of 1944. Then a film badge was introduced in the second half of 1944. Metering data recorded for the period beginning June 26, 1944 are based primarily on film meter data and recorded, not on a worker's individual worksheet but on a 'Kardex Card'. Memoranda found in worker's file and/or supplemental metering data were utilized where applicable in evaluating or computing the dose. Film badges were evaluated weekly June 1944 until July 1956, when quarterly readings were initiated.

It was believed that the PC readings were more reliable than the film badge before June 25, 1944, although the film meter was first issued about May 1, 1944. The film meter issued after about May 1, 1944 consisted of a case film packet allowing two density readings, a 'window' reading and a 'shield' reading. Like the PC, the film meter involved calibration for detection of gamma radiation.

Kardex cards utilized through the year 1946 had a "G" column and a "B" column. The "G" dose value represented gamma radiation and the "B" column on the Kardex card represented beta radiation exposure. In the early 1960's when Mancuso summarized individual data from the Kardex cards, two doses were calculated: (1) a whole body dose, also called DC dose, obtained from column "G", and (2) a superficial dose, also called DS dose, which was obtained from the Kardex cards by adding the two columns "G" and "B" together.

For the years 1945-46, the primary source of data were the film meter; PC data were utilized only to supplement the film badge data. Beginning with the first week and extending up through the eighth week of 1947 which ended on February 23, the gamma and beta radiation were recorded together. Beginning with the ninth week of 1947, the uranium was also recorded in the DS

column with gamma and beta radiation. For the year 1948, no significant changes occurred in dosimetric technique.

Not only did the exposures of interest change over time at ORNL, but changes in the dosimeters occurred as well. Changes in meter devices occurred between 1949 and 1960. From 1944 though the first half of 1956, dose data were summarized from worksheets onto Kardex Cards. Beginning with the second half of 1956, data were derived directly from Kardex Cards without an intermediate summary step (Hart, 1966, p. 6). Dose evaluation techniques were modified from time to time during the 1949-1960 period in order to keep abreast of improvements in dosimetry technology and changes in maximum permissible dose concepts as reported by the National Commission on Radiation Protection (NCRP). Techniques utilized in deriving the DC (alternatively designated as "penetrating dose", whole body dose or critical organ dose) remained relatively unchanged; however significant modifications began taking place starting in 1951 which affected calculation of the superficial dose.

Beginning with the second half of 1951, an adjustment in reading was made to account for gamma exposure that may have been double counted. This adjustment usually resulted in causing dose to be adjusted downward. Beginning on or about November 26, 1951, all workers were issued steel badge meters with their pictures on the outside of the badge. This was a major policy change since before that time only employees working in areas where exposure was known to have occurred were monitored. In late 1951, all employees entering the main ORNL area were required to carry a film meter whether or not they had general access to designated radiation exposure zones (Hart, 1966, p. 7). This means that prior to 1951 monitoring was only required for workers entering designated areas where the potential for exposure was presumed to exist (Checkoway *et al.*, 1983).

Beginning on or about September 24, 1953, a plastic film badge meter containing four filters was introduced, which replaced the single-filter stainless steel version. The four filters (plastic, copper, lead, and cadmium) were utilized for the purpose of determining depth dose measurements as suggested by the NCRP. No serious attempt was made to utilize the full capacity

of the multi-filter badge until the beginning of the second half of 1956. The historical documents do not explain why the capability of this type badge was underutilized. Starting in July 1956 through 1960 four depth dose measurements were presumably obtained: (1) a skin dose (Ds - note this is different from DS), (2) a moderately penetrating dose (Dm -- which is recorded as DS on the Mancuso worksheet), (3) a eye lens dose, and (4) a penetrating dose (Dp). The moderately penetrating dose (Dm) was the nearest measurement to the DS superficial dose. The DS dose previously discussed is composed of both gamma and beta radiation exposures. Thus the Dm moderately penetrating dose measure appears on the Mancuso worksheet for the above designated period of time, 1956-1960. The penetrating dose (Dp) value corresponds to the whole body dose, DC value (Hart, 1966, p. 7).

Beginning in 1961 only two depth dose measurements were made routinely from badge meter data. These included the skin dose designated as Ds and the critical organ dose designated as Dc. The film was incapable of absorbing low energy radiation below 80 mg/cm^2. The Ds and Dc recorded for the 1961-1964 period of time is, respectively, the DS moderately, penetrating dose, and the DC whole body dose, reported to Mancuso. It is believed that the Ds value recorded during the 1961-1964 era is closest to a true estimate of the superficial dose concept than any other data examined in the survey conducted in 1966 (Hart, 1966, p. 8).

Film badges were used until 1975 at which time the thermoluminescent (TLDs) dosimeters were introduced. The previous discussion is important because the dosimetry information from early years of plant operation as summarized for the Mancuso study serve as the estimates for "external penetrating gamma radiation" in the 1984 X-10 analysis. The original entries for individual weekly readings were summed manually on an adding machine into a single annual number -- the annual dose. Quarterly readings were handled the same way after 1955. The Mancuso worksheets were double checked if the DC on card or machine tape was greater than 5 mSv (0.5 rem) (Hart, 1966, p. 10). Data have been updated subsequently from personnel files and used in analysis of the ORNL cohort.

The major limitation of these data is that exposure below the level of detection for the film meter were common. Since the level of detection for film badge was 0.0030 Sv (30 mrem), and the film was read weekly, then over the course of 1 year, a worker could conceivably receive up to 10.5 mSv (1.5 rems) per year of exposure that would go unrecorded. In general, if exposure occurred below the level of detection, then '0' dose was recorded. Those with a true zero exposure were also recorded as zero.

Since some workers wore both PC and film badge for a short period during early 1944, a study was conducted to validate and quantify the amount of exposure misclassification (Tankersley *et al.*, J. Appl. Occup. Hygiene. in press). Based on computer simulation using pocket-chamber readings and film badges, Tankersley *et al.* (in press) found that significant doses of exposure may have been unrecorded. Authors found that as the recorded mean exposure increased, so did the amount of potentially missed dose. If exposure was underestimated proportionally between deceased and alive, then the true measure of association would be expected to be less than observed. If exposure underestimation was greater in the deceased than those still alive, then the measure of association would be underestimated.

III. RESULTS FROM PREVIOUS FOLLOW-UP STUDIES OF THE ORNL COHORT

This section summarizes three studies that have been conducted using data from ORNL.

A. Dissertation of Naima A.K. Abd Elghany

The purpose of this study was to determine if there was excess cancer mortality in the ORNL cohort using a nested case-control design with follow-up from 1943 through 1977. There were 423 cancer deaths and 846 matched controls, some of whom were still alive. Two controls were frequency matched for race, year of birth, and year of first employment. Exposure and job categories were summarized. Univariate analysis and logistic regression were performed. Results showed odds ratios ranging from 1.03 to 1.50, for continuous versus categorical dose groupings, respectively. It was found that a significantly higher proportion of cases worked in maintenance, construction and welding, but there was no association between working in these jobs and cancer from radiation exposure. There was no support in the data for the hypothesis that long employment in jobs with high potential for chemical exposure was related to cancer risk (Elghany, 1983, p. 180).

Smoking prevalence was estimated in the cases and controls from pre-employment physical exams, but smoking was not related to cancer mortality (OR=0.48, 95% CI=0.2, 1.16) when exposure (>0 and 0) and smoking (yes/no) were treated as dichotomous. Seventy-nine percent of the cases or controls smoked compared to non-smokers in a sample of 224 male workers. A higher proportion of cases smoked (86.2%) than controls (77.4%) based on reporting at first employment physical exams.

Certain subgroups encountered higher cancer mortality than others. Result of univariate analysis showed that the cancer mortality was statistically significantly higher among workers with the following characteristics:

older than age 39 when first hired,

terminated employment after age 47, but before 1960,

died later than 1960, and

older than age 66 at death.

An elevated odds ratio for mortality was found among individuals who were not monitored for internal radiation. Monitoring for internal radiation exposure was not instituted until 1951 and after 1951, only for workers with potential for radionuclide exposure. Those not monitored for internal radiation were either first employed before 1951, or after 1951 worked in areas presumed *not* to have exposure potential to internal radionuclides. The author did not stratify before and after 1951 to compare if there is a difference in mortality for workers not monitored for internal radiation. These results suggest (1) that radionuclides were an important source of exposure prior to 1951, and (2) that after 1951 exposure to radionuclides was more widespread than believed at the time, or workers were in areas where they should not have been without being monitored.

The data suggested an increased mortality risk for those hired older than age 39, implying that the older the age at first exposure, the higher the susceptibility to radiation related cancers. The influence of exposures prior to employment at ORNL may have caused sufficient changes to initiate the carcinogenic process that could be promoted by exposure to radiation and other carcinogens at ORNL. Of course, older age also puts one at increased risk for cancer, since background cancer risk increases independent of exposure. Excess deaths among the older age group (70-79) suggest that a long latency period for cancer development was in effect (Elghany, 1983, p. 185). The results suggested that those hired early in the plant operations who were older when hired, but who lived long enough to develop cancer, and these were the high risk group (Elghany, 1983, p. 185). The empirical induction period (EPI) for most cancers was more than 20 years since first hired (Elghany, 1983, p. 187). The analysis supports the observation that exposure during the WWII era was more harmful than after 1946, when radiation safety practices improved. A slight dose-response gradient was found for increasing cancer mortality risk with increasing radiation dose levels (Elghany, 1983, p. 187). Using stepwise logistic regression, the

best fitting model included only 3 variables: year of hire, age at hire, and number of years since first hired (Elghany, 1983, p. 169) using categorical data.

B. Checkoway *et al.*, 1985

The first retrospective cohort study of the ORNL cohort to be published in a peer-reviewed journal was Checkoway *et al.*, 1985. All white males (n=8375) hired between 1943 and 1972 who worked more than 30 days were eligible for inclusion. At the end of follow-up in 1977, there were a total 966 deaths, of which 194 were cancer. The cohort contributed 164,004 person-years of observation. The study methods included an internal comparison group and an EIP. There was no gradient of cause specific-mortality identified, but leukemia was elevated in engineering (SRR=2.4) and maintenance workers (SRR=3.12).

C. Wing *et al.*, 1991

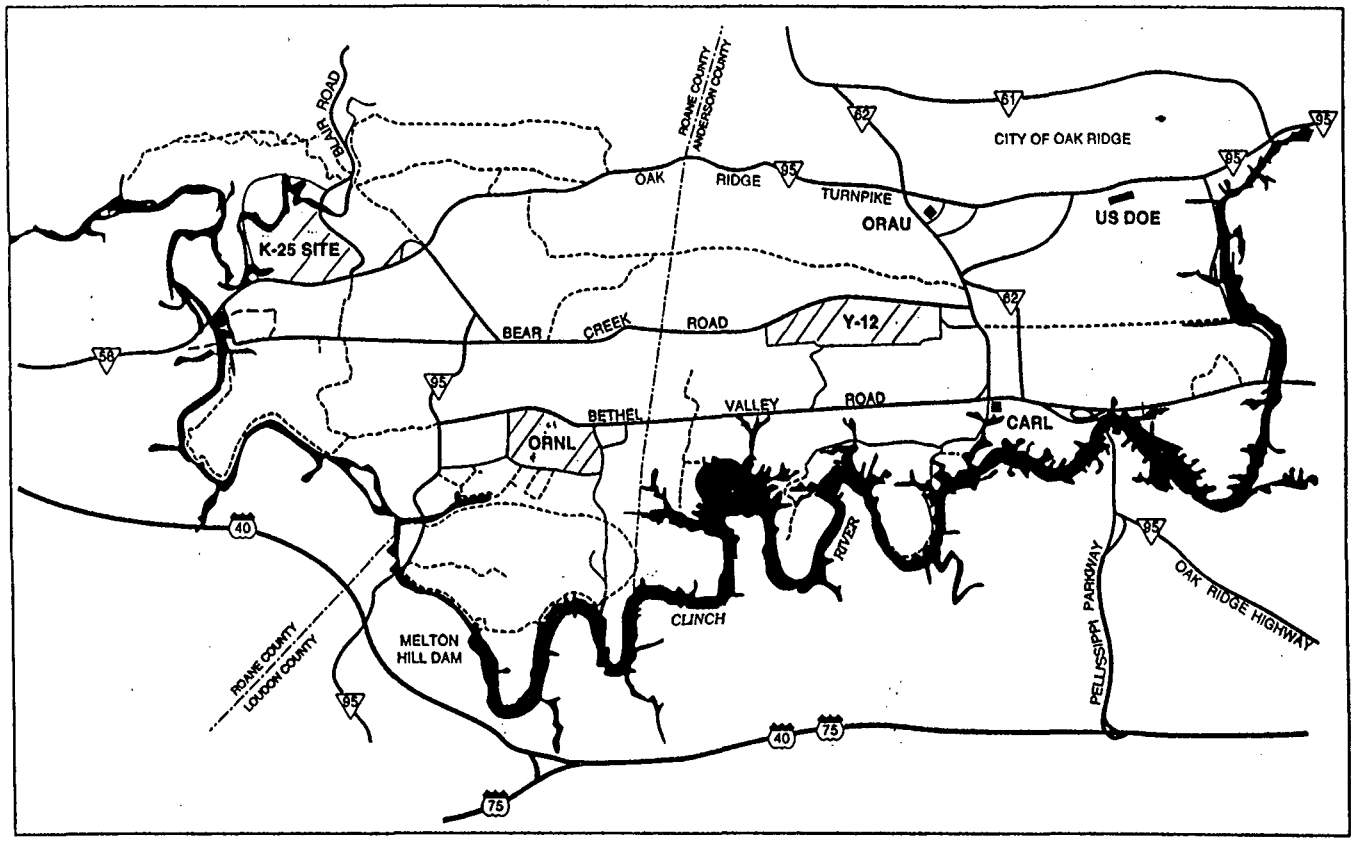
This study included added seven additional years of follow-up to Checkoway *et al.* (1985). There were 580 additional deaths in the ORNL cohort between 1977 and 1984. Thus, with follow-up through 1984 there were 1524 total deaths and 346 immediate causes of cancer death and 34 contributory causes, including 215,680 person-years of follow-up. After accounting for age, birth cohort, paycode, and worker status, external radiation with a 20 year empirical induction period was related to all cause death (2.68% increase per 10 mSv) primarily due to an association with cancer mortality (4.95% per mSv). Cumulative dose was related to lung cancer with a 10-year empirical induction period (p=0.02), but not a 20 year lag (p=0.08). Finding of the ORNL follow-up through 1984 were much greater that dose estimated from other nuclear cohort studies of follow-up of the atomic bomb survivors. Re-analysis of the ORNL cohort data was the subject of this dissertation.

D. Wing *et al.*, 1993

After publication of Wing *et al.*, 1991, a second analysis of the cohort appeared in 1993 which addressed criticisms of the initial Wing *et al.* paper. Criticisms of the 1991 publication included absence of stratification by job category and other potential chemical and metal exposures in the analysis. Using the same cohort eligibility and follow-up period as Wing *et al.*, 1991, this historical cohort study produced maximum likelihood estimates using Poisson regression techniques with an internal comparison group. Radiation exposure was associated with increases in the ratio of observed to expected deaths for radioisotope production and chemical operations, but not in physics, engineering or unknown jobs (Wing *et al.*, p. 271). Overall, Wing *et al.* concluded that removing potential confounding of job categories and chemical exposures did not reduce the estimated risk of all-cancer mortality from radiation exposure as the findings in the Wing *et al.*, 1993 were similar to Wing *et al.*, 1991. There were differences in the covariates and interaction terms used in the two studies and only all-cancer mortality was used as the outcome. No other cancer groups were evaluated.

Figure 2.1

Map of the Oak Ridge Reservation Showing Locations of K-25, Y-12, and X-10 (ORNL) facilities.



(Adapted from: Johnson and Schaffer, 1994, p. 4)

CHAPTER 3

METHODS

I. DESCRIBING THE SECONDARY DATASET: WING ET AL., 1991

A. Data Acquisition Through DoE

Data for this dissertation were obtained through the Department of Energy's (DoE) Comprehensive Epidemiologic Data Resource (CEDR), an archive of public data compiled from studies conducted to evaluate the mortality experience of DoE contract workers at the National Laboratories. Researchers at the University of Chapel Hill School of Public Health (UNC-SPH) created the data tape used for this analysis. These analytic data files are stored at Lawrence Berkeley National Laboratory (LBNL) which maintains the CEDR database for DoE (DoE/EH-0339, August 1993).

The DoE requires that users of data acquired through CEDR receive a version of the data that ensures confidentiality of all workers. Therefore, variables that could potentially identify an individual worker have been rounded as follows:

birthdate -- July 1st of year of birth;
hiredate -- 15th day of month hired;
termdate -- 15th day of month employment terminated;
date of last observation -- July 1st of year last observed in follow-up; and
date of death -- July 1st of year of death.

B. Person -Years Calculation

The total number of person-years reported by Wing *et al.* (1991) was 215,680 (Steve Wing, personal communication). The method of Wing *et al.* did not calculate exact person-years (Pearce and Checkoway, 1987). Use of CEDR data required rounding of certain dates. Rounding dates of entry and exit in the cohort modestly affected the estimated number of person-years

(Table 3.1, in text). Rounded date of hire and date of last observation used in calculating follow-up time for this dissertation resulted in a loss of 1,819 person-years, with 213,861 person-years remaining when using the person-year calculation method published by Pearce and Checkoway, 1987. UNC provided this author the computer code used for calculating person-years in Wing *et al.*, 1991, which was necessary in order to reproduce published results.

For calculating person-time of follow-up, the computer code rounded the difference between dates of entry and exit to the next *lowest* whole integer. This was a particular problem for workers who employed less than 1 year. To retain person-time for workers who were employed for more than 30 days and less than 1 year, follow-up time was set to 1 year for these workers. This resulted in the addition of 89 person-years. Therefore, for this dissertation there are a total of 213,950 person-years of follow-up that is not an exact calculation of total person-time in the ORNL cohort.

Table 3.1 Number of Person-Years in the ORNL Cohort

Total Reported in Wing *et al.*, 1991	215,680
Loss due to Mandatory Rounding of DoE data	- 1,819
Gain due to Rounding of Workers Employed < 1yr	+ 89
Total Person-Years for This Analysis	213,950

C. Deaths

In addition to rounding dates that are personal identifiers, an additional precaution to protect worker confidentiality has been adopted by certain States that have allowed release of death certificate information. These states do not allow listing the ICDA-8 code in data available for public use. Therefore one death is listed as missing, when in fact, permission was denied by the state to list exact cause of death. This is another reason why some study characteristics of Wing *et al.* and the data analyzed in this dissertation differ slightly. Therefore, there are 345 cancer deaths in this analysis, but 346 total cancer deaths in the cohort through 1984.

D. Retrospective Cohort Study Design

Since this dissertation is a re-analysis of existing data collected prior to 1984 on a group of workers whose mortality status was established in 1984, the study design is a retrospective (also called historical) cohort study. The hallmark of a retrospective cohort study is that a group of individuals is identified with certain exposure characteristics using records collected in the past. Then the disease/mortality experience of the group is reconstructed between the time in the past (t_0) and some defined time in the present (t_1). The individuals comprising the cohort are identified, and information on their exposure is obtained, prior to obtaining their disease/mortality experience (Breslow and Day, 1987, p. 3). The ORNL cohort is considered a dynamic cohort since individuals enter and leave the study between t_0 and t_1, whereby individual follow-up is available for every subject.

The advantage of retrospective cohort studies are the following. First, a variety of health endpoints, instead of one, can be evaluated for an exposure. Secondly, recall and selection biases are minimal, since information about cohort members is usually collected prior to study initiation. Third, a historical cohort study can provide direct estimates of mortality rates in the cohort (Breslow and Day, 1987, p. 2). Next, a historical cohort design is useful for studying diseases with long latent periods (Kleinbaum, *et al.*, 1982, p. 64). Finally, results can be obtained relatively quickly.

A disadvantage of cohort studies is that the cohort is usually a selected subgroup of the general population and the disease or mortality experience of the cohort may not be comparable to the general population. The best known example of this lack of comparability is the so-called 'healthy worker effect' (HWE). In short, the conceptual basis for the HWE is that the employed population is generally healthier than the non-employed population of the same agerisk, and their death rates for many causes are lower than the corresponding rates in the general population (Breslow and Day, 1987, p. 18). In a subsequent section, the HWE will be discussed when the

comparison group is non-exposed workers of the same cohort, instead of the general population. Another limitation is that most disease outcomes are rare, such as cancer. Usually the numbers of cancers are insufficient to demonstrate an effect from exposure. Third, some bias may be introduced if vital status and cause of death cannot be ascertained at the end of the study period for a majority of those eligible (lost-to-follow-up). Finally, information on the cohort may not be completely useful, since the data would almost certainly have been collected for other purposes. The advantage of utilizing previously collected data can also be a limitation, since useful data may not have been previously collected, such as a worker's history of smoking.

E. Study Population

The population of X-10 was first enumerated from personnel files in 1964 by Dr. Thomas Mancuso and co-workers from the University of Pittsburgh, and enumeration has been updated subsequently from the same files (Checkoway *et al.*, 1985 p. 526).

A case-control design nested within the ORNL cohort was the subject of a dissertation completed at UNC-SPH in 1983 (Elghany, 1983). The potential study population included all persons who ever worked in the X-10 plant on or after 1943 until December 31, 1977, including persons currently employed at the end of 1977 (423 cases and 846 controls). Exposure was considered from initial employment date until end of follow-up in 1977 or death (Elghany, 1983, p. 58). See Chapter 2 for a discussion of study results.

Using a historical cohort design, Checkoway *et al.* (1985) first published results regarding cancer mortality in the X-10 cohort. Eligibility into the cohort was further refined to include all white males with date of hire between January 1, 1943 and December 31, 1972, a minimum work period of 30 days, and exclusion of workers known to have worked at other DoE facilities or predecessor organizations. Follow-up was through 1977 to ascertain vital status.

Wing *et al.* (1991) used the same eligibility criteria as Checkoway (1985), but follow-up to ascertain vital status was through 1984. Table 3.2 summarizes criteria for entry into the white male cohort. Of the 17,517 workers employed at ORNL between January 1, 1943 and December 31, 1972, 9,199 were excluded, leaving 8,318 white males in the cohort. The number of eligible workers in the Wing cohort differs from the previous report (Checkoway *et al.*, 1985) by 57 workers due to corrected demographic data (erroneous birth and/or termination dates, race or gender information). According to Wing *et al.* women and non-white men were excluded from analysis because they had fewer deaths and lower radiation exposure (Wing *et al.*, 1991).

F. Follow-up of the Cohort

For follow-up through 1984, Wing *et al.* ascertained vital status primarily through employment records and the Social Security Administration for 91.8% of the cohort (96.5% of potential person-years of follow-up), and 1,524 deaths were identified by the end of 1984. Death certificates were obtained from state vital records departments for 1,490 of the deaths. No death certificate was obtained for 34 deaths. Underlying causes of death and contributory cancer causes were coded to the International Classification of Diseases, Adapted, Eighth Revision (ICDA-8). Contributory causes of cancer death (n=34) were included in the internal comparison analysis. The 686 workers of unknown vital status were considered to be alive and contributed person-years of observation up to date of termination of employment, although they were essentially lost-to-follow-up. Workers of unknown vital status tended to have short employment duration and one third were lost after 1982. Workers with less than six month's employment and foreign consultants accounted for most of the people with unknown vital status (Checkoway *et al.*, 1985, p. 526). The cancer deaths counted as missing contributed to follow-up. There were 215,680 person-years of follow-up in the cohort produced by Wing *et al.*

G. Gamma Radiation Exposure

Historical dosimetry practices are reviewed in Chapter 2. To summarize, individual exposures to external penetrating radiation, primarily gamma rays (with some neutrons), were measured using pocket ionization chambers from 1943 until June 1944, film badges from June 1944 until 1975, and thermoluminescent dosimeters (TLDs) since 1975. Since workers wore two pocket chambers (PCs) the lower of the two PC readings were recorded daily at the end of the worker's shift. In a book about the history of radiation protection, Hacker (1987, p. 36) stated that personnel in the health division at ORNL considered the lower reading as correct "since all errors increased apparent exposure." The level of detection for the PC was 0.01 mSv (1 millirem (mrem)) (personal communication, Bill Tankersley, January 13, 1993). Film badges were evaluated weekly from June 1944 until July 1956, when quarterly monitoring was initiated (Wing *et al.*, 1991, p. 1937). It has been acknowledged that dose underestimation prior to 1956

likely occurred. The film badge minimum detection limit was 30 mrem (0.3 mSv). It was often the case that if the limit of detection was not achieved, a dose of zero was recorded, following recommendation of the NRPC (Crawford-Brown, *et al.*, 1989, p. 24). Over a 1 year period this could total approximately 10.5 mSv (1.5 rems) of exposure going unreported (personal communication by Bill Tankersley, ORAU, 1993). Since some workers wore both PC and film badge for a short period during early 1944, a study has been conducted to validate and quantify the amount of exposure misclassification (Tankersley *et al.*, J. Appl. Occup. Hygiene. In press).

Beginning in 1951, dosimeters were incorporated into security badges and all workers were monitored. Before that time, only persons considered at risk were monitored (Frome *et al.*, 1990). Doses were estimated for 4.9% of the work-years missing. Doses were estimated primarily from the individual worker's own data within 2 years of the missing value. Averages for the worker's department in the missing data year were used when no individual data were available. Plant averages by year were used for 0.9% of work years when department averages were not known (Wing *et al.*, 1991). Beginning in 1975 TLDs were measured on a quarterly or annual basis and have a minimum detection level of 0.01 mSv (1 mrem) (personal communication by Bill Tankersley, 1993). Background radiation is assumed to be 0.01 mSv per week in the State of Tennessee which is subtracted when the film badge readings are recorded by the Health Physics Division at ORNL.

The datatape obtained from CEDR provides dose quantification for each worker in annual totals for each year employed and cumulative dose for each year of follow-up. Units of radiation dose are recorded in mrem. Cumulative dose as recorded in mrems represents the quantity 'dose equivalent', which is a measurement unit to combine the physical energy content of radiation with the effectiveness of dose in producing biologic damage .

In much of the radiation epidemiology literature, discussion is presented in units of 'rem'. However, the internationally accepted unit for reporting dose is the Sievert. Therefore, results will be presented in units of millisieverts (mSv) or Sieverts (Sv) (1 rem = 10 mSv)(See discussion in Chapter 1, section IV).

II. DEFINITION AND USE OF PREDICTOR VARIABLES FROM WING ET AL., 1991

A description of the ORNL study population can be found in section E of this chapter. This section describes the predictor variables used in analysis of the ORNL data published by Wing *et al.*, 1991.

There were some similarities and some differences between the analysis of this study and that of Wing *et al.*, 1991. Covariates of interest included in the Wing analysis were: agerisk, birth cohort, active worker status (AWS), paycode, and external radiation dose. Table 3.3 provides a list of variable names and groupings of categorical data used for Poisson regression in the 1991 analysis. Agerisk is the age of the study subject moving through follow-up to the age at last observation. In preparing the data for model fitting, agerisk was stratified into 16- 5-year age categories (15-19, 20-24,...85-89,90+). Prior to model fitting, age was revised to be centered around 52.5. The was done by adding 2.5 to the value for the lower bound of the age category to put age at the category midpoint. Then the midpoint of the age category was divided by 52.5. The purpose of this was to place the intercept of agerisk near the middle of the data at the 50-54 agerisk group. Centering is usually used to increase computational accuracy (Kleinbaum *et al.*, 1982). The natural log of agerisk was taken (agerisk = ln(age +2.5/52.5)) for analyzing various cancer causes, but agerisk was untransformed for analysis of all cause mortality. In Wing *et al.* (1991), agerisk was treated as a continuous variable in all analyses.

Birth cohort was defined by stratifying year of birth into three groups: born before 1905, born between 1905 and 1914, and born in 1915 or later. The referent group was those born before 1905. For leukemia the two older cohorts were combined due to small number of deaths. Year of birth groups were chosen to distribute deaths evenly throughout the three cohorts.

The variable 'active worker status' (AWS) was constructed to explore the healthy worker effect (HWE), since mortality is likely to be particularly high in the year or two succeeding changes in employment, and conversely relatively low in those that continue to work (Breslow and Day, 1987, p. 40). The number of active versus inactive person-years could therefore be

expected to influence the findings regarding mortality in a cohort (Steenland and Stayner, 1991). Person-years while working at ORNL were considered "active person-years", and person-years subsequent to working at the plant were "inactive person-years". Active person-years were coded 1 and not active person-years were coded 0.

Payroll code, referred to as paycode, was used as an indicator of socioeconomic status (SES). Paycode was considered an indicator of unmeasured potential confounders and as a determinant of exposure to radiation (Wing *et al.*, 1991). Paycode was defined as the employee's wage or salary classification when first hired: monthly, weekly, or hourly. Professional positions were monthly (M), while non-union supervisors were weekly (W) and unionized blue-collar workers were hourly (H). No information was available to determine if a worker's payroll classification changed over the course of employment. In Wing *et al.* hourly and weekly categories were combined for model fitting and the referent group in all analyses was monthly.

External radiation dose was grouped as an ordered, categorical variable, but fit as a continuous variable. Eight dose groups were formed: 0, >0 to <20 mSv, 20 to <40 mSv, 40 to <60 mSv, 60 to <80 mSv, 80 to <100 mSv, 100 to <120 mSv, over 120 mSv. The dose categories were recoded to use the midpoint of each dose category in regression giving scores of 0, 10, 30, and 50 mSv up to 110 mSv (the second highest dose category). For the highest dose category, dose associated with the median value of person-years (194 mSv) was used. Using the median value of person-years in the highest dose group was unique compared to approaches in other cohort studies, which used either individual dose values or the mean of the dose category. No rationale was provided for the chosen approach.

Interaction terms were included in model fitting (paycode*cohort, agerisk*active worker status, active worker status*cohort, agerisk*cohort). The combination of interaction terms used in model fitting was inconsistent between cancer outcomes, as were the models themselves (see section IV.A.(2)). Contribution of some of these terms to reduction in residual deviance did not contribute to fit of the data. There was insufficient descriptive data provided in the published manuscript or supporting documents to indicate a rationale for choosing these terms.

III. TIME RELATED FACTORS TO BE CONSIDERED IN ANALYSIS

On the basis of information obtained from earlier analyses as well as the early history of facility operations (see Chapter 2), it was assumed that the following variables may best predict mortality in the ORNL cohort: agerisk, yearrisk, paycode, year of hire, and cumulative dose. For solid cancers, the contribution of cumulative dose to mortality risk using these variables was provided by each empirical induction period (EIP): (1) lag=0, p=0.111; lag=10, p=0.031, and lag=20, p=0.006. Paycode and year of hire were measured at one point in time and do not change as a worker moved through follow-up time.

Few studies of nuclear cohort workers provide information on the role of time-related factors, other than agerisk and yearrisk (see Chapter 1). Time-related factors that change as a worker moves through follow-up have not been rigorously explored in the ORNL data. A decision was made *a priori* to evaluate time-related factors in the absence of paycode, particularly, in order to identify potential covariates that may not have otherwise been detected. Paycode was found to provide a significant contribution to explaining mortality in the ORNL cohort. The complex components of behavior and lifestyle that are likely quantified by paycode may be related to factors in this present analysis, in ways that are unknown. However, the role of these variables as independent time-related predictors have not been established in this data. Thus, a cautious approach may lead to identification of time-related variables suitable for inclusion with paycode in future analysis. Noting how the relationship between cumulative dose and other variables change by outcome group when paycode is included in statistical modeling may help to elucidate the meaning and influence of paycode, which was expected to be substantial.

It would have simpler to specify covariates and select a stepwise statistical procedure to automate and optimize variable selection from the many that have been constructed based on data in the ORNL public use dataset. However, part of the process

of conducting dissertation research is formulation of a research hypothesis and then testing the hypothesis, prior to knowing what the results will be. In the occupational epidemiology literature, there is compelling evidence that time-related factors that change as a worker moves through follow-up time are related to cancer mortality and this was a hypothesis in analysis of the ORNL cohort data.

A. Retaining Time-Related Variables Used by Wing et al., 1991

The format used in this section is to provide a rationale for the variable's inclusion in the current analysis, as well as describing how the variable will be used. Table 3.4 summarizes the variables and cutpoints for this analysis. There are three variables retained from the 1991 analysis: agerisk, cumulative dose, and active worker status. Both agerisk and cumulative dose are defined differently in this analysis than in Wing *et al.*, 1991, but active worker status was not redefined.

(1) Agerisk

Rationale: The probability of developing cancer over a certain period increases as one advances in age. A worker who has not left the cohort is eligible to develop disease, and therefore is considered "at risk" for disease or death. As a worker increases in age and moves through calendar time, risk of death increases independent of exposures that may enhance mortality. Thus, age at risk (i.e. 'agerisk') is a time-related variable. In workers from the DoE facility located in Hanford, Washington, Gilbert *et al.* (1993) found that simple agerisk stratification fit data significantly better than agerisk transformation (such as use of the Weibull function), but concluded that agerisk transformation and centering were adequate methods for adjusting for agerisk in the ORNL cohort (Gilbert *et al.*, 1993). Most other cohort studies of nuclear workers stratified agerisk in five year groups to generate deaths and person-years (Gribbin *et al.*, 1993; Kendall *et al.*, 1992; Checkoway *et al.*, 1985; Beral *et al.*, 1988; Beral *et al.*, 1985), and then included agerisk as a variable in model fitting.

More importantly, Gilbert suggested that agerisk should not be conceptualized simply in terms of birth cohort. Cancer mortality increases as a worker ages, no matter when birth occurred. Because the risk of death increases with age, agerisk increases in a linear fashion with length of follow-up. Gilbert (1993), in a combined analysis from three DoE facilities (Hanford, ORNL, Rocky Flats), found that agerisk over 75 was associated with a 30% excess relative risk of cancer mortality per 10 mSv increase in exposure. This was about 30 times greater than the percentage increase in excess relative risk of cancer due to radiation exposure adjusted for agerisk (Gilbert *et al.*, 1993, p. 415). Further, it was found that the effect of agerisk on mortality persisted when accounting for a 10-year cancer latency period. Not surprisingly, agerisk may be correlated with other time related variables. Even in a combined analysis of geographically separated facilities, agerisk was seen as a very strong effect modifier (Gilbert et al, 1994, p. 414).

Use: The number of person-years that a worker contributes to follow-up will be grouped into 16 5-year incremental categories of agerisk (15-19, 20-24, 25-29,....80-84, 90). 'Agerisk' will be used as a variable to classify person-years and deaths by age at risk. For Poisson regression analysis, agerisk will be treated as continuous to calculate relative risk and categorical to calculate excess relative risk. Its contribution to Goodness-of-Fit will be assessed for both measures of association (see Chapter 3, Section IX.J. for discussion of goodness-of-fit).

(2) Cumulative Exposure

Rationale: Cumulative exposure is an overall measure of past exposure history referred to simply as 'dose'. In the literature on nuclear workers, the number of cut points and the width of each dose category vary from study to study. For example, Gribbin *et al.* (1993) used 10 dose categories from 0 to >= 500 mSv; Checkoway *et al.* (1985) used four dose categories 0 to >= 50 mSv; and Gilbert *et al.* (1993) used five dose categories 0 mSv to >=200 mSv. Gilbert *et al.* (1993) found that the use of dose as a continuous versus categorical variable was the most influential factor in the estimate of excess relative risk in re-analysis of the ORNL cohort data (Gilbert *et al.*, 1994, p. 419). If using a categorical variable, the width and number of dose

categories greatly influence the precision of the parameter estimate as well as the value of the estimate. Arbitrary exposure cutpoints may also introduce misclassification of exposure. It is hypothesized that use of the median value of the highest dose category causes some inflation of mortality risk in Wing *et al.* (1991) and that a few deaths in the highest dose category may be responsible for earlier findings.

Use: The number of person-years that a worker contributes to follow-up will be grouped into 13 categories of cumulative dose. 'Dose' will be used as a variable to classify person-years and deaths by cumulative exposure. The influence of dose will be investigated and goodness-of-fit assessed. Cumulative dose will be grouped into the following categories reported in mSv: 0, >0- <10, 10-<50, 50-<100, 100-<150, 150-<200, 200-<250, 250-<300, 300-<350, 350-<400, 400-<450, 450-<500, >=500. Forty-seven percent of the cohort received less than 10 mSv (1 rem). Dose will be recoded prior to model fitting so that the parameter estimates can be interpreted in terms of the midpoint of the dose category per mSv. Dose will be fit as a continuous variable and added as the last predictor variable in regression analysis for all outcomes evaluated.

(3) Active Worker Status

Rationale: According to Breslow and Day (1987, p. 40), mortality is particularly high in the year or two succeeding changes in employment, and mortality is lowest in those not changing employment. They propose that a common way to alleviate this problem is to treat a person as if employed by two or three years after ceasing employment to determine if it captures aspects of the HWE. Specifically what happens is, the person-years are divided into "active" person-years (person -years while still working at ORNL) and "inactive" person-years (person-years subsequent to working at ORNL). According to Steenland and Stayner (1991), the percentage of active and inactive person-years can be expected to influence findings of mortality studies. Furthermore, workers employed the shortest duration contribute the most inactive person-years and have the highest mortality. They found an upward trend for cancer among inactive person-

years and that high SMRs were concentrated in the first one to two years after leaving employment, which suggested that some workers leave employment because they are ill (Steenland and Strayer, 1991, p. 421). Steenland and Stayer (1991) confirm recommendations of Gilbert (1982) that confounding effects of employment status should be controlled partially through lagging exposures.

Use: The number of person-years that a worker contributes to follow-up will be grouped two categories of worker status. 'Work', the variable name, will be used to classify person-years and deaths according to employment status at ORNL. For Poisson regression, 'work' will be formulated in the same way as Wing *et al.* (1991): as a dichotomous variable, where active working years were coded as 1 and not active were coded 0. The person-years associated with inactive employment status will be lagged two years. These two years of person-time will be considered as active. For model fitting, 'work' will be included as a covariate to estimate relative risk and as a stratification variable to estimate excess relative risk. Its contribution to Goodness-of-fit will be assessed.

B. Time-Related Factors Not Previously Explored

Time-related factors are potential effect modifiers that are not addressed in published results from earlier analysis of the ORNL cohort. Time-related factors or temporal factors can be defined as all potential determinants or modifiers of disease risk that vary as a person goes though follow-up time (Thomas, 1983). Time-related factors are predictive of disease in occupational cohort studies and will be confounders if they are associated with exposure (Checkoway *et al.*, 1989). Thus, it is premature to make generalizations about cancer mortality in this cohort as being due to radiation exposure without understanding the temporal aspects of worker employment and potential exposure as the cohort moves forward in time.

Pearce and coworkers (1986) list four time-related factors that result in confounding due to influence of the healthy worker effect: age at first employment, duration of employment (DOE), length of follow-up (LOF), and agerisk. These factors are not four independent factors but are related to each other. Another time-related variable that influences the exposure-disease relationship is empirical induction period (EIP) (see Chapter 1, section I.A) (defined crudely as the interval from first employment until death) (Thomas, 1983, p. 354).

In studies where the exposure of interest is simply employment in a particular industry, or in a specific job type within the industry, it is convenient to use age at hire as an indicator of agerisk at first exposure and duration of employment as an indicator of duration of exposure (DOE). These terms have been used interchangeably depending on the context (Pearce *et al.*, 1986).

Of those factors associated with the healthy worker effect, agerisk is the strongest predictor (Checkoway *et al.*, 1989, p.90). In general, agerisk and yearrisk are the two strongest predictors of disease in occupational studies (Checkoway *et al.*, 1989, p.90). Strict reliance on cumulative exposure as the sole exposure variable may waste information, since temporal sequencing of exposure could go unnoticed. Calendar year could be considered a surrogate for how cumulative dose changes over time and as an indirect means for assessing period effects.

One design advantage which favors many of the recent radiation epidemiology studies is the use of an internal comparison group using the Poisson regression approach for grouped data. This approach was used in Wing *et al.* However, according to Checkoway (1989), use of an internal comparison group will not eliminate bias if the exposed and unexposed groups differ according to time-related factors under consideration (Checkoway *et al.*, 1989, p.89). Finally, as mentioned in Chapter 1, Gilbert and colleagues (1993) suggest that risk estimates may differ by subgroups in the ORNL cohort. It is also suggested the effects of agerisk result from biases that are not well understood, and that the modifying effects of time related factors should receive additional scrutiny (Gilbert *et al.*, 1994 p. 418). Therefore, time-related factors must be considered in analysis of the ORNL cohort and the rationale for each follows.

(1) Yearrisk

Rationale: The probability of cancer developing over a certain period increases as a worker advances through chronological time and hence, calendar time. A worker who has not left the cohort is eligible to develop disease, and therefore is considered "at risk" for disease or death. As a worker increases in age and moves through calendar time, risk of death increases independent of exposures that may enhance mortality. For this reason age at risk (i.e. agerisk) and year at risk (i.e. yearrisk) are used frequently as stratification variables in cohort studies. In analysis of the ORNL cohort which included follow-up through 1977, Checkoway and coworkers (1985) stratified data by agerisk and calendar year (5 year intervals). Agerisk and yearrisk were also used as stratification variables in Gribbin *et al.*, 1993; Gilbert *et al.*, 1993(a); Gilbert *et al.*, 1993(b); Kendall *et al.*, 1992; Beral *et al.*, 1988; and Beral *et al.*, 1985.

Use: The number of person-years that a worker contributes to follow-up will be grouped into 5-year incremental categories of calendar time (1945-49, 1950-54, 1955-59, 1960-64, 1965-69, 1970-74, 1975-79, 1980-84). 'Yearrisk' will be used as a variable to classify person-years and deaths by calendar time. Workers hired before 1943 are rounded to 1945-1949. For Poisson regression analysis, yearrisk will be treated as continuous to calculate relative risk and categorical

to calculate excess relative risk. Its contribution to Goodness-of-Fit will be assessed for both measures of association (see Chapter 3, Section IX.J. for discussion of goodness-of-fit).

(2) Length of Follow-up

Rationale: The mortality of employed persons is lowest, relative to the general population, during the period immediately following initial employment (Pearce *et al.*, 1986). This has been illustrated in a variety of occupational settings (McMichael *et al.*, 1974). In general, mortality increases with length of time employed, since the selection factors that made workers healthier at the beginning of employment tend to wear off. Risk ratios slowly approach those of the general population as follow-up continues and may eventually exceed risk in the general population with longer follow-up time. With longer follow-up time, the worker may live longer than the general population to develop disease. With longer follow-up it may be that the factors that made the worker healthier than the general population have worn off. For example, once retiring, workers may no longer engage in physical labor and become less active. With longer follow-up, a worker may become less healthy than the general population, because enough time has elapsed for adverse occupational exposure to manifest in disease.

In the literature, 'length of follow-up' refers to the same interval as time since hire when eligibility criteria are based on all workers hired since plant opening and a worker's follow-up begins when hired, not several years after initial employment. Flanders (1993) showed that results may be biased if length of follow-up is associated with both cumulative exposure and mortality but remains uncontrolled in the analysis (Flanders *et al.*, 1993). This is because workers hired early had the longest time to accumulate exposure, typically, the highest cumulative exposures, and the longest length of follow-up. Workers hired early (who have worked longer) tend to have higher mortality rates relative to recent hires because of attenuation of the factors that initially made them healthier. In the ORNL cohort, workers hired in the 1940's

and 50's received higher exposures than workers hired in the 1970's when exposures were much lower.

Flanders *et al.*, 1993 demonstrate the need to control for length of follow-up especially for internal comparisons. Flanders *et al.* point out that 'lagging' exposure (i.e., assigning the follow-up experience of early years of exposure into the unexposed category, as done in the ORNL cohort), may exacerbate the confounding of length of follow-up (when higher exposures did exist), since those early years of follow-up will be assigned to the unexposed category driving the estimated relative risk downward (Flanders *et al.*, 1993, p. 340).

Use: 'Length of follow-up' will be used as a variable to classify person-years and deaths by the amount of time that the cohort member has been under follow-up. The range of length of follow-up is 0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-40. The lower bound of the 5-year interval will be cut points for length of follow-up: 0, 5, 10, 15, 20, 25, 30, 35, 40. For Poisson regression, length of follow-up will be treated as a continuous variable to calculate relative risk and a categorical variable to calculate excess relative risk. Its contribution to Goodness-of-Fit will be assessed for both measures of association (see Chapter 3, Section IX.J. for discussion of goodness-of-fit).

(3) Duration of Employment

Rationale: Although the relative mortality advantage of employed persons diminishes with length of follow-up, (previous section), a reduction in mortality is most pronounced among workers with the longest duration of employment (Pearce *et al.*, 1986, p.98). The latter association is attributable to the survival of relatively healthier persons in the industry (Pearce *et al.*, 1986, p. 98). As mentioned in an earlier section, Gilbert *et al.* (1982) showed elevated risk for all-cause mortality using an internal comparison among terminated workers compared to employed workers, and among short-term workers compared to long-term workers. Gilbert *et al.* (1989) suggested stratification on duration of employment could reduce potential bias and

demonstrated that absence of control for duration of employment may lead to inappropriate conclusions (Gilbert *et al.*, 1989, p. 181).

According to Beebe (1982), duration of employment will be an effect modifier if the effect of a given dose depends on the rate at which exposure was delivered. For example, a non lethal dose of radiation may be less ineffective - due to cellular repair - if an equivalent dose is delivered in smaller fractions over a lengthy period than over a relatively short period. On the other hand, cumulative radiation exposure depends to some extent on duration of employment. A longer DOE implies an increased probability that cellular repair systems will fail and a permanent cellular transition will occur (Beebe, 1982). Fifty-eight percent (58%) of the ORNL cohort worked five years or less.

Use: The number of person-years that a worker contributes will be grouped into 5-year incremental categories of 'duration of employment' (0, 5, 10, 15, 20, 25, 30, 35, 40). 'Duration of employment' will be used as a variable to classify person-years and deaths by the amount of time that the cohort member has been employed. For Poisson regression analysis, duration of employment will be treated as continuous to calculate relative risk and as a categorical variable to calculate excess relative risk. Its contribution to Goodness-of-Fit will be assessed for both measures of association (see Chapter 3, Section IX.J. for discussion of goodness-of-fit).

(4) Empirical Induction Period

Rationale: The term empirical induction period (EIP) is composed of two parts: (1) the induction period, or time from first exposure to beginning of disease, and (2) latency interval, the time between beginning of disease to diagnosis (Rothman, 1981). Exposures after disease begins are not relevant. In historical cohort studies, the EIP has been estimated as the time from first employment (instead of recorded exposure), since unrecorded exposures are possible, and until death (instead of onset of disease), since the onset of disease is rarely known. The interval is

commonly referred to as the 'latency' interval, but in this discussion the term empirical induction period will be used. The EIP will be approximated as the time from first employment until death.

Discussion abounds in the literature about what is the proper terminology for the period from exposure until disease development (Checkoway *et al.*, 1989; Thomas 1983; Thomas 1988; Pearce *et al.*, 1986). Choice of the correct EIP is not straight forward when the exposure varies over an extended period of time, with varying intensity for different individuals. Intensity of exposure during follow-up cannot be taken into account in this analysis. Based on data from clinical radiotherapy studies and the atomic bomb survivor cohort studies, the minimal latency period from exposure to disease has been estimated to be 2-years for leukemia and at least 10-years for solid tumors. These EIP intervals have been used extensively in studies estimating mortality in nuclear worker cohorts, such as Hanford.

Based on a review of the literature, there are two approaches for introducing an EIP. Approach 1 introduces a 'latent' interval and 'lags' cumulative dose. Approach 2 'lags' cumulative dose and does not include a 'latent' interval. The 'latent' interval is now described. Some studies removed the first five years of deaths and person-years, since these deaths and person-years were assumed to be unrelated to the exposure-disease relationship. Exposure for members who remain in the cohort during the five year interval are still cumulated, so that approach 1 does not assume a threshold dose exists for those remaining in the cohort. When follow-up time begins after five years, cumulative dose is that dose which the worker acquired over the five year interval, plus any subsequent exposure. Deaths during this interval are omitted. For those deaths that are removed, it can be assumed that the theoretical threshold dose (if it exists) was: (1) not reached, or (2) if the threshold was reached, the level of exposure was (a) safe or (b) not the cause of mortality due to insufficient induction. For lack of a better term, the interval where deaths and person-years are removed is called the 'latent' interval. Studies in nuclear worker cohorts that include a 'latent' interval are: Checkoway *et al.*, 1985; NAS, 1991; Kendall *et al.*, 1992; Gilbert *et al.*, 1993(b); and Wing *et al.*, 1993. The limitation of using a 'latent' period is that removing person-years reduces study power.

Once the disease process has been initiated, there is an interval where exposures may be accumulated, but are not considered as contributing to mortality. This interval is commonly referred to as the 'lag' interval. Approach 2, 'lagging' dose, is a technique which pushes cumulative exposure forward by the number of years specified in the lag interval. For a worker with 10 years of person time and a 5 year lag, exposure for the first five years of follow-up would be set to zero and exposure for each of the remaining person-years would be the cumulative exposure achieved five years prior. Real time exposure for the last five person-years would be eliminated but the total number of person-years for the worker would not change. The approach attempts to separate exposures occurring before and after disease initiation. Since all deaths, person-years, and exposures are included in the cohort using this method, this approach does not assume a threshold exists. Studies in nuclear worker cohorts that include a 'lag' interval are: Checkoway *et al.*, 1985; Beral *et al.*, 1985; Smith and Douglas, 1986; Beral *et al.*, 1988; Wing *et al.*, 1991; Gribbin *et al.*, 1993; Kendall *et al.*, 1992; Gilbert *et al.*, 1993(b).

During preparation for this analysis, it was discovered that 'lagging' is used to refer to both approach 1 and approach 2. This seemed confusing, since it was known that approach 1 and approach 2 differ slightly. The question arose as to whether incorporating approach 1 versus approach 2 would produce differing parameter estimates for cumulative dose. Secondly, a series of intervals (0, 10, 20) were tested to determine if differences in parameter estimates would be detected due to the size of the interval. Thus, there were two goals in analysis of the EIP: (1) determine the difference between approach 1 and approach 2, and (2) assess the magnitude of the difference between with increasing interval width, 0, 10, and 20. Two cancer groupings were selected since the empirical induction period for solid cancers and leukemias differ, based on follow-up of the atomic bomb survivor cohort.

Approach 1, which was used by Gilbert *et al.*, 1993(b), incorporates a lag, by removed the first five years of deaths and person-years and subsequently lagging dose. Approach 2, used by Wing et al, 1991, incorporates an induction period by lagging dose. The null hypothesis was that there was no difference between these two approaches. The combinations for solid cancer are

presented below. Latency=5 with lag=5, approach 1, would be expected to produce a similar parameter estimate for cumulative dose as latency=0 with lag=10, approach 2. Latency=5 and lag=15, approach 1, would be expected to produce similar parameter estimates for cumulative dose as latency=0 with lag=20, approach 2.

Solid Cancers		Leukemias	
Latency	*Lag*	*Latency*	*Lag*
0	0	0	0
5	5	0	2
0	10	5	2
5	15	5	5
0	20	0	10

For leukemias, latency=0 and lag=2 would be expected to produce the same parameter estimates as latency=5 and lag=2. Results of latency=0 and lag=10 are expected to be similar to latency=5 and lag=5. Intervals reflecting an EIP greater than 10 years (latency=5 and lag=15; latency=0 and lag=20) for solid cancers are exploratory. EIP intervals greater than two years for leukemia are also exploratory. The EIP that produces the largest parameter estimate in a well-fitting model may be assumed to better reflect the empirical induction period for low-dose radiation and cancer. The induction period for low-dose radiation may be longer than high-dose acute radiation exposure, since cumulative dose may require a longer period to produce additive effects culminating in cancer mortality.

IV. STATISTICAL ANALYSIS

A. Data Replication of Wing et al., 1991

It was necessary to reproduce results of Wing *et al.* for several reasons. First, it was necessary to determine that the same data used to generate Wing *et al.* (1991) was the same data being used in this analysis. This could be achieved by replicating findings using the same procedures and techniques as described in Wing *et al.*, 1991. Secondly, reproducing results was necessary to provide a better understanding of methods used for data management and statistical analysis in Wing *et al.* (1991). This allowed the current study to depart from earlier analysis, having gained knowledge with respect to the similarities and differences in conduct of data analysis. Knowledge of these differences was thought to be important in making conclusions from the current analysis.

To duplicate results as published in Wing *et al.* (1991) methods enumerated in background documentation referenced in the publication were followed. Investigators at UNC-Chapel Hill provided a computer program to generate tables of data suitable for statistical analysis. The UNC-SPH computer program was a modified version of a computer program originally published by Pearce and Checkoway (1987) that generates deaths and person-years cross-classified by variables under study. Results for all cancer mortality (lag=20) displayed in Table 4 of the published manuscript were generated using the same statistical procedures and software (Generalized Linear Iterative Models (GLIM)) as described in Wing *et al.*, 1991.

(1) Conversion from GLIM to S-plus

Because replication was successful with GLIM, it was decided to replicate results using S-plus, a UNIX-based statistical software. S-plus is the preferred analytic program because it has elements of both a programming language and biostatistical package. Additionally, graphics capabilities allow interactive display of data. Using S-plus, the results of all-cancer mortality

(lag=20) were exact to three decimal places. With this high degree of concurrence, it was decided to proceed with all subsequent analysis using S-plus. Replication of descriptive cohort data and graphics as presented in Wing *et al.* (1991) was also successfully completed.

(2) Model Fitting Using Internal Comparison and Poisson Regression

Wing *et al.* (1991) adjusts cumulative dose using three different models for four different outcomes using three empirical induction periods (0, 10, 20) for each outcome. Results from the manuscript for these outcomes were reproduced:

1. All causes: agerisk (16 levels), cohort (3 levels), paycode (2 levels), active worker status (2 levels), paycode*cohort, agerisk*active work, active work * cohort. Lag = 0, 10, 20

2. All cancer: agerisk (16 levels), cohort (3 levels), paycode (2 levels), active worker status (2 levels), paycode*cohort, and agerisk*active work. Lag= 0, 10, 20.

3. Lung cancer: agerisk (16 levels), cohort (3 levels), agerisk *cohort. Lag = 0, 10, 20.

4. Leukemia: agerisk (16 levels), cohort (3 levels), agerisk *cohort. Lag=0, 10, 20.

B. Descriptive Information about Time-Related Variables

As discussed earlier, time-related factors can be important confounders or effect modifiers in an exposure-disease association. Further, description of the cohort in terms of vital status can assist to locate differences in characteristics of survival between diseased or exposure groups.

The following descriptive statistics will be provided: mean, standard error, and range. Descriptive statistics will be grouped by vital status groups: all cohort, known deaths (excluding cancer deaths), cancers, and alive (means alive at end of follow-up on 12/31/84). Vital status will be evaluated by exposure category. The time-related variables for which descriptive statistics will be provided include those enumerated in Table 3.4: DOSE, DOE, LOF, AGERISK, and YEARRISK. Worker status is a binary variable.

The time-related variables have a continuous distribution, but will be broken into discrete, ordered categories for frequency distribution (count and percent) analysis. Histograms

will be provided for certain time-related variables to facilitate examining the shape of the distribution.

C. Disease Outcomes of Interest

There were 1,524 deaths in the ORNL cohort, of which 346 were cancer. One death was listed as missing in the dataset, since New York City, NY denied permission to identify the ICDA-8 code for public use data accessed through CEDR. Thus, the total number of cancers listed as immediate cause of death for this analysis was 345. The total number of deaths listed as immediate cause was revised downward to 1,523. The following outcomes were evaluated:

1. All cancers (ICDA-8 140-209)
2. Solid Cancers (All cancers excluding leukemia) (ICDA-8 140-203, 208-209)
3. Lung cancers (ICDA-8 162-163)
4. Solid Cancers, excluding lung
5. Solid Cancers, excluding smoking-related
6. Solid Cancers and Lung, excluding other smoking-related
7. Solid Cancers, excluding upper respiratory and upper digestive cancers
   (ICDA-8 142-145, 151-160, 170-203, and 209)
8. Smoking-related cancers, excluding esophagus (Group I)
   (ICDA-8 Lung 162-163, Larynx 161, Nasopharynx 147, Bladder 188, Pancreas 157)
9. Smoking-related cancers, including esophagus (Group II)
   (ICDA-8 Lung 162-163, Larynx 161, Nasopharynx 147,
   Bladder 188, Pancreas 157, and Esophagus 150)
10. Smoking-related (Group II), excluding lung
11. All leukemias (204-207)
12. Leukemias, excluding chronic lymphocytic leukemia (CLL) (ICDA-8 204-207,
    excluding 204.1)
13. Non-cancer causes, excluding external causes (ICDA-8 0-139, 210-799)
14. All causes of death

All-cancers, outcome 1, evaluates the crude association between radiation exposure and cancer mortality. Leukemias are separated from solid cancer in outcome 2, solid cancers, since

studies of the atomic bomb survivors indicate conclusively that radiation-induced leukemias have a different empirical induction period than solid cancers. Lung cancers, outcome 3, have been associated with radiation as well as smoking in earlier studies and were associated with cumulative dose in Wing *et al.*, 1991. Lung cancers are the largest single cancer group. Solid cancer excluding lung, outcome 4, serves to check on the result of solid cancers and lung cancers as separate categories. Solid cancers excluding smoking-related, outcome 5, was included since there was no independent variable to assess the role of tobacco consumption on the cancer burden in this cohort. Removing the smoking-related cancers and comparing the difference in parameter estimates with solid cancers will provide some assessment of the role of tobacco-linked cancer deaths. Solid cancers and lung (without other smoking related), outcome 6, can be compared to solid cancers excluding smoking-related to assess the role of lung cancer within the smoking-related cancer group. Solid cancers excluding upper respiratory and upper digestive, outcome 7, was created to evaluate the role of bladder and pancreatic cancers by excluding these cancers.

Two groups of smoking-related cancers allow comparison of the contribution of esophageal cancers to cancer risk. Group I, outcome 8, excludes esophageal cancers and Group II, outcome 9, does not. This comparison was done since cancers of the esophagus were found to have a large impact on results (Gilbert *et al.*, 1993, p. 412). A third smoking-related category includes the smoking-related cancers, except lung cancer. This was created since it was found early in the current analysis that lung cancer was not associated with cumulative dose.

Finally, chronic lymphocytic leukemias (CLL) were removed from leukemias in outcome 12, since there has been no association with CLL and radiation exposure in the ABS cohort or other nuclear cohort studies (Gilbert *et al.*, 1993). Outcome 13, which excludes cancer deaths and deaths due to injuries, poisonings, accidents, and other external causes,
was created to determine if non-cancer endpoints show an association with radiation exposure.

Since the purpose of analysis is to identify trends with cumulative dose that contribute to mortality, both immediate and contributory causes of death are included in outcomes for multivariate analysis. Inclusion of all cancers mentioned on the death certificate maximizes

statistical power to better evaluate mortality trends with dose. According to Little *et al.*, (1993, p. 105), it is not expected that there would be differential reporting of cancers on death certificates among the dose groups. For the purposes of investigating trends of relative risk with dose, the use of any mentioned cancers on the death certificate should not introduce bias. Table 3.5 summarized the cancer groupings by immediate and contributory causes. There were 345 immediate cancer deaths and 34 contributory cancer deaths. There were no deaths due to thyroid cancer and only 1 death due to multiple myeloma (ICDA-8 203) in the ORNL cohort.

D. Cross-Classification to Generate Grouped Data for Analysis

Before moving to a discussion of Poisson regression, it was important to describe how tables of data for regression analysis were generated, since Poisson regression analysis requires counts of deaths and person-years by category. A computer program written by Pearce and Checkoway (1987) was implemented using the ORNL data (Appendix 1). The objective of this program was to generate a table of deaths and person-years cross-classified by variables under study. These seven variables were: type (2 levels), agerisk (16 levels), yearrisk (8 levels), worker status (2 levels), length of follow-up (9 levels), duration of employment (9 levels), and cumulative dose (13 levels).

An eighth column in the table was generated by cross-classification of these variables (Appendix 2). In this eight column table, variable 'type' had two levels; if type=0 then deaths were in the eighth column. If type=1 then person-years were in the eighth column. Only column 8 contained useful information -- deaths and person-years. A ninth column was added by cutting the eight column table into half and moving the person-years, where type=0 into the column next to deaths. Appendix 2 provides an example of this procedure.

There were many rows with no deaths, but person-years, as well as many rows with no person-years and no deaths. Records with no deaths or person-years of observation were omitted for analysis, since no information is contained in these rows. These procedures were followed to

generate a separate table of data for each outcome by induction interval. This cross-tabulation of deaths and person-years was used as data in statistical analysis. The factors that define the multidimensional table were independent variables for model fitting.

E. Poisson Regression: Log-Linear Model Fitting Using Time-Related Factors

Poisson regression is a log-linear modeling technique, because the logarithm of expected deaths is modeled as having a Poisson distribution. This analytical technique has gained popularity for use in cohort studies for two primary reasons. First, patterns of exposure-disease relationships can be elucidated from large amounts of data, like that collected for occupational studies, by grouping variables into categories. Secondly, since data are grouped into categories, the comparison group need not be external to the cohort, but can be within the cohort. For this analysis, the reference category (i.e. comparison group) were those in the zero dose group.

Poisson regression analysis was conducted in the context of Generalized Linear Models (GLM) using Splus software (Statsci, 1995). A large number of different techniques are unified by the concept of generalized linear models (Spector, 1994, p. 231). In matrix notation the linear model can be extended to a generalized linear model represented in the following way:

$$y = g(X\beta) + e^*$$

where $g(\cdot)$ is the link function that can change to accommodate a variety of models, and e^* was an error distribution that may come from a variety of different distributions, including the binomial, Poisson, and normal distributions (Spector, 1994, p. 231). In Splus, the link and error distribution are specified in the 'glm' model formula using argument 'family=poisson'. The 'family' argument packages both the Poisson error distribution (variance μ) and the multiplicative, log-linear link function, $\log(\mu)$. The link function describes how the overall mean depends on linear predictors (Chambers and Hastie, 1993, p. 1997). The link function in 'glm' assumes a linear relationship between the outcome and independent variables.

GLM using the Poisson link function was used to estimate parameters by maximum likelihood (ML)(Chambers and Hastie, 1993, p. 242). ML techniques generate parameter estimates for independent variables by searching for the value that most likely produced the observed data. In Splus maximum likelihood estimation uses the iterative re-weighted least squares (IRLS) algorithm.

The log-linear model can be written as a multiplicative model for expected cell counts or can be written where the main effects are a linear function of the logarithm of the expected cell counts, which is shown below:

$$\log(\text{expected counts}) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \ln(\text{person-years})$$

where α is the intercept, β_1 through β_6 represent parameter estimates for agerisk, yearrisk, worker status, length of follow-up, duration of employment, and cumulative dose, respectively, and x_1 through x_6 represent the factors (agerisk, yearrisk, worker status, LOF, DOE and DOSE). A summary of cut points and levels for each predictor variable can be found in Table 3.4. Indicator variables were automatically constructed as part of the computer regression program. The first level of each factor is coded zero and subsequent levels are equally spaced and ordered. Factors effects are estimated relative to the first level. Dose, originally recorded in millirem (mrem), was converted to rems and recoded to the mid-point of the dose category with the following cutpoints. The equivalent measure in Sieverts (Sv) is also presented (1 rem = 0.01 Sv). One rem is 100 times smaller than a Sv.

Level	Range (mrem)	Recoded to Rems	Seivert Equivalent
0	0 (reference category)	0	0
1	0+-<1000	0.5	0.005
2	1,000-<5000	2.5	0.025
3	5000-<10,000	7.5	0.075
4	10,000-<15,000	12.5	0.125
5	15,000-<20,000	17.5	0.175
6	20,000-<25,000	22.5	0.225
7	25,000-<30,000	27.5	0.275

8	30,000-<35,000	32.5	0.325
9	35,000-<40,000	37.5	0.375
10	40,000-<45,000	42.5	0.425
11	45,000-<50,000	47.5	0.475
12	>50,000	82.5	0.825

The range for the last dose category was 50,000 mrem to 114,405 mrem; the mid-point of the range was 82,202. Cumulative dose was then fit as a continuous variable. The Poisson model allows residual analysis in GLM so that the contribution of added terms can be evaluated while holding fixed those already fit (Chambers and Hastie, 1993, p. 222).

Main effects were added in the following order: agerisk, yearrisk, worker status, length of follow-up, duration of employment, and dose. As each main effect was added, the GLM model generated a variety of information. The primary approach for identifying contribution of an added variable was the nested model approach. The method starts out with a simple model, including only the intercept term. Then, a variable, such as agerisk, was added, and the contribution of the addition of this variable to the reduction in residual deviance is compared to the null model with only an intercept term. Next, yearrisk was added and the contribution of yearrisk to reduction in residual deviance was compared to the model that included the intercept and agerisk. The final nested model compares a formula where all main effects are added (intercept + agerisk+ yearrisk + worker status + lof + doe) to a formula with all main effects plus dose. The contribution of dose to the main effects model can be assessed by the deviance difference, i.e. change in residual deviance, that results from adding dose to the model. The significance of adding a parameter to the model is assessed by subtracting the residual deviance of the smaller model from the residual deviance of the larger model and comparing the difference using a chi-square test with 1 degree of freedom ($\chi_1^2 = 3.84$).

It is convenient to summarize a series of fitted models in an 'Analysis of Deviance Table', which will be presented for each outcome by empirical induction period. Inference is based on the deviance difference between two nested models. In Splus the term 'Deviance' refers to 'deviance difference'. A computer program for generating results is provided in Appendix 3.

F. Poisson Regression: Model Fitting Using Linear Excess Relative Risk

In the previous section, a multiplicative (log-linear) model was used to generate parameter estimates using Poisson regression. A second type of model structure, the linear excess relative risk, is presented in this section. This dissertation was originally planned with the goal of comparing results between the log-linear model and the linear excess relative risk model. This comparison seemed necessary, since much controversy surrounded Wing *et al.* (1991), in part, because the analysis failed to incorporate the linear excess relative risk model.

The linear excess relative risk model has been preferred in analysis of cohorts exposed to low-level radiation, such as ORNL, so that results from analysis of these cohorts would be comparable with results from follow-up studies of the atomic bomb survivor (ABS) cohort, which experienced higher exposure. It is desirable that results in estimated mortality risk be comparable between these two exposure groups, since public health standards are based on extrapolation from the ABS cohort data. Empirical findings from study of nuclear cohort populations completes a gap in our understanding of the health effects of low-dose radiation, but more importantly serves to 'check' that public health standards based on extrapolation do not underestimate risk.

The 'linear' in linear excess relative risk has been adopted as preferred statistical methodology after several decades of follow-up of the ABS cohort. Researchers at the Radiation Effects Research Foundation (RERF) determined that the linear excess relative risk model was the simplest model that provides the best goodness-of-fit (largest deviance difference) for solid cancers, compared to the log-linear or linear-quadratic models (Shimizu *et al.*, 1990). (See Chapter 1, section D for a thorough discussion).

There are two major differences between this model and the log-linear model as currently used. The intercept term in the linear excess relative risk model goes through zero. Since the 'true' shape of the dose-response curve at low doses is unknown in human populations, it is assumed that the dose-response curve for nuclear worker populations is linear and crosses the y-

axis at zero. There is controversy about this assumption, but for purposes of radiation protection, caution is taken not to underestimate risk.

Secondly, cumulative dose is not transformed onto the logarithmic scale using a linear excess relative risk model, whereas the log-linear model assumes that once transformed cumulative dose is linear on the logarithmic scale. According to Gilbert *et al.* (1989), the linear excess relative risk model is preferred over the log-linear model, because comparisons can be made to the ABS cohort data. Futhermore, Gilbert and colleagues state for lower doses, the log-linear function $\exp(\beta z)$ is approximately equal to the linear function $1 + \beta z$. The linear excess relative risk model tends to give larger risk estimates and wider confidence interval (Gilbert *et al.*, 1989).

The goal of comparing results between the linear excess relative risk model and the log-linear model cannot be completely achieved, primarily due to limitations in analytical capacity. While the log-linear model was fit using time-related factors agerisk, yearrisk, worker status, length of follow-up, duration of employment, and dose, the linear excess relative risk model allowed use of three variables or less, depending on the levels of stratification. Fewer category levels of agerisk and yearrisk were allowed than in the log-linear model. A complete analysis using all levels of each time-related factor was not possible, since a student version of the software was available to conduct analysis.

The linear excess relative risk model (ERR) is obtained from a statistical model designed around the ERR. In simplest terms, the ERR = RR - 1, where RR is the relative risk. If ERR = RR-1, then RR = 1 + ERR. The model used in this analysis takes the following form:

$$RR = s\,[\,1 + \beta_1\,\text{dose}]$$

where s indicates adjustment of the background mortality rate, and β_1 is the ERR. The RR is modeled as a linear function of dose. The coefficient β_1 is referred to as the excess relative risk and is expressed as a proportional increase over baseline per unit of dose (Gilbert *et al.*, 1990, p. 919). The symbol s represents stratification to make adjustment of the background

mortality rate. A more technical summary describing the ERR model can be found in Peterson *et al.*, 1994 (p. 3-7).

A student version of the regression program AMFIT, contained in the software EPICURE©, was used to obtain estimates of the ERR. AMFIT is fundamentally a Poisson regression program designed to be used with grouped cohort follow-up data and was developed by statisticians at RERF in Japan. The rate to be modeled is computed as the ratio of cases to person-years for each record in the input dataset (Epicure Use's Guide, 1993, p. 37). AMFIT models the Poisson mean as a piecewise constant hazard on fixed time intervals. This means that death rates were assumed constant within fixed time intervals and exposure categories. It was assumed that the variability within time intervals and exposure categories was small relative to variability between intervals. Because of this assumption, it was possible to use maximum likelihood estimation to obtain the ERR (Epicure User's Guide, 1993, p. 11).

Time-related variables were used for stratification using the STRATA command. Stratification of a categorical variable essentially removes the influence of that variable as a possible confounder with cumulative dose as well as possible interactions. Stratification adjusts the background rate for factors affecting the background rate (Epicure User's Guide, 1993, p. 207).

The data prepared for Poisson regression in the previous section were read into AMFIT. Not all dataframes used in log-linear analysis were used in ERR analysis. Only three lag intervals (lag=0, 10, and 20) were used to model the ERR. Using the student version of EPICURE© precluded analysis for all levels of each categorical variable, as presented in Table 3.4. When stratifying by only one variable, cutpoints were the same as those presented in Table 3.4, except for agerisk which was eight categories instead of 16 and yearrisk which was four instead of eight levels. When stratifying by two or more variables, fewer levels were possible.

Because the number of categories by which three variables could be stratified was reduced relative to the log-linear approach, a decision was made to introduce paycode as a third stratification variable with agerisk (5 levels) and yearrisk (4 levels). This would allow closer

comparison of results with other nuclear worker cohort studies, and control for residual confounding. The following levels for stratification were used:

Strata Cutpoints for Single Stratification Variables		Levels
1. AGERISK	<45, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75+	8
2. YEARRISK	1945-49, 1950-54, 1955-59, 1960-64, 1965-69, 1970-74, 1975-79, 1980-84	8
3. LOF	0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-41	8
4. DOE	0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-41	8
5. WORKER STATUS	0,1	2

Strata Cutpoints for More than One Stratification Variable		Levels
6. AGERISK	<45, 45-54, 55-64, 65-74, 75-90	5
7. YEARRISK	1945-54, 1955-64, 1965-74, 1975-84	4
8. LOF	<10, 10-19, 20-29, 30-41	4
9. DOE	<10, 10-19, 20-29, 30-41	4
10. PAYCODE	0, 1, 2	3

Dose was read into AMFIT as a categorical variable with 12 levels. The cutpoints for dose as measured in millirem were recoded into Sieverts:

Level	Range	Recoded to Sieverts
0	0 (reference category)	0
1	0+-<1000	0.005
2	1,000-<5000	0.025
3	5000-<10,000	0.075
4	10,000-<15,000	0.125
5	15,000-<20,000	0.175
6	20,000-<25,000	0.225
7	25,000-<30,000	0.275
8	30,000-<35,000	0.325
9	35,000-<40,000	0.375
10	40,000-<45,000	0.425
11	45,000-<50,000	0.475
12	>50,000	0.825

The range for the last dose category is 50,000 mrem to 114,405 mrem; the mid-point of the range is 82,202. Dose was centered to mid-category and recoded to be a continuous variable for analysis with AMFIT.

Outcomes evaluated were: solid cancers only, leukemias excluding CLL, solid cancers, removing smoking-related, and smoking-related.

After stratification, the NULL model was fit to the data constraining β_1 to be zero. With the data stratified and the null model fitted, dose was fit using the LINEAR command. Thus there are no parameter estimates for the time-related variables. The influence of covariates were removed through stratification. The unexposed category with zero cumulative exposure was the comparison group (i.e. interval comparison group).

What was referred to as the 'deviance difference' approach used in log-linear models analysis was the same approach used in the ERR analysis. In the ERR analysis the deviance difference was measured as the likelihood ratio test (LRT)(LRT=deviance difference). The likelihood ratio test requires a nested model approach, comparing the difference in deviance between the null model and that with the addition of dose, where dose was added as a continuous variable. The likelihood ratio test was used to demonstrate a well-fitting change in deviance. The deviance from the current model is subtracted from that of the null model and the difference in number of free parameters is computed. In this analysis the difference between nested models will always be 1, which has a $\chi 2$ distribution with 1 degree-of-freedom ($\chi 2 > 3.84 = p<0.05$).

The coefficient associated with dose is the percent increase in mortality at the 1 Sv level. This is the unit of risk for excess relative risk coefficients, which are in units of percent per Sievert (%/Sv) (Peterson *et al.*, 1994, p. 9-1). The estimated relative risk at 1 Sv would be 1 + ERR. For example, if a regression coefficient fitting the ERR model is 0.5, then the mortality rate is 50% higher in the exposed population, or, 1 + 0.5 = 1.5 times greater than the baseline mortality rate in the nonexposed population. The value 0.5 is the excess relative risk and the value 1.5 is the relative risk (RR).

The summary parameter table and results generated by AMFIT include the following: parameter estimate for cumulative dose, standard error, null deviance and degrees of freedom, model deviance and degrees of freedom, likelihood ratio statistic and p-value, and confidence

interval (CI) for the parameter estimate. The CI was calculated as two-sided (β +/- 1.96*std.err) (Epicure User's Guide, 1993, p. 52).

G. Limitations of Data Analysis

(1) Exclusion of Paycode in Log-Linear Model Fitting

A decision was made *a priori* to exclude the variable paycode from log-linear analysis, since the presence of paycode could influence the relationship of time-related factors to mortality and/or cumulative dose. It was decided to include paycode in linear excess relative risk analysis as a stratification variable, since it was determined after data analysis had begun that results using linear excess relative risk model would not be comparable to results from log-linear analysis. The two statistical approaches were comparable, since the same degree of stratification using each model could not be achieved with time-related variables.

(2) Measurement Error of Exposure

(a) *Dosimeter Readings, and Level of Detection*

The quality of radiation measurements become even more important when exposures have been very low. In the ORNL cohort most workers received repeated low doses of radiation. Accuracy of the measuring instruments, reporting of levels near the limit of detection, and the pattern of dose accumulation are important considerations.

The difficulty with film badge measurements was estimating exposure from measurements made below the film's limit of detection. Weekly readings could promote cumulative dose underestimation if badges were not sufficiently exposed to reach a minimum detectable dose of 30 mrem (0.3 mSv). The individual's documentation for a film with an exposure below the detection limit might be recorded as the detection limit or may be recorded as zero depending upon ORNL protocol at the time. In a years time, a worker could have received up to 1.5 rem (0.015 Sv) that would be unrecorded or recorded as zero. Tanksersley *et al.* (in

press) recently showed that unrecorded exposures were highest in those with the highest recorded exposure.

(b) *Background Radiation Exposure*

The total external gamma-ray and cosmic-ray radiation in US cities averages from 0.7 mSv (0.07 rem) to 2 mSv (0.2 rem) per year (NCRP, 1987). The geographic distribution of natural exposure and the variability in life-style, and individual mobility introduces the potential for exposure misclassification, especially when exposure is a fraction above average background (Harley, 1991). Background exposure at ORNL was assumed to be 0.01 mSv per week (State of Tennessee) and subtracted from the readings by health physics personnel (Tankersley, personnal communication).

(c) *Exposure to Radiation at Non-DoE Facilities*

The amount and types of radiation that ORNL employees may have received prior to 1943 is unknown. Many of these workers were relocated from contractor facilities, such as Dupont Corporation, or university research laboratories, such as the University of Chicago Physics Department. These institutions are non-DoE facitlites. Those working in nuclear research who relocated from one area of the country to another may have received substantial doses that would not be recorded (Strom, 1991, p. 69). These workers would be eligible for inclusion in the ORNL cohort. For example, Enrico Fermi, a Nobel Laureate in Physics who is probably in the ORNL cohort, worked in nuclear physics in the 1920's and 1930's receiving large doses that would not have been monitored before 1943 (since standard radiation exposure monitoring did not exist). Large doses of exposure received by members of the ORNL cohort employed at non-DoE facilities prior to 1943 would not be reflected in dose information that forms the basis for radiation risk estimates. Large unrecorded doses in cohort members would tend to overestimate mortality risk from exposure in the ORNL cohort. White men who were known to have been employed at other DoE facilities (such as Los Alamos, NM or Hanford, WA) were excluded from

eligibility in the ORNL cohort. The eligibility criteria included those who were hired between January 1, 1943 and December 1, 1972 with no history of working at another DoE facility.

(d) *Exposure to Workplace Chemicals*

There was extensive exposure to paints, solvents, asbestos, and other chemicals used in construction and maintainence operations at ORNL. According to ORNL, monitoring data from exposures in air are available for mercury, lead, beryllium, and nickel. Biological monitoring (i.e. urine) programs were initiated in the 1950's for mercury and nickel, and in 1949 for lead. Monitoring data are also available for perchloroethylene and carbontetrchloride (ORAU Symposium, 1992), both of which cause liver cancer in mice. Benzene, a known human carcinogen, was used at ORNL, but the available information did not indicate exposure to benzen was montiored. Nickel is listed as a human carcinogen; beryllium and lead have been shown to cause cancer in animals (Goyer, 1991, p. 632). The fact that biological specimens were collected for these carcinogens suggests that exposures were of concern. Exposure to known and probable carcinogens in the workplace have not been incorporated into analysis of ORNL mortality risk estimates. The contribution of chemical exposure to mortality burden in this cohort may never be adequately determined.

(e) *Consumption of Tobacco Products*

The influence of the cigarette smoking and chewing tobacco on cancer mortality in the ORNL cohort could not be assessed. Yet, tobacco consumption, particularly cigarette smoking, is an important confounder. Data was collected on smoking for a twenty-five percent (25%) random sample of the ORNL study population (Elghany, 1993). Data recorded during pre-employment physical examination were abstracted from the medical charts for approximately seventy percent (70%) of this sample (70% of 25%). The remainder were missing smoking information on their medical records. A

larger proportion of cases were smokers, though there was no statistically significant difference in the smoking status between cases (86.2%) and controls (77.4%). Elghany (1993) found that eighty percent (80%) of the ORNL sample were smokers at the time of the pre-employment physical. Thus, cigarette smoking is an uncontrolled confounded in the ORNL cohort.

Table 3.2

Cohort Definition and Vital Status as of December 31, 1984
for 8,318 White Males Employed at ORNL between 1943-1972
as Obtained from DoE's Comprehensive Epidemiologic Data Resource

Eligibility: White males hired between 1/1/43 and 12/31/72
who worked at least 30 days only at ORNL
Follow-up: Through 12/31/84

Total Workers*		17,517	
Exclusions			
	Worked less than 30 days	469	
	Unknown information	426	
	Women	3792	
	Nonwhite	805	
	Employment in other DoE plants (c)	3707	
White male study cohort (%)		8318	
	Missing		1(0.01)(a)
	Known Alive		6108(73.4)
	Status Unknown		686(8.2)
	Deaths (%)		1523(18.3)
		No death certificate	34(2.23)
		Cancers	345(22.6)(a)
		Known Natural Deaths(d)	972(64.0)
		External Causes	172(11.3)
Total Person-Years of Follow-up			213,950(b)

* Includes females and nonwhites from January 29, 1943 to December 31, 1984
(a) One death is counted as missing, since New York City did not grant permission for CEDR to release ICDA-8 cancer code. Total deaths are 1,524 as published by Wing et al.
(b) Total person years differ using rounded dates. Unrounded person-years for the entire cohort are 215,680, as published by Wing et al.
(c) Exclusions include working at Y-12 or K-25, which are other plants on the Oak Ridge Reservation.
(d) Known Natural Deaths excludes deaths from cancers and injuries, poisoning, accidents, and other external causes of death.

Table 3.3

Cutpoints Used for Model Fitting in Wing et al., 1991(a)

Age(b)	15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90-95
Birth cohort (c)	<1905 (referent) 1905-1914 >1915
Active worker status	0 - not active (referent) 1 - terminated worker but still considered working
Paycode(d)	monthly (referent) weekly hourly
Cumulative Dose (mSv)(e)	0, >0-19, 20-39, 40-59, 60-79, 80-109, 110-119, 120+

(a) Variables "type" and "internal monitoring" are not included in model fitting, but used to construct multi-dimensional table.
(b) Age was stratified into 16 5-year intervals. Then age was tranformed and centered around 52.5. (e.g. log(age + 2.5) / 52.5).
(c) Birth cohorts 1905-1914 and <1905 were combined in leukemia regression analysis, and used as the referent.
(d) Weekly and hourly workers were combined in regression analysis.
(e) Midpoint of the dose category was used in regression, except in the highest dose category where the median value of person-years in the highest dose category was used (194 mSv).

Table 3.4

Cutpoints Used for Time-Related Factors in Current Analysis

DOE	Duration of employment (not the same as duration of exposure) (0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40)
LOF	Length of follow-up: number of person-years contributed by the worker from entry into the cohort until death, end of study period, or lost to follow-up, whichever occurs first. (0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40)
AGERISK	Attained age is a worker's age at any point in follow-up. (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90
CALYR	Calendar year is the chronological year at any point in time as a worker passes through follow-up. (1945-49, 1950-54, 1955-59, 1960-64, 1965-69, 1970-74, 1975-79, 1980-1984)
WORKER STATUS	Whether the worker has retired or is still working, lagged by two years. (0, 1)
CUMULATIVE DOSE	Cumulative dose is annual dose summed yearly for overall measure of past exposure (in mSv) >0-<10, 10-<50, 50-<100, 100-<150, 150-<200, 200-<250, 250-<300, 300-<350, 350-<400, 400-<450, 450-<500, >=500.

3.5 Summary of Cancer Deaths Grouped for Model-Fitting
by Immediate and Contributory Causes of Cancer

Cancer Group	TOTALS	Number of Cancer Deaths	
		Immediate Cancer	Contributory Cancer
1. All Cancers	379	345	34
2. Solid cancers(a)	349	317	32
3. Lung cancers	104	96	8
4. Solid cancers, no lung	245	221	24
5. Solid cancers, no smoking-related(b)	205	182	23
6. Solid cancers and lung(c)	309	278	31
7. Solid cancer, no respiratory (d) and upper digestive	232	207	25
8. Smoking-related (Group I) (e)	138	129	9
9. Smoking-related (Group II) (f)	144	135	9
10. Smoking-related (Group II), excluding lung cancer	40	39	1
11. All Leukemias	30	28	2
12. Leukemia excluding CLL (g)	23	23	0

(a) solid cancers excludes leukemia (n=30)
(b) excludes leukemias (n=30), lung (n=104), larynx (n= 4), nasopharnyx (n=1), bladder (n=3), pancreas (n=26), and esophagus (n=6)
(c) excludes smoking-related cancers
(d) excludes leukemias (n=30), nasopharynx (n=1), hypopharynx (n=1), ill-defined lip (n=1), esophagus (n=6), larynx (n=4), and lung (n=104) (includes bladder and pancreas)
(e) includes lung (n=104), larynx (n= 4), nasopharnyx (n=1), bladder (n=3), pancreas (n=26)
(f) includes lung (n=104), larynx (n= 4), nasopharnyx (n=1), bladder (n=3), pancreas (n=26), and esophagus (n=6)
(g) excludes chronic lymphocytic leukemia (n=7)

CHAPTER 4

RESULTS

I. VITAL STATUS AND MISSING INFORMATION

After exclusions enumerated in Table 3.2, at the end of follow-up on December 31, 1984, Table 4.1 shows that 73.4% of the cohort was alive, 18.3% were deceased and 8.2% had unknown vital status and were considered lost to follow-up. Based on rounding of person-years, there were 213,950 person-years in the cohort for this analysis (see Chapter 3, I.B. for discussion). Those alive contributed 167,941 person-years, those deceased contributed 37,875 person-years, and those with unknown vital status contributed person-years of observation up until termination of employment (9,636 person-years).

In some cases the vital status was unknown (n=686; 8.2%). Those with unknown vital status were assumed alive at the end of follow-up, but only contributed person-years up until termination of employment. Assuming that workers were alive when they are not could have the effect of artificially lowering mortality rates if some of the unknowns had, in fact, died before end of follow-up. However, counting person-years until date of termination for those with unknown vital status minimizes loss of information.

For others the vital status was known, but the cause of death could not be obtained from a death certificate. There were 34 (2.23%) deaths for which cause of death was not obtained from a death certificate. These deaths were only included in analysis of all-cause deaths.

There were 469 workers who were employed for less than 30 days, the minimum employment period for eligibility into the study, and thus, are not included in this analysis. The gender distribution and vital status of workers employed for less than 30 days were not available from data in the CEDR archive.

In terms of cumulative exposure by vital status, 78.4% of deceased received exposures above zero. Seventy-four percent of those alive at the end of follow-up received greater than zero

exposure. Sixty-six percent of those with unknown vital status received greater than zero dose (Table 4.1).

II. DESCRIPTIVE INFORMATION ABOUT TIME-RELATED VARIABLES

A. Mean, Standard Error, and Range

Table 4.2 presents mean, standard error, and range for time-related variables grouped by (1) entire cohort, (2) known deaths, (3) cancer deaths, and (4) still alive. Looking across the row for duration of employment, mean duration of employment does not differ greatly by vital status. Mean duration of employment for those still alive, 10.3, is quite similar to the mean duration of employment for cancer deaths (9.9 years). The range of duration of employment for each group is also similar.

The mean length of follow-up by study status ranges from a mean of 23.4 for all known deaths to a mean of 27.5 for known alive. The range of length of follow-up for those still alive is different from the range of length of follow-up for the other groups. Those still alive have a length of follow-up between 12-41 years, while the all cancer group ranges from 0 to 41. This suggests that some still alive have been in the cohort for a minimum of twelve years.

Other notable aspects of this table are that the mean age of hire for those that died of cancer was 37, while the mean year of hire was 1948, which does not differ much from the non-cancer deaths. The mean age of hire for the entire cohort is 28 and the mean year of hire is 1955.

B. Frequency Distributions and Histograms

(1) **Agerisk**

The probability of developing cancer over a certain period increases as one advances in age. A worker who has not left the cohort is eligible to develop disease, and therefore is considered "at risk" for disease or death. As a worker increases in age, risk of death increases independently of

exposures that may enhance mortality. In Table 4.3 agerisk is displayed for deaths of all causes of death and all cancers. Since the tables represent agerisk as a subset of the cohort, namely for only those deceased, then the tables are analogous to age at death. However, agerisk is a slightly different concept that simply age at death, since members of the cohort still alive contribute person-years when stratifying by agerisk. Agerisk represents the age at which these members left the cohort. The age at risk for other cohort members has been omitted from this table. In stratification on agerisk, there would be seven deaths in agerisk group 20, and the person-years for agerisk group 20 would have all person-years in the cohort that contributed to agerisk 20.

In the frequency and percent columns, the distribution of deaths increases as the cohort ages. Agerisk displayed as a continuous variable in Table 4.3a, showed that deaths peaked at agerisk 65 (15.6%) but that deaths are primarily distributed between agerisk 50 and 70, approximately 65% of deaths. The trend for cancer deaths was similar. Between agerisk 50 and 70, 71% of the cancer deaths occurred (Table 4.3b).

(2) Yearrisk

The probability of cancer developing over a certain period increases as a worker advances through chronological time and hence, calendar time. A worker who has not left the cohort is eligible to develop disease, and therefore is considered "at risk" for disease or death. As a worker moves through calendar time, risk of death increases independent of exposures that may enhance mortality. Yearrisk was analogous to year of death in the subset of deaths presented in Table 4.4a and 4.4b, since year at risk for other member of the cohort are not presented. Table 4.4a shows that the number of deaths are increasing as the cohort moves through calendar time, peaking at 1980, which reflects that 26.5% of the cohort died between 1980-1984. Table 4.4b shows that 33% of cancers deaths occurred between 1980 and 1984.

(3) Active Worker Status

Briefly, the rationale for including worker status as a potential confounder is summarized. The reader is referred to Chapter 3, Methods, for a more thorough discussion. Whether or not a worker has recently left employment, such are retirement, influences overall mortality in a cohort. This aspect of the health worker effect is not confined to comparisons between exposure groups, since odd peaks of mortality can occur in relation to changing jobs (i.e. going from working to retirement)(Breslow and Day, 1987, p. 40). The percentage of 'inactive' versus 'active' person-years can be expected to influence findings of mortality studies. Furthermore, workers employed the shortest duration have the highest mortality and contribute the most inactive person-years. Breslow and Day (1987) have suggested that in order to account for the odd peaks in mortality that can occur immediately after leaving the workplace, the first two person-years years after retirement and deaths should be treated as if the individual is still employed. Specifically, the person-years are divided into "active" person-years (person -years while still working at ORNL) and "inactive" person-years (person-years subsequent to working at ORNL).

For solid cancers, this change in status resulted in 74.5% of 260 deaths classified as occurring two years after ceasing work, while 89 (25.5%) deaths occurred either while still employed or within two years of leaving employment (Table 4.5). The person-years in table 4.5 represent all person-years in the cohort (n=213,950). The person-years are split between those classified as active and inactive. Active status include person-years for workers which are (1) dead but still considered alive, based on a two year lag, and (2) alive and currently employed at ORNL (n=95,123). Inactive person-years include person-years for workers who are deceased, lost to follow-up, or otherwise no longer in the cohort.

(4) Duration of Employment

Table 4.6 breaks down duration of employment (DOE) into three groups: entire cohort, known natural deaths, and cancer deaths. The most notable element of the DOE frequency distribution (Table 4.6) is that over 55% of the cohort worked less than five years. Twenty-nine

percent (29%) of the entire cohort was employed between 15 and 41 years, while twenty-seven percent (27%) of the non-cancer deaths and thirty-five (35%) of the cancer deaths were employed between 15 and 41 years. Only 3,715/8,318 (44.6%) of the cohort members worked five years or more. The range of DOE is 30 days to 41 years with the mean DOE at 9.3 years (std. err = 0.12);

The distribution of DOE is highly skewed toward workers employed less than five years. For this reason, a histogram displaying the natural logarithmic distribution of DOE was provided in Figure 4.1a. Taking the natural log of DOE makes the distribution more symmetric and normally distributed. While the distribution of DOE was transformed to the natural log scale, the cutpoint labels on Figure 4.1a (<1, >=1, >=7, and >=20) are displayed on the arithmetic scale for easier interpretation. The histogram indicates that 2,880 (34.6%) of the cohort was employed less than one year, and 2,321 (27.9%) of the workers were employed between one year and less than seven years. Approximately 16% (n=1,314) were employed between seven and 19 years, while the remainder of the cohort (n=1,803 or 21.68%) were employed 20 years or more. From the frequency distribution and histogram it is concluded that over one-half of those employed less than five years were actually employed less than one year.

(5) Length of Follow-up (years)

Table 4.7 presents a frequency distribution for length of follow-up (LOF) by three groups: entire cohort, non-cancer deaths, and cancer deaths. Most of the cohort was followed between 15 and 41. Eighty-four percent of the cancer group was followed between 15 and 41 years, while 81 percent (81%)of the non-cancer deaths and 83 percent (83%) of the entire cohort were followed between 15 and 41 years. The mean length of follow-up for these three groups did not differ, 25.6, 24.1 and 24.2 years, respectively, for the entire cohort, non-cancer, and cancer deaths.

The histogram for length of follow-up (Figure 4.1b) closely corresponds to the frequency distribution for the entire cohort. There were 138 cohort members who had 'zero' LOF recorded, but presumably were employed at least 30 days in order to be included in the cohort. The

documentation and other materials with the ORNL dataset did not describe this group adequately. Of the 138 workers with zero LOF, 123 workers were included in the 686 workers for whom vital status was unknown. The cut points for the frequency distribution and for the histogram differ slightly, since the histogram cutpoints were computer generated based on distribution of the data. Nevertheless, it is evident from the data that much of this cohort contributed between 15 and 40 years to follow-up.

(6) **Cumulative Dose**

A worker's individual dose value accumulated yearly over a working lifetime represents cumulative dose. Figure 4.2 demonstrates the overall low exposure in the cohort. Over 40% of the entire cohort received approximately 10 mSv (1 rem) exposure over a working lifetime. The solid line, representing a cumulative exposure curve for the entire cohort, falls off rapidly after 50 mSv (5 rem) of cumulative exposure. For comparison purposes, the amount of cumulative exposure allowed per year in an occupational setting is 50 mSv (5 rem) (Shapiro, 1990, p.338). The middle peak, indicated by short closely spaced dashes, represents the group of deaths remaining after excluding cancer deaths and external causes of death. Over 60% of non-cancer deaths received approximately 10 mSv of cumulative dose. The sharp peak at 10 mSv represents the all cancer group (immediate causes of death only). It is evident that approximately 80% of this group received approximately 10 mSv of cumulative exposure.

The density distribution displays a three curves in the right tail. The first curve is between 100 mSv (0.1 Sv) and 500 mSv (0.5 Sv), which represents 24 deaths. Further out in the right tail, the two small peaks between 500 mSv and 1000 mSv (1 Sv) represent 1 death from esophageal cancer and one death from laryngeal cancer. For comparability purposes, the range between 500 mSv and 1000 mSv would be considered greater than low-dose exposure in the atomic bomb survivor (ABS) cohort (Shimizu *et al.*, 1990, p. 121), while 100 mSv would be considered in the low-dose range relative to exposures experienced by the ABS. The density distribution is a

smoothed representation of cumulative dose, so the curves do not correspond perfectly to cutpoints at 100 mSv, 500 mSv and 1000 mSv.

Table 4.8 shows a breakdown of cancer deaths by cumulative dose. From this display it can be seen that the two deaths in the right tail of Figure 4.2 are cancers of the esophagus and larynx, respectively. It is also evident that over 50% of the lung cancer deaths received cumulative dose less than the annual occupational limit of 50 mSv. There are six lung cancer deaths occurring in the dose range between 100 mSv to 150 mSv. There was one death from laryngeal cancer in the 850-900 mSv dose group. This was the highest dose group in which a cancer death occurred.

Table 4.9 categorizes cumulative dose into four groups: 0, less than 50 mSv, 50 mSv to less than 100 mSv and greater than 100 mSv presented for four broad outcome groups. Only 16.8% of the cancer group received zero exposure, while over 20% of workers in the other groups received zero dose. The second dose category (>0-49.9) corresponds nicely to the density curve presented in Figure 4.2), showing that a majority (90%) of the exposed cohort received less than the annual occupational limit over their working lifetime, while 86% of exposed cancer deaths received less than the annual occupational limit over their working lifetime. For the last dose category (100+ mSv), it is evident that the cancer group received a larger cumulative dose than other workers. This is evident by evaluation of the median dose (50% percentile) of exposed cancer deaths, which shows that 50% of 345 cancer deaths were below 6.1 mSv and 50% were above, while 75% of 345 cancer deaths were below 17.8 mSv and 25% were above 25 mSv. Median values were calculated including deaths in the unexposed group.

The range of dose for those still alive indicate that the worker who received the largest dose in the cohort was still alive at the end of follow-up in 1984. Workers who died of non-cancer causes (n=972) received a wider range of cumulative dose than cancer deaths (0-920.7 mSv versus 0-852.2 mSv). However, based on the 75% percentile, a larger dose was received by 25% of the cancer group (17.8 mSv) than by 25% of the non-cancer deaths (16.1 mSv) or alive group (11.7 mSv).

III. CAUSES OF DEATH

There were a total of 1524 deaths in the ORNL cohort between January 1, 1943 and December 31, 1984. As mentioned earlier, one cancer death is coded as missing making available 1523 total deaths including 379 cancer deaths (immediate and contributory).

Table 4.10 shows the break down of cancer deaths by immediate and contributory causes of death. The largest number of cancer deaths for immediate cause of death category was lung cancer (n=96), followed by large intestine (n=34), leukemia (n=28), and pancreas and prostate both having 25 deaths. Closely paralleling immediate cause of death, the largest number of contributory cause of death was also lung cancer (n=8), followed by prostate (n=5), and large intestine (n=3). There was two contributory deaths for leukemia and one contributory death for pancreatic cancer.

Table 4.11 shows outcomes for non-cancer causes of death. By far the largest disease burden in this cohort occurred from heart attack (n=386), and other diseases of the circulatory system (n=352).

IV. EMPIRICAL INDUCTION PERIOD

It has been established that development of cancer has a latency period. To date, little has appeared in the epidemiologic literature discussing statistical modeling of cancer latency and its impact on estimates of mortality risk. Few papers were found in the literature which contrasted various assumptions about cancer latency (Checkoway *et al.*, 1989). A systematic evaluation of computational approaches to incorporating an induction period was needed to develop a better understanding of the differences between assumptions. It was discovered that two approaches were referred to as the same phenomenon.

Lack of consistency between computational approaches for introducing an empirical induction period (EIP) may be an important methodologic consideration when comparing study results. For example, both Gilbert *et al.* (1993) and Wing *et al.* (1991) refer to a 10-year lag, but

10-year lag was not computed in the same way. If methodologic approaches differed, then results may not be comparable. Both techniques are analytic and employed to increase probability of detecting a true dose-related change in the disease or mortality experience of a cohort. The terms are not clearly defined and are used in varying ways by different investigators.

The null hypothesis here was that no difference in estimated mortality risk results between approaches to incorporating an empirical induction period. This hypothesis was not rejected. Results of this investigation lead to the conclusion that, while approaches to incorporating an empirical induction period differ computationally, parameter estimates do not differ. Different approaches did not lead to significantly different mortality risk. Three sections follow. Section A describes 'latency with lagging', while section B describes 'lagging' only. Section C graphically displays parameter estimates demonstrating there was essentially no difference between approaches.

A. Latency with Lagging Dose

For simplicity in terminology, 'latency' refers to removing deaths and person-years during some specified interval for analysis of cohort data, and 'lag' refers to shifting dose of individual cohort members. For example, a 10-year lag (Gilbert *et al.*, 1993) means that (1) the first five years of person-years and deaths are not counted, and (2) dose is lagged for five years from first year of cumulative dose. A 10 -year lag is, therefore, composed of a 5-year interval in which deaths and person-years are removed (plus the fractional year in which the worker entered the cohort), and a 5-year interval when dose is lagged. These two intervals together constitute a 10-year lag, since dose received in the first year of follow-up is not included until 10 years later (Gilbert, personal communication). An excerpt and interpretation from Gilbert *et al.*, 1993 follows:

"For example, a worker who initiated employment in 1950, and received doses of 10 mSv, 5 mSv, and 25 mSv in 1950, 1951, and 1952 respectively, would begin contributing person-years at the beginning of 1956. With a 10-year lag, this worker would be assigned 0 mSv for each of the years 1956-1960, 10 mSv for the year 1961, 15 mSv for the year 1962, and 40 mSv for 1963 and all succeeding years of follow-up." A 10-year lag is displayed in the following way:

cal yr	actual pys	analytic pys	actual cumdose	analytic cumdose	
1950	1	---	10	---	Started work in 1950
1951	2	---	15	---	These five-plus person-years are
1952	3	---	40	---	not counted in the cohort.
1953	4	---	40	---	
1954	5	---	40	---	
1955	6	---	40	---	
				Assign dose 0 for 1956-1960	
1956	7	1	40	0	
1957	8	2	40	0	The worker contributes
1958	9	3	40	0	9 person-years of follow-up
1959	10	4	40	0	to the cohort. Cumulative dose
1960	11	5	40	0	is 40 mSv.
1961	12	6	40	10	
1962	13	7	40	15	
1963	14	8	40	40	
1964	15	9	40	40	
1965	16	10	40	40 -- worker dies and leaves follow-up in 1965	

It appears that the last year of follow-up could be handled in two ways. The last year of follow-up could be rounded to mid-year. In the example above, this would mean that the worker would contribute 9.5 person-years of follow-up to the cohort. Secondly, the last person-year of follow-up may be included in the calculation of total person-years. For the example above, this would mean that the person-year for 1965 would not be counted as part of the total number of person-years, so that the worker would contribute 9 person-years of follow-up.

B. Lagging Dose Only

In contrast to Gilbert *et al.* (1993), Wing *et al.*, 1991 used a 'lag only' approach. Lagging dose is an approach that results in cumulative dose being shifted forward by the number of years in the lag interval. Real-time cumulative exposure at the end of follow-up, the width of the lag interval, becomes omitted. The total number of person-years and deaths are retained. This approach attempts to isolate the range of cumulative dose in the past that is relevant for disease development and ignore cumulative dose further out in follow-up that is unlikely to be related to disease development. A 10-year lag is displayed in the following way:

cal yr	actual pys	analytic pys	actual cumdose		analytic cumdose	
1950	1	1	10		0	Started work
1951	2	2	15		0	
1952	3	3	40		0	
1953	4	4	40		0	
1954	5	5	40		0	
1955	6	6	40	Additional	0	
1956	7	7	40--	cumdose between	0	
1957	8	8	40	1955 and 1964 is not	0	The worker contributes
1958	9	9	40	included in analysis.	0	15 person-years of follow-up
1959	10	10	40		0	is 40 mSv.
1960	11	11	40		10	
1961	12	12	40		15	
1962	13	13	40		40	
1963	14	14	40		40	
1964	15	15	40		40	
1965	16	16	40		40 -- worker dies and leaves follow-up in 1965	

In this example for one hypothetical worker, a worker does not accumulate an annual increase in dose after 1952. Thus, cumulative dose between 1952 and 1964 is not modified by subsequent exposures. When dose is lagged by 10 years (see 'actual cumdose' column), the cumulative dose from 1956 through 1964 is not included in analysis. These person-years become the '0' dose group that appears in column 'analytic cumdose'. Lagging dose by 10 years would not incorporate exposure beyond cumulative dose recorded in 1955 for this hypothetical worker. All person-years that this worker contributes to follow-up are kept in the cohort.

C. Graphical Display of Dose Coefficients

Because it was recognized that two computational approaches exist in the same body of literature, but referred to interchangeably, it was hypothesized that some difference in the parameter estimate may result due to the differences in the method for incorporating an empirical induction period (EIP).However, based on follow-up through 1984 in the ORNL cohort, no bias was detected using the following the following combinations:

Solid Cancers		Leukemias	
Latency	*Lag*	*Latency*	*Lag*
0	0	0	0
5	5*	0	2
0	10**	5	2
5	15	5	5
0	20	0	10

The rationale for these combinations is presented in detail in Chapter 3, Methods. The latency:lag combination that includes latency=5:lag=5 is analogous to an approach used by Gilbert *et al.*, 1993* while the latency:lag combination latency=0:lag=10 corresponds to the approach used by Wing *et al.*** In the radiation epidemiology literature, latency=5:lag=5 and latency=0:lag=10 were assumed to incorporate the same induction period, namely a 10-year 'lag'.

Figure 4.3 shows estimated dose coefficients for all cancers using the five latency: lag combinations. It can be seen that there is little difference in the value of the dose parameter estimate between latency=5:lag=5 (dose = 0.020) and latency=0: lag=10 (dose = 0.021), which are assumed to incorporate the same 10-year interval. At an EIP of 20 years, latency=5:lag=15 (dose = 0.032) shows no difference from latency=0:lag=20 (dose = 0.033), however, the dose coefficient is markedly increased between intervals 10 and 20.

Figure 4.4 shows parameter estimates for solid cancers (no leukemias). The same pattern for the EIP can be found for solid cancers as found with all cancers. After removing leukemias, the dose parameter estimates actually become more similar when comparing latency=5: lag=5 (dose = 0.021) to latency=0: lag=10 (dose = 0.021). There is very little difference between the dose parameter estimates comparing latency=5: lag=15 (dose = 0.032) to latency=0:lag=20 (dose = 0.033).

Figure 4.5 shows parameter estimates for smoking-related cancers. There is no difference between the latency: lag combinations. In fact, there was essentially no difference between latency: lag combinations for any of the outcomes evaluated in the ORNL cohort.

In the ORNL cohort no difference was found comparing latency=5:lag=5 with latency=0:lag=10 or comparing latency=5:lag=15 with latency=0:lag=20. It is believed that lagging dose only, approach 2, is more suitable to the analysis of cohort data, since approach 2 retains all deaths and person-years in the cohort. In Figure 4.6, parameter estimates do not change, since the first year of cumulative dose is assigned in 1961 for approach 1 and 1960 for approach 2, respectively (Figure 4.6). The major difference in approaches is the loss of person-years. No difference in mortality risk due to choice of approach exists in the ORNL cohort, which could be due to overall low exposures in this cohort. It is unknown whether differences would be found in another cohort, that received larger exposures or greater variability in dose. At the very minimum, these results help to visualize how the induction period was calculated.

The estimated dose coefficients for all cancers, solid cancers, and smoking-related cancers, increased with increasing lagged dose. Increasing mortality risk with increasing lagged dose was

most pronounced in the smoking-related cancers. This increase in risk with lagged dose was consistently demonstrated in all cancer outcomes, with the exception of lung cancers. Between an induction period of 10 and 20 years lung cancer mortality risk does not change, and may even decline.

In general, however, these results suggest that cumulative exposure received in the last 20-years of follow-up are not as important in mortality risk as exposures received prior to the last 20-years of follow-up. This gradient of larger coefficients with increasing lagged dose is consistent for cancer outcomes that are significantly related to cumulative dose and for cancer outcomes that are not significantly related to cumulative dose.

Figure 4.6 Summary of Two Approaches to Incorporate an EIP

Actual Exposure			Approach 1		Approach 2	
cal yr	pys	cumdose	latency with lagged dose		lagged dose	
1950	1	10	---	Deaths and	0	Started work
1951	2	15	---	person-years	0	
1952	3	40	---	are not counted	0	
1953	4	40	---		0	
1954	5	40	---		0	
1955	6	40	---		0	
1956	7	40	0	Contributes	0	
1957	8	40	0	9 person-years	0	The worker contributes
1958	9	40	0	of follow-up	0	15 person-years of follow
1959	10	40	0	Cumulative dose	0	up to the cohort.
1960	11	40	0	is 40 mSv.	10	Cumulative dose
1961	12	40	10		15	is 40 mSv.
1962	13	40	15		40	
1963	14	40	40		40	
1964	15	40	40		40	
1965	16	40	40		40 -- worker dies and leaves follow-up in 1965. Person-year in which death occurs is not counted.	

V. RESULTS FROM MODEL FITTING USING TIME-RELATED FACTORS

A. Poisson Regression: Results of Log-Linear Model Using Time-Related Factors

To assess the importance of individual time-related factors, Appendix 4 shows an 'Analysis of Deviance Table' for 13 outcomes by five latency and lag combinations. Both immediate and contributory causes of deaths are included in these results. Results for non-cancer outcome do not include latency and lag combinations. The components of an 'Analysis of Deviance Table' are as follows. Column heading 'Deviance', which is more correctly called deviance difference, reports the difference in deviance between each model and the one fitted immediately before it and 'df' is the difference in degrees of freedom between each model (always 1 in this analysis). A large deviance between nested models reflects that the added variable fits the model well. 'Residual df ' are the number of observations minus the number of estimated coefficients. 'Residual deviance' is the amount of unexplained variation. Deviances between nested models have chi-square distributions. The analysis of deviance table reports the effect of sequentially including each term starting from the NULL model up to adding dose last. The NULL model is a constant, and is the mean number of deaths if an intercept is present in the model. Each row of the table corresponds to a term in the model. The 'P(chi-sq)' gives the tail probability of the chi-square distribution corresponding to the 'df' and 'Deviance' columns, or simply the p-value for the addition of the variable to reduction in model deviance. The p-value is the significance probability of obtaining a more extreme value of the chi-square test statistic than the test statistic observed, calculated under the null hypothesis. The p-value is an assessment of the likelihood that the observed results occurred by chance alone.

In presenting the results, emphasis is given to testing whether cumulative dose has systematic influence on the risk of cancer mortality, with the influence of other variables removed from the data. The dose coefficients estimate the percentage increase in mortality per 10 mSv

exposure. In general the limitation of these analyses is that paycode was not included as a confounder. A second limitation is that there may be variables included in stratification that do not contribute to improvement of overall model fit to the observed data.

(1) All Cancers, Leukemias, and Non-Cancer Deaths

Table 4.12 shows parameter estimates for cumulative dose for each latency:lag combination, subsetted from the full deviance table that appears in Appendix 4. After adjusting for the effects of agerisk, yearrisk, worker status, length of follow-up, and duration of employment, the estimated coefficients for dose in 'all cancers' (n=379) are significant at all levels of the EIP. This is evident due to the P(chi-sq) which assesses the significance of adding cumulative dose to the model relative to χ_2 with 1 degree of freedom. A deviance difference greater than 3.84 indicates a probability less than 0.05. The dose coefficients, standard error, deviance, and p-value increase in a positive direction as the dose is lagged at greater intervals (Table 4.12). Similarity between the two EIP approaches was demonstrated. The standard errors are small relative to the dose coefficients, suggesting that there is small variability around mean cumulative dose. Cumulative dose appears to be significantly related to all-cancer mortality in this cohort, adjusting for time-related factors. For example, at lag=10, the contribution of cumulative dose to explaining cancer mortality was (0.021, p=0.01). Confounding from paycode has not been removed from analysis, so the dose coefficients may be overestimated, since paycode is related to mortality and may be a proxy for exposure.

Leukemia have been associated with cancer mortality in the atomic bomb survivor (ABS) cohort and in other nuclear worker cohorts. Seven of 30 leukemia deaths were chronic lymphocytic leukemia (CLL). Due to the small numbers, of both all leukemias and leukemias excluding CLL, the standard errors were larger than the dose coefficients, and thus, unstable (Table 4.12). Similar to findings of Wing *et al.* (1991), an association between cumulative dose and mortality could not be detected for either leukemia outcome group.

Chronic lymphycytic leukemia (CLL) has not been associated with radiation exposure in the ABS cohort and is usually omitted from leukemias in the analysis of nuclear cohort data. There were 7 deaths of CLL in the ORNL cohort. When removing these deaths the parameter estimate for dose improved slightly, even though there are seven fewer deaths. Nevertheless, the standard error and 95% confidence limits indicate instability in these estimates. The deviance does not change greatly with increasing lag, such as found with all cancers.

A non-cancer category was evaluated to identify if cumulative dose was associated with non-cancer deaths. This category, which excluded suicides, accidents, poisoning, and other external causes of death, was primarily composed of deaths from heart attack or heart disease. No empirical induction period was evaluated, since cancer was not an endpoint. The parameter estimate for cumulative dose was 0.010 (p=0.08). The reduction in deviance with cumulative dose added to the model was 3.0. This suggests that exposure to radiation was not related to non-cancer deaths.

(2) Solid Cancer Groupings

Leukemias have been shown to have a shorter induction period than cancers of other organ sites. For this reason, results from analyses are typically presented removing leukemias from the all cancer grouping and reporting results as solid tumors or cancers excluding leukemia. Table 4.13 presents solid cancers and subsets of solid cancer groupings. When removing leukemias from all cancers (solid cancers), as done in most nuclear worker studies, the number of deaths are reduced by approximately 30 from 379 to 349 solid cancer deaths. The coefficients for dose in the solid cancer grouping did not change, when removing leukemia deaths. For example, at lag=20, the dose coefficient was 0.33, while for solid cancers, at lag=20, the dose coefficient was 0.33. This suggests that death from leukemia does not strongly influence the mortality burden in this cohort, when controlling for the effects of time-related factors. Deviance resulting from addition of cumulative dose in the model increased and remained significantly associated with solid cancer

mortality at each level of the EIP. For example, the dose coefficient increases from 0.016 at lag=0 to 0.033 at lag=20.

Lung cancer was the largest group of cancer deaths in this cohort comprising 104/379 (27.4%) of the total cancer deaths. Estimated dose coefficients indicate that cumulative dose did improve overall model fit for lung cancer. However, estimates are unstable, since the standard errors are as large or larger than the parameter estimates. This suggests that there is wide variability around the mean value for cumulative dose. Duration of employment is significantly related to lung cancer mortality (p=<0.00, lag=10 and lag=20). The data suggest there was no difference in lung cancer mortality among exposure groups. This may or may not be true. Since the smoking prevalence in this cohort was very high 80% and radiation exposure generally low, difference in mortality due to radiation exposure may been masked by cigarette smoking.

When excluding lung cancer from solid cancer, the third group presented in Table 4.13, it is seen that cumulative dose contributes to goodness-of-fit of the model at each level of empirical induction period. For example, at lag=0, the dose coefficient was 0.019 (p=0.04), while at lag=20, the dose coefficient was 0.04 (p=<0.00).

Table 4.13 shows that when smoking-related cancers are removed from solid cancers, results are more similar to the lung cancer group. This outcome group has 205 deaths. The deviance difference is low and cumulative dose was unrelated to cumulative dose. The parameter estimates are smaller than the standard error which suggests wide variability around mean cumulative dose in solid cancers that are not smoking related.

Results of adding cumulative dose last to the model containing time-related variables is presented for a grouping of solid cancers and lung, but excluding other smoking related cancers (n=309). Not surprisingly, removing smoking-related other than lung, closely parallel results when all smoking-related cancers are removed from solid cancers. Even with 309 deaths, instability in the parameter estimate is suggested, due to large standard errors for cumulative dose at each lag.

The last grouping presented in Table 4.13 are solid cancers (including bladder and pancreatic cancers) but excluding the other smoking-related cancers (n=232). The parameter

estimates at lag=0 and lag=10 are extremely low. The standard errors are larger than the dose coefficients which means there is wide variability around mean cumulative dose in this group of cancer deaths. Pancreatic and bladder cancers have been associated with cigarette smoking in epidemiologic studies. The low deviances suggests that cancers of the pancreas and bladder cancers do not improve model fit to the observed.

(3) Smoking-related Cancer Groups

Smoking-related cancers were important in the overall dose-response relationship between cancer mortality and cumulative dose. When removing smoking-related cancers from solid cancers, the relationship between mortality and cumulative dose was removed. Smoking-related cancers include cancers of the lung, larynx, nasopharnyx, bladder, pancreas, and esophagus. Table 4.14 presents a summary of dose coefficients for smoking-related cancer groups. Smoking related cancers (Group I) include respiratory cancers as well as bladder and pancreatic cancers, but not esophageal (n=138). With zero lag, cumulative dose does not provide improve overall model fit for this outcome. With increasing lag, cumulative dose does provide improvement to overall model fit (lag=0, p=0.124; lag=10, p=0.05, lag=20, p=0.03).

In Table 4.14, the next category was smoking-related cancers that include esophageal cancers (Group II) (n=144). This group indicates that cumulative dose provides a significant improvement to overall model fit, relative to smoking-related cancers (Group I), reflecting the addition of six esophageal cancers. The increase in deviance difference when adding esophageal cancers to the smoking-related cancer category indicates that these six cancer deaths have strong influence over cancer mortality in this cohort. It can be seen that the deviance was large and significant (>3.84 = p-value <0.05) at each EIP interval. The standard error is small relative to the parameter estimate and the confidence intervals are non-negative.

Finally, when removing lung cancers, but including esophageal cancers (n=40) (the last outcome group in Table 4.14), it is evident that this outcome provides the best model fit, highest

deviance, lowest standard error, even with as few as 40 deaths. This is not surprising since two cancer deaths with the highest cumulative dose were cancers of the esophageal and larynx (Table 4.8).

A variety of outcomes were evaluated using a series of empirical induction periods. In general, with increasing induction period, higher mortality risk resulted, regardless of whether cumulative dose contributed to overall model fit. Cumulative dose significantly added to overall model fit with solid cancers, however, cumulative dose did not add significantly to overall model fit with solid cancers excluding smoking-related. For smoking-related cancers, cumulative dose added significant improvement to overall model fit. For lung cancers, cumulative dose did not contribute to overall model fit, but smoking-related cancers excluding lung provided the largest deviance difference of any outcomes evaluated. These results suggest that smoking-related cancers, excluding lung cancers, could be radiation-related. The influence of cigarette smoking on mortality risk cannot be assessed in this data, however, it was known that the prevalence of smoking was high (80%). In the literature, there is evidence that the risk of lung cancer from asbestos exposure is greater in smokers than non-smokers. An analogy could be relevant here, namely that, risk of mortality from smoking-related cancers due to radiation exposure may be greater in smokers than non-smokers.

B. Poisson Regression: Results Using Linear Excess Relative Risk

Excess relative risk (ERR) estimates were provided for the following outcomes: solid cancers (n=349), lung cancers (n=104), smoking-related (n=144), and smoking-related excluding lung cancers (n=40), adjusting for agerisk (8 levels), yearrisk (8 levels), and paycode (3 levels), Tables 4.15, 4.16, 4.17, and 4.18, respectively. For results of ERR analysis adjusting for time-related factors, the reader is referred to Appendix 5, which contains results for solid cancers, lung cancers, and smoking-related cancers. These tables will not be discussed further.

Each table in this section presented results of ERR analysis and log-linear analysis stratified by agerisk, yearrisk, and paycode. Lag intervals 0, 10, and 20 are shown, since no difference was detected in approaches for introducing an empirical induction period. The parameter estimate obtained from ERR analysis was the change in excess relative risk of mortality per Sievert (Sv) of cumulative dose. The relative risk at 1 Sv would be interpreted as 1 + ERR. The ERR does not require exponentiation. An important point is that, when stratifying by a variable using the STRATA command, the influence of that variable is removed. However, the influence of other potential confounders are not removed unless specified in the STRATA command or in some other way. Therefore, the value for the ERR may still be confounded by influence of other variables. A two-sided 95% CI was calculated (β +/- 1.96*std.error). Large values for the likelihood ratio (LR), which is similar to the deviance difference, reject the null hypothesis that cumulative dose does not contributes to fit of the data.

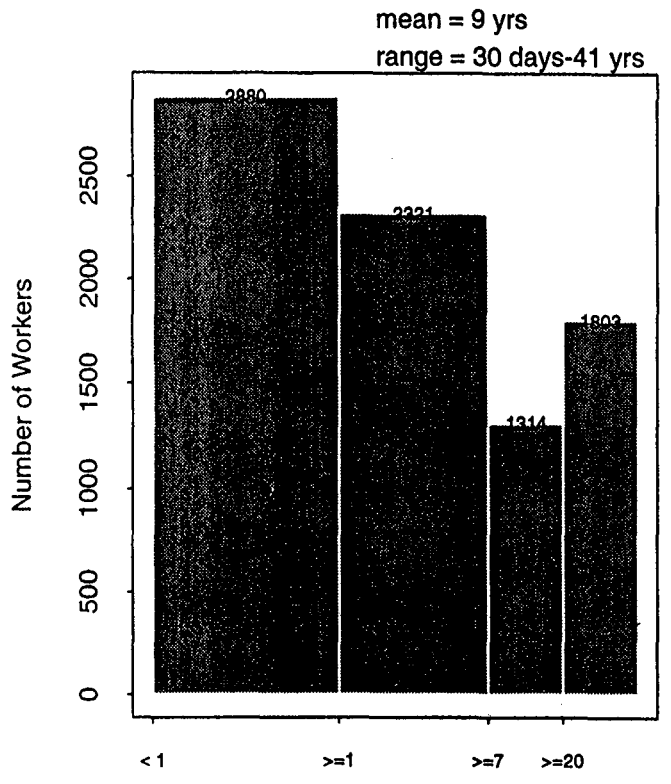
Components of the results tables are as follows: dose coefficient at 1 Sievert exposure (which is the ERR), deviance difference (also referred to as the likelihood ratio statistic), and the p-value for the addition of cumulative dose to null model. Inference is made with the deviance difference (likelihood ratio), compared to $\chi_{2,\,1df}$ where $\chi_{2>3.84} = p<0.05)$.

For solid cancers (n=349), Table 4.15 shows that the ERR at 1 Sv increased with increasing lag interval for each strata evaluated. The deviance difference also increased with

increasing lag. Comparing solid cancer results to log-linear results, the same trend is evident. The log-linear model provides a better improvement of goodness-of-fit primarily due to a higher degree of stratification on agerisk than the ERR model. For lung cancers (n=104) (Table 4.16), the ERR and log-linear models suggest that cumulative dose does not improve model fit. This was the same trend seen when adjusting for time-related factors, with many more strata and without adjustment for paycode. Paycode added significantly to model fit with lung cancers, but cumulative dose did not.

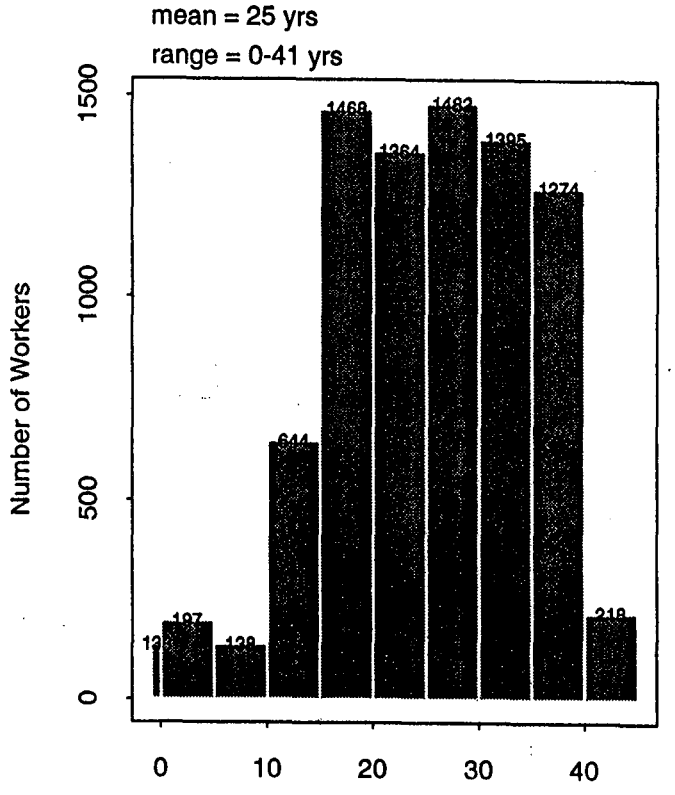
Table 4.17 displays smoking-related cancers (n=144). ERR estimates are larger than log-linear estimates, but the log-linear model provides a larger deviance difference reflecting, a better improvement of model fit with cumulative dose added compared to the ERR model. Large differences between the ERR and log-linear model emerge with a subset of smoking-related cancers, excluding lung cancers (n=40)(Table 4.18). The ERR and log-linear models differ with respect to dose coefficients at lag=20 (lag=20, ERR=25.1 and LL=6.1). The log-linear model provides a better goodness-of-fit, suggested by the larger deviance. However, this large difference in dose coefficient between these two models, suggests that number of stratification levels may not be the only feature that defines this difference.

Figure 4.1 Histograms of Duration of Employment (Natural Log Scale) and Length of Follow-up, ORNL, 1943-1984, (n=8318)



Duration of Employment (Years), Natural Log Scale*

Figure 4.1a, *Cutpoints converted to arithmetic scale



Length of Follow-up (Years)

Figure 4.1b

Figure 4.2 Distribution of Cumulative Dose (Log-10 Scale) for Immediate Cancer Deaths, All Cohort, and Non-Cancer Deaths at ORNL between 1/1/43 and 12/31/84

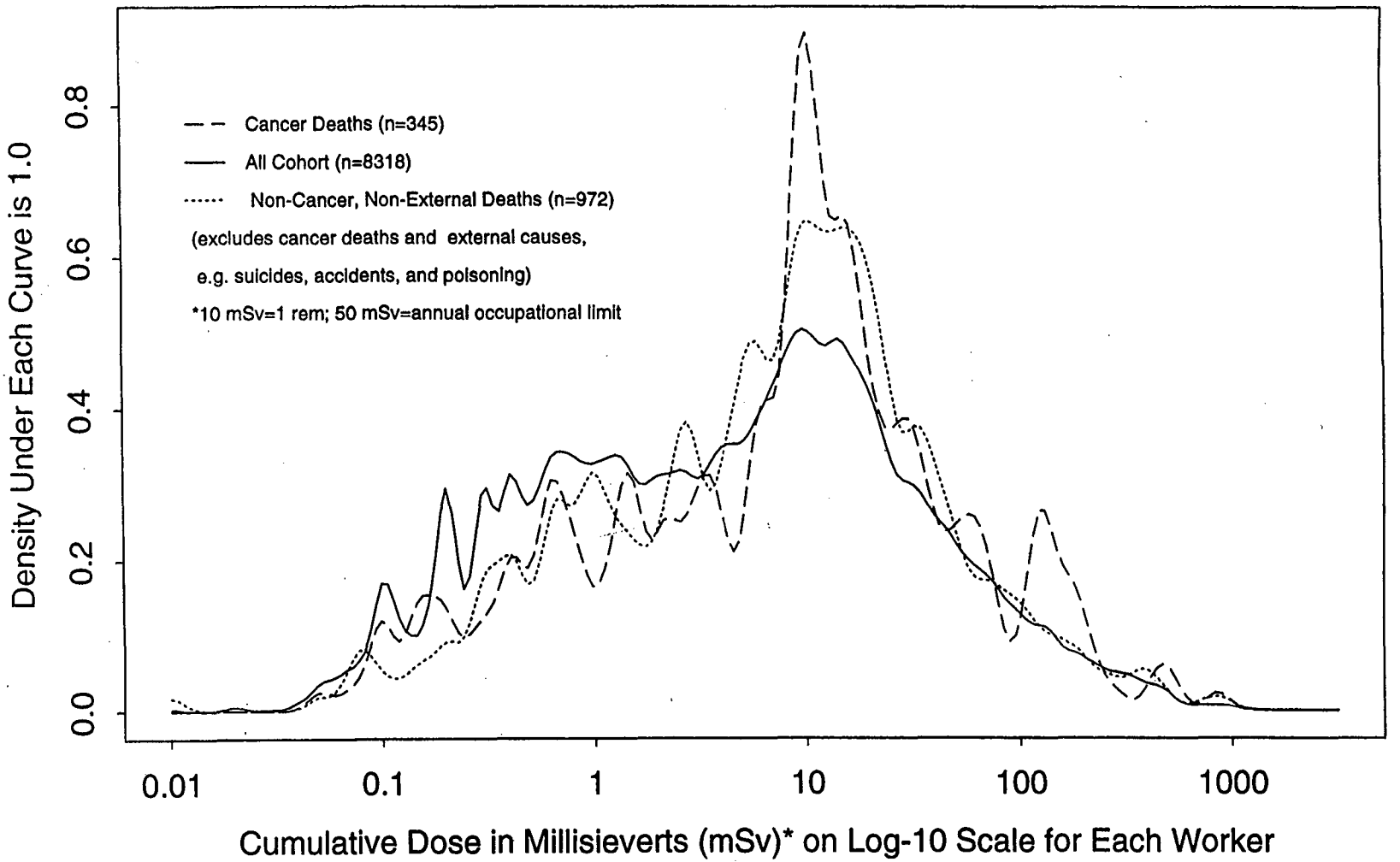


Figure 4.3 Estimated Dose Coefficients* (with 95% Confidence Intervals),
All Cancers, by Latency and Lag Intervals,
White Males, ORNL, Follow-up 1/1/43 to 12/31/84

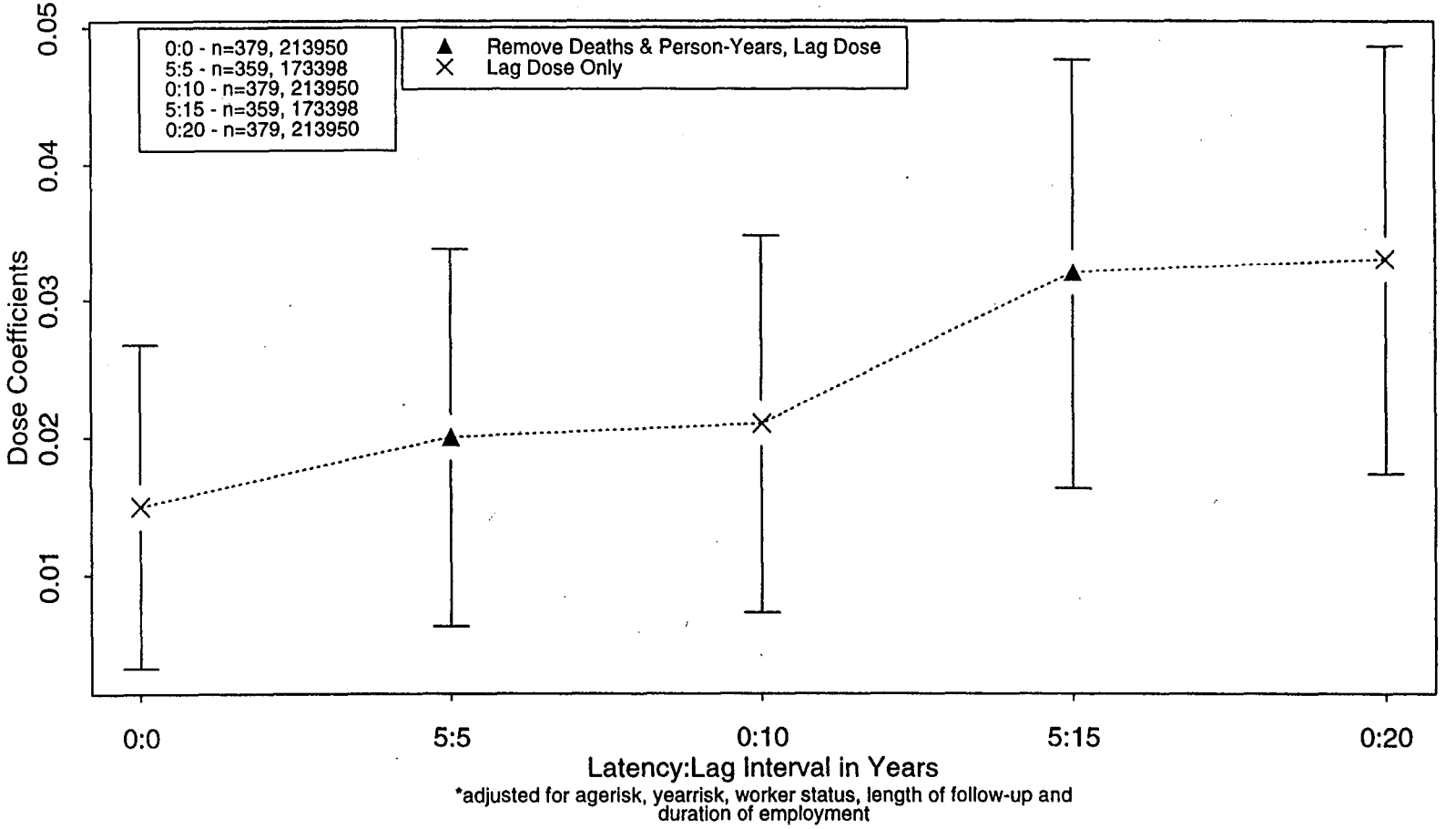


Figure 4.4 Estimated Dose Coefficients* (with 95% Confidence Intervals),
Solid Cancers - no Leukemias, by Latency and Lag Intervals,
White Males, ORNL, Follow-up 1/1/43 to 12/31/84

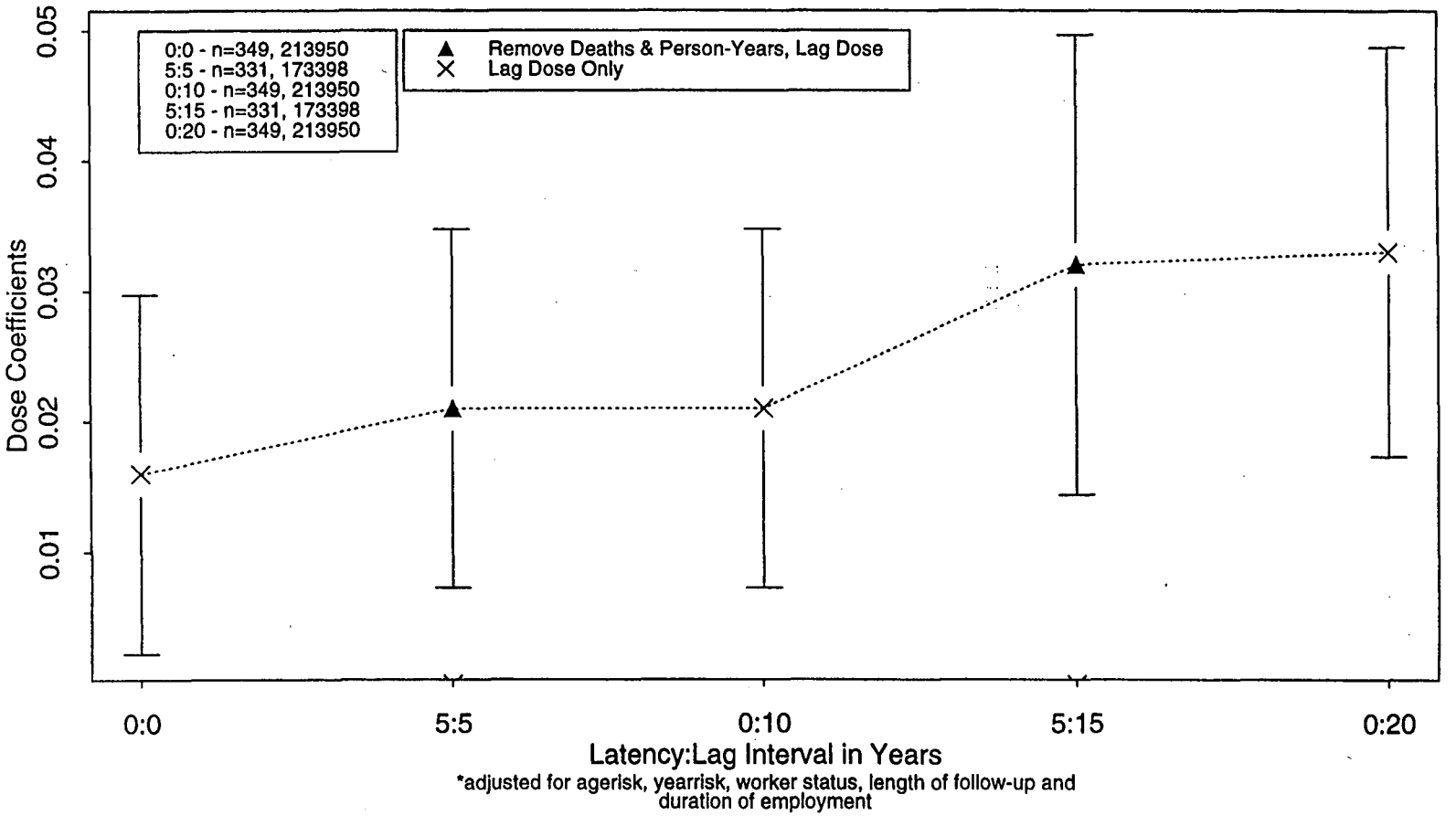
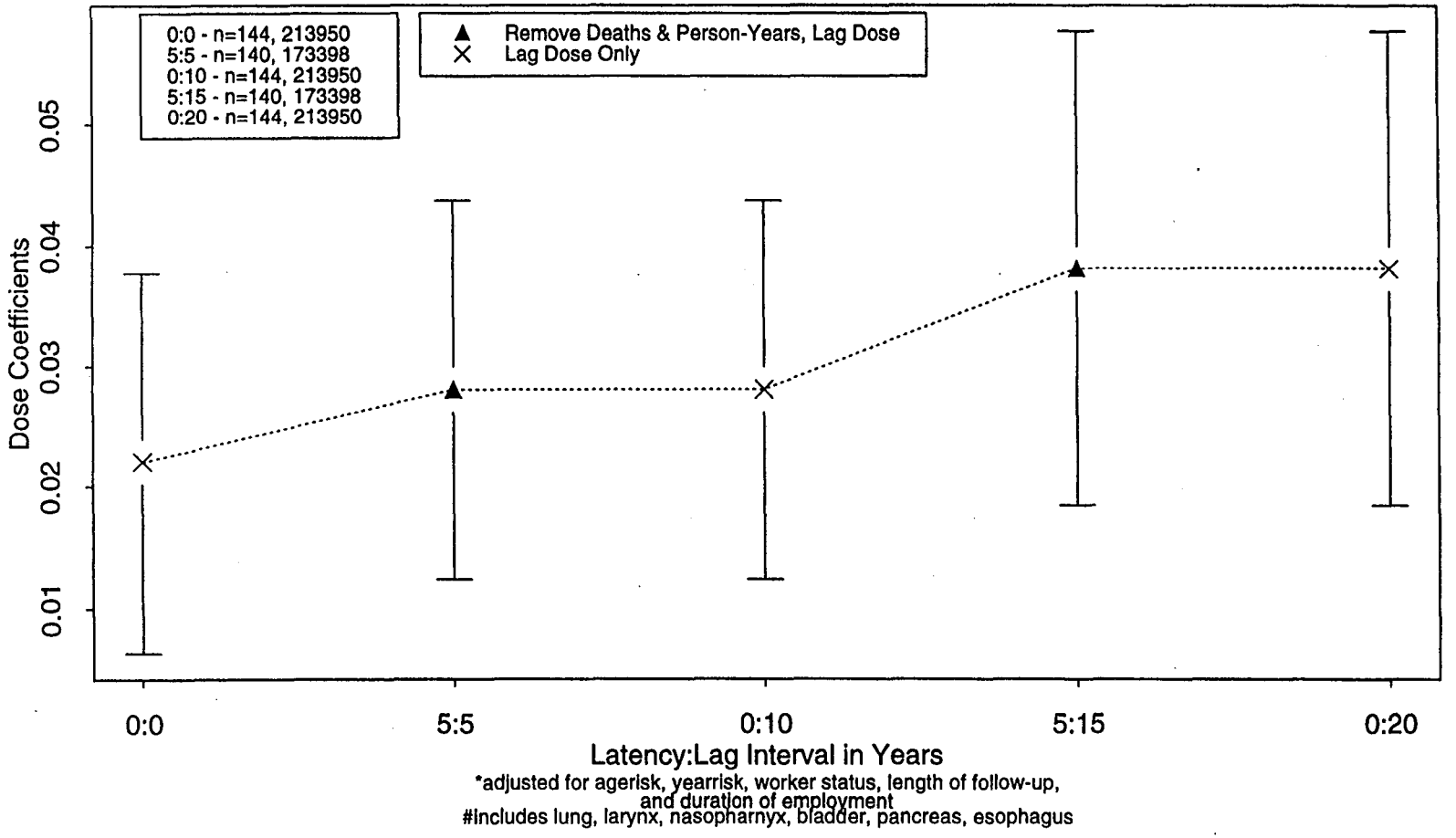


Figure 4.5 Estimated Dose Coefficients* (with 95% Confidence Intervals), Smoking-Related Cancers#, by Latency and Lag Intervals, White Males, ORNL, Follow-up 1/1/43 to 12/31/84



*adjusted for agerisk, yearrisk, worker status, length of follow-up, and duration of employment
#includes lung, larynx, nasopharnyx, bladder, pancreas, esophagus

Table 4.1

Vital Status by Exposure Group at End of Follow-up, December 31, 1984,
8,318 White Males Hired between 1/1/43 and 12/31/72, ORNL

	Number(%)	Person Years	Exposure > 0(a) No.(%)	Exposure = 0.0 No. (%)	Total
Known Alive	6108 (73.4)	167,941	4541 (74.3)	1567 (25.6%)	100%
Dead	1523 (18.3)	37,875	1194 (78.4%)	330 (21.6%)	100%
Unknown	686 (8.2)	9,636	454 (66.2%)	232 (33.8%)	100%
	8318 (100)	213,950	6189	2129	

(a) Exposure is defined as employed at ORNL > 30 days and hired between 1/1/43 and 12/31/72 with cumulative dose as recorded on dosimeter > 0.0 mSv.
(b) 1 death counted as missing

Table 4.2

Descriptive Statistics for Time-Related Variables
at End of Follow-up, December 31, 1984

	All Cohort (n=8318)		Non-Cancer Deaths(a) (n=972)		Cancer Deaths (b) (n=345)		Still Alive (n=6108)	
	mean(std.err)	range	mean(std.err)	range	mean(std.err)	range	mean(std.err)	range
LOF(c)	25.6 (0.10)	0-41	24.1 (0.31)	0-41	24.37 (0.52)	0.0-40	27.5 (0.10)	12.0-41
DOE(d)	9.3 (0.13)	0.08-41.3	8.31(0.31)	0.08-36.9	9.9 (0.57)	0.10-38.5	10.3(0.15)	0.08-41.3
YOB (e)	1925 (0.14)	1880-1954	1909 (0.36)	1880-1946	1911(0.57)	1881-1941	1928(0.14)	1892-1954
YOH (f)	1955 (0.09)	1943-1972	1948 (0.16)	1943-1972	1948 (0.28)	1943-1967	1956 (0.1)	1943-1972
YOT(g)	1965 (0.14)	1943-1984	1956 (0.33)	1943-1984	1959 (0.66)	1943-1984	1967 (0.17)	1943-1984
YOD(h)	1972 (0.10)	1944-1984	1972(0.29)	1944-1984	1973(0.49)	1947-1984	NA	NA
AOH(i)	29 (0.09)	16-67	38 (0.32)	16-67	37 (0.5)	16-64	27 (0.09)	16-62
AOT(j)	39 (0.9)	16-79	47(0.41)	17-69	47 (0.69)	17-68	35 (0.18)	16-79
AOD(k)	61 (0.14)	20-93	63 (0.4)	24-92	62 (0.63)	24-92	NA	NA

(a) excludes deaths from immediate cancers (ICDA8/9 140-209; n=345) and injuries, poisonings, accidents, other external causes of death (ICDA8 or ICDA9 800-999; n=172)
(b) immediate cancer deaths; no contributory cancer deaths included.
(c) length of follow-up
(d) duration of employment
(e) year of birth
(f) year of hire
(g) year of termination
(h) year of death
(i) age at hire
(j) age at termination
(k) age at death

Table 4.3a

Frequency Distribution of Number of Deaths
All Causes, by Agerisk

Agerisk	Frequency	Percent	Cumulative Frequency	Cumulative Percent
20	7	0.5	7	0.5
25	22	1.4	29	1.9
30	31	2.0	60	3.9
35	37	2.4	97	6.4
40	84	5.5	181	11.9
45	104	6.8	285	18.7
50	160	10.5	445	29.2
55	196	12.9	641	42.1
60	219	14.4	860	56.5
65	238	15.6	1098	72.1
70	198	13.0	1296	85.1
75	113	7.4	1409	92.5
80	77	5.1	1486	97.6
85	26	1.7	1512	99.3
90	11	0.7	1523	100.0

Table 4.3b

Frequency Distribution of Number of Deaths
All Cancers, by Agerisk

Agerisk	Frequency	Percent	Cumulative Frequency	Cumulative Percent
20	1	0.3	1	0.3
25	2	0.5	3	0.8
30	7	1.8	10	2.6
35	6	1.6	16	4.2
40	11	2.9	27	7.1
45	27	7.1	54	14.2
50	40	10.6	94	24.8
55	50	13.2	144	38.0
60	52	13.7	196	51.7
65	73	19.3	269	71.0
70	60	15.8	329	86.8
75	28	7.4	357	94.2
80	15	4.0	372	98.2
85	4	1.1	376	99.2
90	3	0.8	379	100.0

Table 4.4a

Frequency Distribution of Number of Deaths
All Causes, by Yearrisk

Yearrisk	Frequency	Percent	Cumulative Frequency	Cumulative Percent
40	2	0.1	2	0.1
45	26	1.7	28	1.8
50	55	3.6	83	5.4
55	94	6.2	177	11.6
60	146	9.6	323	21.2
65	216	14.2	539	35.4
70	255	16.7	794	52.1
75	326	21.4	1120	73.5
80	403	26.5	1523	100.0

Table 4.4b

Frequency Distribution of Number of Deaths
All Cancers, by Yearrisk

Yearrisk	Frequency	Percent	Cumulative Frequency	Cumulative Percent
45	4	1.1	4	1.1
50	14	3.7	18	4.7
55	16	4.2	34	9.0
60	23	6.1	57	15
65	56	14.8	113	29.8
70	61	16.1	174	45.9
75	80	21.1	254	67.0
80	125	33.0	379	100.0

Table 4.5

Distribution of Deaths and Person-Years by Worker Status,
Solid Cancers (a)

	Worker Status at Time of Death		
	Inactive	Active	Total
Deaths	260	89	349
Person(b) Years	118,827	95,123	213,950

(a) Worker status is lagged for two years, meaning that workers are considered still working for two additional years after leaving ORNL. 89 deceased workers are considered alive and working as a result of using a two year lag. Cancer deaths are immediate and contributory causes.
(b) Person-years for active workers include those that are dead and considered alive, as well as, those still alive in the cohort. Person-years for inactive include those that are deceased, who have been deceased more than two years.

Table 4.6

Number (and Percent) of ORNL Cohort by Duration of Employment in Years by Group as of December 31, 1984

	Entire Cohort No. (%)	Non-Cancer Deaths(a) No. (%)	Cancer Deaths No. (%)
Duration (Yrs)			
>30d- <5	4603 (55.34)	517 (53.19)	165 (47.83)
5 - 9	790 (9.5)	114 (11.73)	40(11.59)
10-14	445 (5.35)	78 (8.02)	24 (6.96)
15-19	571 (6.86)	87 (8.95)	32 (9.28)
20-24	525 (6.31)	86 (8.85)	36 (10.43)
25-29	583 (7.01)	55 (5.66)	24 (7.96)
30-34	523 (6.29)	28 (2.88)	19 (5.51)
35-44	278 (3.34)	7 (0.72)	5(1.45)
Totals	8318 (100)	972 (100)	345 (100)
Mean DOE	9.3	8.3	9.4
Std. error	0.12	0.31	0.57
Range	0.8-41	0.082-36.9	0.11-38.5

(a) Non-cancer deaths exclude deaths from cancer and external causes of death, such as accidents and suicides.

Table 4.7

Number (and Percent) of ORNL Cohort by Length of Follow-up in Years by Group as of December 31, 1984

	Entire Cohort No. (%)	Non-Cancer Deaths (a) No. (%)	Cancer Deaths No. (%)
Follow-up (yrs)			
0	138 (1.66)	6 (0.62)	1 (0.29)
>0 - <5	173 (2.08)	19 (1.95)	15 (4.35)
5 - 9	133 (1.6)	59 (6.07)	18 (5.2)
10 - 14	479 (5.76)	89 (9.16)	18 (5.2)
15 - 19	1422 (17.1)	134 (13.79)	45 (13.04)
20 - 24	1316 (15.82)	162 (16.67)	58 (16.81)
25 - 29	1433 (17.23)	176 (18.11)	71 (20.58)
30 - 34	1581 (19.01)	172 (17.7)	66 (19.13)
35 - 39	1165 (14.01)	145 (14.92)	49 (14.2)
40 - 41	478 (5.75)	10 (1.03)	4 (1.16)
Totals	8318 (100)	972 (100)	345 (100)
Mean LOF	25.6	24.1	24.4
Std.error	0.1	0.31	0.51
Range	0-41	0-41	0-40

(a) Non-cancer deaths exclude deaths from cancer and external causes of deaths, such as accidents and suicides.

Table 4.8

Number of Immediate Cancer Deaths by Cumulative Dose Category, between 1/1/43 and 12/31/84, White Males, ORNL

Cancer Deaths (ICDA8 or 9)	Cumulative Dose Categories in mSv														
	0	>0-10	>10-50(a)	>50-100	>100-150	>150-200	>200-300	>300-400	>400-500	>500-600	>600-700	>700-800	>800-900	>900-1000	Totals
Major salivary glands (142)			1												1
Unspecified Mouth (145)	1	1													2
Nasopharynx (147)	1														1
Hypopharynx (148)		1													1
Ill-defined lip/oral cavity (149)		1													1
Esophagus (150)		2	1	1		1				1					6
Stomach (151)	1	11	4												16
Small Intestine, duodenum (152)		1		1											2
Large Intestine (153)	11	14	5	1	1	1			1						34
Rectum(154)	2	1		1	1										5
Liver, bile ducts(155)				1											1
Gallbadder(156)	1	1	3												5
Pancreas (157)	2	14	7		2										25
Nasal Cavities(160)	1														1
Larynx(161)		1	1	1									1		4
Lung (162-163)	13	38	30	5	6	2	1		1						96
Bone and cartilage (170)		1													1
Connective/soft tissue(171)		2	1				1								4
Melanoma (172)	1	4	1	1											7
Other malignant skin(173)		1													1
Prostate (185)	6	10	8	1		1									26
Testis(186)		1	1												2
Bladder (188)	1	1				1									3
Kidney/unspecified urinary (189)	2	4	3				1								10
Brain/CNS (191-192)		11	4												15
Origin unknown (195)		2	1												3
Secondary Lymph Nodes(196)		1													1
Secondary Respiratory/															0
Digestive (197)	2	2	1												5
Secondary Malignancy(198)	1	1	2												4
Malignant, no site listed(199)	4	6	2		1										13
Lymphosarcoma and/or															0
reticulosarcoma (200)	3	1	4	1	1										10
Hodgkin's Disease (201)		3	1	1											5
Other lymphatic (202-203)		3	2												5
Leukemia (204-207)	5	9	13		1										28
Myelofibrosis (209)			1												1
TOTAL Cancer Deaths	58	149	97	15	13	6	3	0	2	1	0	0	1	0	345

(a) 50 mSv = 5rem, the annual occupational limit

Table 4.9

Cumulative Dose (mSv) Categories by Status at End of Follow-up, December 31, 1984

Cumulative Dose(c)	Entire Cohort No. (%)	Person Years	Incidence Density(f)	Non-Cancer Deaths(a) No. (%)	Person Years	Incidence Density	Cancer Deaths(b) No. (%)	Person Years	Incidence Density	Known to be Alive No. (%)	Person Years	Incidence Density(h)
0	2,129(25.6)	53,133	0.040	210 (21.6)	5,319	0.039	58 (16.8)	1,555	0.037	1,567 (25.7)	42,062	NA
>0 - 49.9 mSv	5,551(66.7)	145,874	0.038	681 (70.1)	16,923	0.040	246 (71.3)	6,141	0.040	4,056 (66.4)	114,088	NA
50 - 99.9 mSv	317 (3.8)	7,763	0.041	38 (3.9)	808	0.047	15 (4.4)	341	0.044	249 (4.08)	6,276	NA
100+ mSv	321 (3.9)	7,180	0.045	43 (4.4)	839	0.051	26 (7.5)	519	0.050	236 (3.86)	5,515	NA
Totals	8,318 (100)	213,950	0.039	972 (100)	23,889	0.041	345(100)	8,556	0.040	6108 (100)	167,941	
median dose(e)		1.45			4.3			6.1			1.4	
75th percentile(f)		11.45			16.1			17.8			11.7	
dose range		0-1144.1			0-920.7			0-852.2			0-1144.1	

(a) Non-cancer deaths excludes deaths from immediate cancers (ICDA8 140-209) and external causes, such as injuries, poisoning, accidents and other external causes of death (n=172) (ICDA8 800-999).
(b) There were 346 primary cancer deaths; 1 cancer death coded as missing at State's request.
Deaths are for immediate cause of death; 34 contributory caues are not included.
(c) 50 mSv (5 rem) has been the cumulative dose permitted annually in occupational settings since 1958 (1 rem = 10 mSv).
(d) Median is the 50% percentile.
(e) For the entire cohort, 75% of 8318 observations for cumulative dose were below 11.45 and 25% of observations were above 11.45 mSv.

Table 4.10 Summary of the Cancer Deaths in the ORNL Cohort by Immediate and Contributory Causes as of December 31, 1984

Malignant Cancer Types (140-209)*	Immediate	Contributory
Major salivary glands (142)	1	0
Floor of mouth(144)	0	1
Unspecified Mouth (145)	2	0
Nasopharynx (147)	1	0
Hypopharynx (148)	1	0
Ill-defined lip/oral cavity (149)	1	0
Esophagus (150)	6	0
Stomach (151)	16	1
Small Intestine, duodenum (152)	2	0
Large Intestine (153)	34	3
Rectum(154)	5	1
Liver, bile ducts(155)	1	1
Gallbadder(156)	5	0
Pancreas (157)	25	1
Nasal Cavities(160)	1	0
Larynx(161)	4	0
Lung (162-163)	96	8
Bone and cartilage (170)	1	0
Connective/soft tissue(171)	4	0
Melanoma (172)	7	0
Other malignant skin(173)	1	0
Prostate (185)	26	5
Testis(186)	2	0
Bladder (188)	3	0
Kidney/unspecified urinary (189)	10	1
Brain/CNS (191-192)	15	1
Origin unknown (195)	3	1
Secondary Lymph Nodes(196)	1	0
Secondary Respiratory/Digestive (197)	5	0
Secondary Malignancy(198)	4	0
Malignancy, no site listed site(199)	13	1
Lymphosarcoma and/or reticulosarcoma (200)	10	2
Hodgkin's Disease (201)	5	1
Other lymphatic (202-203)	5	4
Leukemia (204-207)	28	2
Myelofibrosis (209)	1	0
TOTAL Cancer Deaths	345	34

*(ICDA8 or ICDA9 codes)

Two immediate cancers listed as benign: thyroid (226), and unspecified, bone (238)

One contributory listed as benign: unspecified bone (238)

Table 4.11 Summary of Non-Cancer Causes of Death
in the ORNL Cohort as of December 31, 1984

	Totals*
Primary Tuberculosis (011)	**2**
Septicemia (038)	**3**
Viral Hepatitis (070)	**1**
Endocrine, Nutritional, Metabolic Diseases and Immunity Disorders(240-279)	**15**
Diseases of Blood and Blood-forming Organs(280-289)	**2**
Mental Disorders (290-319)	**5**
Diseases of the Nervous System and Sense Organs(320-389)	**9**
Diseases of the Circulatory System(390-459)	**738**
Hypertension(401-405)	13
Acute myocardial infarction(410)	386
Past MI diagnosis(412)	151
Intercerebral hemorrhage(431)	29
All other	159
Diseases of the Respiratory System (460-519)	**73**
Pneumonia (486)	14
Emphysema(492)	21
Pulmonary insufficiency (519)	16
All other	22
Diseases of the Digestive System (520-579)	**45**
Chronic liver disease(571)	23
All other	22
Diseases of the Genitourinary System (580-629)	**16**
Diseases of Skin and Subcutaneous Tissue (680-709)	**2**
Diseases of Musculoskeletal System and Connective Tissue (710-739)	**2**
Congenital Anomalies (740-759)	**2**
Symptoms and Ill-Defined Conditions(780-799)	**55**
Non-specific Low Blood Pressure(796.3)	44
Accidents, Poisoning and Violence (800-999)	**172**
Missing Causes of Death	**34**
TOTAL NON-CANCER	**1176**

* Category totals are bold, subcategory totals are not

Table 4.12

Summary of Dose Coefficients (a)
for All Cancers and Leukemias
by Empirical Induction Period, Log-Linear Model Fitting

All Cancers

EIP	Dose Coefficients	Std.Err.	95% CI(b)	Deviance(c) Difference	P(chi-sq)d	Person Years	Deaths
0, 0	0.015	0.006	0.002, 0.028	4.10	0.043	213950	379
5, 5	0.020	0.007	0.007,0.034	6.36	0.012	173398	359
0,10	0.021	0.007	0.007, 0.034	6.69	0.010	213950	379
5,15	0.032	0.008	0.016, 0.048	9.59	0.002	173398	359
0, 20	0.033	0.008	0.017, 0.049	10.51	0.001	213950	379

Leukemias

EIP	Dose Coefficients	Std.Err.	95% CI	Deviance Difference	P(chi-sq)	Person Years	Deaths
0, 0	0.006	0.025	-0.044, 0.055	0.05	0.831	213950	30
0, 2	0.006	0.026	-0.045, 0.057	0.05	0.826	213950	30
5, 2	0.008	0.026	-0.043, 0.059	0.07	0.788	173398	28
0, 10	0.012	0.025	- 0.037, 0.062	0.18	0.671	213950	30
5, 15	0.030	0.026	-0.020, 0.080	0.90	0.343	173398	28

Leukemias Excluding CLL (e)

EIP	Dose Coefficients	Std.Err.	95% CI	Deviance Difference	P(chi-sq)	Years	Deaths
0, 0	0.012	0.025	-0.037, 0.061	0.19	0.665	213950	23
0, 2	0.013	0.025	-0.035, 0.062	0.23	0.629	213950	23
5, 2	0.014	0.025	-0.065, 0.064	0.23	0.629	173398	22
0, 10	0.013	0.025	-0.035, 0.062	0.23	0.629	213950	23
5, 15	0.037	0.025	-0.011, 0.085	1.32	0.250	173398	22

(a) per 10 mSv. Cumulative dose added last and adjusted for agerisk, yearrisk, worker status, length of follow-up, and duration of employment.
(b) 2-sided 95% Confidence Interval around parameter estimate.
(c) Deviance difference is the amount of variation which is explained by adding dose to the model.
(d) P(chi-sq) is the probability, based on a chi-square distribution (1 df), that the change in residual deviance as extreme as the one attributed to dose would occur by chance.
(e) excludes chronic lymphocytic leukemia

Table 4.13

Summary of Dose Coefficients (a) for
Solid Cancers and Lung Cancer Groups,
by Empirical Induction Period, Log-Linear Model Fitting

Solid Cancers -- Leukemias Excluded

EIP	Dose Coefficients	Std.Err.	95% CI(b)	Deviance(c) Difference	P(chi-sq)(d)	Person Years	Deaths
0, 0	0.016	0.007	0.003, 0.029	4.21	0.040	213950	349
5, 5	0.021	0.007	0.007, 0.035	6.24	0.012	173398	331
0, 10	0.021	0.007	0.008, 0.035	6.63	0.010	213950	349
5, 15	0.032	0.009	0.015, 0.049	8.66	0.003	173398	331
0, 20	0.033	0.008	0.017, 0.050	9.58	0.002	213950	349

Lung Cancers

EIP	Dose Coefficients	Std.Err.	95% CI	Deviance Difference	P(chi-sq)	Person Years	Deaths
0, 0	0.009	0.013	-0.015, 0.034	0.45	0.502	213950	104
5, 5	0.015	0.013	-0.011, 0.04	0.96	0.327	173398	100
0, 10	0.015	0.013	-0.011, 0.041	1.02	0.313	213950	104
5, 15	0.012	0.022	-0.031, 0.054	0.23	0.629	173398	100
0, 20	0.013	0.021	-0.029, 0.054	0.29	0.593	213950	104

Solid Cancers, excluding lung

EIP	Dose Coefficients	Std.Err.	95% CI	Deviance Difference	P(chi-sq)	Person Years	Deaths
0, 0	0.019	0.008	0.003,0.034	4.15	0.042	213950	245
5, 5	0.024	0.008	0.008, 0.04	5.62	0.018	173398	231
0, 10	0.024	0.008	0.008, 0.041	5.96	0.015	213950	245
5, 15	0.039	0.009	0.021, 0.057	10.04	0.002	173398	231
0, 20	0.040	0.009	0.022, 0.058	10.97	0.001	213950	245

Solid Cancers, excluding smoking-related (e)

EIP	Dose Coeficients	Std.Err.	95% CI	Deviance Difference	P(chi-sq)	Person Years	Deaths
0, 0	0.005	0.012	-0.019, 0.029	0.14	0.711	213950	205
5, 5	0.007	0.014	-0.021, 0.035	0.19	0.661	173398	191
0, 10	0.008	0.014	-0.02, 0.036	0.29	0.593	213950	205
5, 15	0.022	0.016	-0.009, 0.052	1.26	0.262	173398	191
0, 20	0.025	0.015	-0.005, 0.054	1.75	0.186	213950	205

Table 4.13 (Continued) Summary of Dose Parameter Estimates for Solid Cancer and Lung Cancer Groups

Solid Cancers and Lung, excluding other smoking-related (f)

EIP	Dose Coefficients	Std.Err.	95% CI	Deviance Difference	P(chi-sq)	Person Years	Deaths
0, 0	0.007	0.009	-0.01, 0.024	0.53	0.469	213950	309
5, 5	0.011	0.01	-0.008, 0.03	1.00	0.318	173398	291
0, 10	0.012	0.01	-0.007, 0.03	1.19	0.276	213950	309
5, 15	0.018	0.013	-0.008, 0.043	1.38	0.241	173398	291
0, 20	0.020	0.013	-0.004, 0.045	1.88	0.170	213950	309

Solid Cancers, excluding respiratory and upper digestive(g)

EIP	Dose Coefficients	Std.Err.	95% CI	Deviance Difference	P(chi-sq)	Person Years	Deaths
0, 0	0.005	0.012	-0.018, 0.027	0.14	0.705	213950	232
5, 5	0.007	0.013	-0.019, 0.033	0.25	0.618	173398	218
0, 10	0.008	0.013	-0.017, 0.034	0.34	0.559	213950	232
5, 15	0.023	0.014	-0.005, 0.051	1.83	0.176	173398	218
0, 20	0.026	0.014	-0.001, 0.052	2.34	0.126	213950	232

(a) per 10 mSv. Cumulative dose added last and adjusted for agerisk, yearrisk, worker status, length of follow-up, duration of employment.
(b) 2-sided 95% Confidence Interval around parameter estimate.
(c) Deviance difference is the amount of variation which is explained by adding dose dose to the model.
(d) P(chi-sq) is the probability, based on a chi-square distribution (1 df), that the change in residual deviance as extreme as the one attributed to dose would occur by chance.
(e) excludes cancers of the lung, larynx, nasopharnyx, bladder, pancreas, and esophagus
(f) excludes smoking-related cancers listed in (e), except lung
(g) excludes cancers of the nasopharynx, hypopharynx, illdefined lip, esophagus, larynx, and lung, but includes bladder and pancreas

Table 4.14

Summary of Dose Coefficients (a) for
Smoking-Related Cancer Groups,
by Empirical Induction Period, Log-Linear Model Fitting

Smoking-Related Cancers without esophageal (Group I) (e)

EIP	Dose Coefficients	Std.Err.	95% CI(b)	Deviance(c) Difference	P(chi-sq)(d)	Person Years	Deaths
0, 0	0.017	0.009	-0.002, 0.035	2.36	0.124	213950	138
5, 5	0.022	0.010	0.003, 0.042	3.78	0.052	173398	134
0, 10	0.023	0.010	0.004, 0.042	3.84	0.050	213950	138
5, 15	0.032	0.012	0.009, 0.056	4.51	0.034	173398	134
0, 20	0.033	0.012	0.009, 0.056	4.58	0.032	213950	138

Smoking-Related Cancers with esophageal (Group II)(f)

EIP	Dose Coefficients	Std.Err.	95% CI	Deviance Difference	P(chi-sq)	Person Years	Deaths
0, 0	0.022	0.008	0.007, 0.038	5.6	0.020	213950	144
5, 5	0.028	0.008	0.012, 0.044	7.9	0.005	173398	140
0, 10	0.028	0.008	0.013, 0.044	8.1	0.004	213950	144
5, 15	0.038	0.010	0.018, 0.057	8.1	0.004	173398	140
0, 20	0.038	0.010	0.018, 0.058	8.2	0.004	213950	144

Smoking-Related (Group II), excluding lung cancers

EIP	Dose Coefficients	Std.Err.	95% CI	Deviance Difference	P(chi-sq)	Person Years	Deaths
0, 0	0.039	0.01	0.019, 0.059	8.61	0.003	213950	40
5, 5	0.045	0.01	0.025, 0.065	10.45	0.001	173398	40
0, 10	0.045	0.01	0.025, 0.065	10.39	0.001	213950	40
5, 15	0.060	0.01	0.037, 0.082	12.80	<0.00	173398	40
0, 20	0.059	0.01	0.037, 0.081	12.59	<0.00	213950	40

(a) per 10 mSv. Cumulative dose adjusted for agerisk, yearrisk, worker status, length of follow-up, duration of employment.
(b) 2-sided 95% Confidence Interval around parameter estimate.
(c) Deviance difference is the amount of variation which was explained by adding dose to the model.
(d) P(chi-sq) is the probability, based on a chi-square distribution (1 df), that the change in residual deviance as extreme as the one attributed to dose would occur by chance.
(e) includes cancers of the lung, larynx, nasopharnyx, bladder, pancreas
(f) includes cancers of the lung, larynx, nasopharnyx, bladder, pancreas, and esophagus

Table 4.15

Comparison of Linear Excess Relative Risk and Log-Linear Models
Solid Cancers by Empirical Induction Period

	Solid Cancers (n=349)					
	ERR(a)			Log-Linear(d)		
EIP	Dose Coefficient(b)	Deviance(c) Difference	P-value	Dose Coefficient	Deviance Difference	P-value
lag=0	1.4	1.9	0.16	1.3	3.3	0.06
lag=10	2.2	3.5	0.06	1.9	5.8	0.01
lag=20	5.2	6.6	0.01	3.1	9.3	<0.01

Table 4.16

Comparison of Linear Excess Relative Risk and Log-Linear Models
Lung Cancer by Empirical Induction Period

	Lung Cancers (n=104)					
	ERR(a)			Log-Linear(d)		
EIP	Dose Coefficient	Deviance Difference	P-value	Dose Coefficient	Deviance Difference	P-value
lag=0	0.7	0.1	0.7	1.0	0.5	0.4
lag=10	2.1	0.7	0.4	1.7	1.4	0.2
lag=20	2.3	0.3	0.6	2.0	0.8	0.4

(a) per 1 Sv. Dose added after stratification on agerisk (8 levels), yearrisk (8 levels), and paycode (3 levels).
(b) coefficient for cumulative dose.
(c) Deviance difference measures the change in goodness-of-fit by adding dose to the model. Large deviance reflects well fitting model.
(d) per 1 Sv. Dose added to model after agerisk (16 levels), yearrisk (8 levels), and paycode (3 levels).

Table 4.17

Comparison of Linear Excess Relative Risk and Log-Linear Models
for All Smoking-Related Cancers by Empirical Induction Period

	Smoking-Related (n=144)(a)					
EIP	ERR(b)			Log-Linear(e)		
	Dose Coefficient(c)	Deviance(d) Difference	P-value	Dose Coefficient	Deviance Difference	P-value
lag=0	3.2	4.0	0.04	2.3	6.3	0.01
lag=10	5.1	6.4	0.01	3.0	6.7	<0.01
lag=20	9.1	7.9	<0.01	6.1	14.5	<0.01

Table 4.18

Comparison of Linear Excess Relative Risk and Log-Linear Models
Smoking-Related Excluding Lung Cancers by Empirical Induction Period

	Smoking-Related Excluding Lung Cancers (n=40)					
	ERR			Log-Linear		
EIP	Dose Coefficient	Deviance Difference	P-value	Dose Coefficient	Deviance Difference	P-value
lag=0	10.1	6.6	0.01	4.1	10.0	<0.01
lag=10	13.5	8.0	<0.01	4.7	12.2	<0.01
lag=20	25.1	11.0	<0.01	6.1	14.5	<0.01

(a) includes cancers of the lung (n=104), larnyx (n=4), nasopharynx (n=1), bladder (n=3), pancreas (n=26), and esophagus (n=6)
(b) per 1 Sv. Dose added after stratification on agerisk (8 levels), yearrisk (8 levels), and paycode (3 levels).
(c) coefficient for cumulative dose.
(d) Deviance difference measures the change in goodness-of-fit by adding dose to the model. Large deviance reflects well fitting model.
(e) per 1 Sv. Dose added to model after agerisk (16 levels), yearrisk (8 levels), and paycode (3 levels).

CHAPTER 5

DISCUSSION

The primary purpose of this dissertation was to determine if elevated mortality previously found in the ORNL cohort can be explained as due to:

I. Confounding due to time-related factors not previously considered,
II. Selection bias resulting from methods to incorporate an empirical induction period,
III. Grouping of cancer outcomes,
IV. Type of statistical model chosen.

Once having determined if these factors influence mortality, other analyses were performed, including investigation of outliers in the data and the influence of paycode. This analysis was primarily exploratory in design and execution. This was evident by the several hypothesis that were evaluated independently, but also in combination, with an objective to refine our understand of the role of radiation exposure in this cohort based on comparing and combining methodologic approaches. In this section each hypothesis is presented and the findings are summarized and discussed.

I. TIME-RELATED VARIABLES

Kleinbaum *et al.* (1982, p. 244) define a confounder as a 'risk factor' for the disease under study whose 'control' in some way (either singly or in conjunction with other variables) will reduce or completely correct a bias when estimating the (true) exposure-disease relationship. Time-related factors have been shown to be confounders in many occupational epidemiology studies (Checkoway *et al.*, 1989; Pearce *et al.*, 1986). Yet, few studies of nuclear cohort workers provide information on the role of time-related factors, other than agerisk and yearrisk. Time-related factors which change as a worker moves through follow-up have not been rigorously explored in the ORNL data. In particular, resent results of re-analysis of the ORNL data by Gilbert *et al.* (1993) suggest that the influence of time-related factors on estimating cancer

mortality in this cohort is not well understood (Gilbert *et al.*, 1993, p. 418, 420). The reader is referred to Chapter 3 for a discussion of the rationale for each of these.

Time-related factors included in this analysis were: agerisk, yearrisk, worker status, length of employment, and duration of employment. In univariate analysis duration of employment and length of follow-up were found to confound the relationship between mortality and cumulative exposure. There was evidence of confounding, since the crude measure of risk with cumulative dose differed from the adjusted measure of risk for duration of employment and for length of follow-up. Not only did the adjusted measure differ, but for duration of employment, the significant relationship between cumulative dose and mortality was completely explained by the addition of duration of employment. This was also found for length of follow-up.

In multivariate analysis, independent variables were related to mortality. After including covariates agerisk, yearrisk, worker status, length of employment, and duration of employment, cumulative dose was added last. The contribution of each variable as it was added sequentially to the model was assessed using the nested model approach. Two variables were related to mortality when added sequentially, agerisk and duration of employment. Agerisk was related to all mortality outcomes. Duration of employment was significantly associated with lung cancer mortality, and smoking-related cancers, including and excluding esophageal cancers when adjusting for agerisk, yearrisk, worker status, and length of follow-up. Duration of employment was not associated with the grouping, solid cancers excluding lung or solid cancers and lung excluding other smoking-related. It is unclear why including lung cancer with other solid cancers would result in masking the effect of duration of employment in this combined group.

Findings for duration of employment differ from those expressed by Pearce *et al.* (1986), which stated less mortality occurs in workers with the longest duration of employment. This was not true for lung cancer mortality. Cumulative radiation exposure depends to some extent on duration of employment as suggested by the correlation between these variables (r=0.66). It could be possible that a longer duration of employment implies an increased probability that cellular repair systems will fail and a permanent cellular transition occur (Beebe, 1982). Fifty-eight percent

of the ORNL cohort worked five years or less. Duration of employment was an independent predictor for lung cancer deaths.

An outcome consisting of non-cancer causes of death, excluding external causes was constructed to evaluate deaths that were not due to cancer, suicides, accidents, poisoning, as well as other external causes of death. This groups was primarily composed of employees who died of heart disease (n=972). Agerisk, yearrisk, worker status, and duration of employment when added sequentially as independent predictors improved overall model fit for this group of workers. Cumulative dose and length of follow-up did not significant add to improvement of overall model fit (Appendix 4). Yearrisk and worker status were significantly inversely related to mortality in the non-cancer group. In the cancer group, yearrisk and worker status were not confounders in any of the cancer outcomes evaluated and parameter estimates for these variables were positive. The group of workers who died of non-cancer causes appear to differ from the group of workers who died of cancer, in ways other than exposure to cumulative dose.

II. EMPIRICAL INDUCTION PERIOD

An empirical induction period is an important component of statistical modeling in the analysis of cancer data. The interval identifies the assumed period when exposure has initiated the carcinogenic process. Secondly, the empirical induction period defines an interval after the carcinogenic process has begun, when exposures are assumed to be unrelated to subsequent mortality.

It was hypothesized that the method to incorporate an empirical induction period may influence the parameter estimate for cumulative dose. This hypothesis was developed, since it was discovered that there were two approaches to incorporate an empirical induction period in the radiation epidemiology literature. These approaches were slightly different conceptually and computationally, yet referred to interchangeably.

Using an example of a 10-year lag, the two approaches are briefly summarized. For approach 1, a 10-year lag removed the fraction of the first year of employment and the next five full years of deaths and person-years. Dose was lagged five-years from first year of cumulative dose for those remaining in the cohort. This was referred to as a 10-year lag, since the dose received from the beginning of follow-up was not included until 10-years later (Gilbert, 1995, personal communication). The second approach assigns the first 10-years of cumulative dose to zero, and the last 10 person-years of cumulative dose are removed from analysis. All deaths and person years are retained in the cohort using approach 2.

Three cancer outcomes were evaluated for the empirical induction period. Results shows that the parameter estimates for the two approaches did not differ significantly. For example, on the x-axis in Figure 4.5 , latency5:lag5 and latency0:lag10 have approximately the same parameter estimates (0.022, and 0.023, respectively).

The implication of these findings was that approach 2, lagging dose, was more appropriate than approach 1, since approach 2 retains all deaths and person-years in the cohort, which maintains statistical power. Approach 1, removing all deaths and person-years during the first five years of follow-up, does not assume a threshold for those remaining in the cohort, since cumulative dose of those remaining in the cohort was counted from entry through the end of follow-up. A rationale for removing these person-years was to allow for an especially strong healthy worker effect (Gilbert *et al.*, 1993(b), p. 590). For those that died during the first five years of follow-up, it was assumed that any exposure received would be highly unlikely to be associated with mortality. Since the overall exposure in this cohort was small, finding no difference in parameter estimates based on choice of empirical induction period, may not preclude a difference being found in a cohort with greater cumulative exposure. For the remainder of this discussion, only approach 2, lagging, will be referenced.

The most important finding related to levels of the empirical induction period (i.e. lag=0, lag=10, lag=20) was that with a longer lagged dose the parameter estimate for dose (and deviance difference) consistently increased for all cancers outcomes except lung. The present analysis only

evaluated three lag intervals. From any of the graphical figures, it can be seen that the estimated dose coefficient changed from lag=10 to lag=20. Evaluating lag=15 would likely smooth out an increase in parameter estimate for dose if displayed on the plot. The optimal empirical induction period for lung cancers may be 15 years. In preliminary analysis using data originally published by Wing *et al.* (1991), lagging dose by 25 years slightly improved the parameter estimate compared to lag=20. By lag=30, the parameter estimate values were in decline and the confidence intervals became very wide, most likely reflecting the few number of workers in exposed groups who had 30 years of follow-up or more.

It is important to evaluate what 'lagging' does. Appendix 6 shows a hypothetical worker who worked 22 years and died in his 23rd year of follow-up. It can been seen that when dose is lagged 20 years, dose for the first 20 years of follow-up are set to zero, and the last 20 years of real time dose are essentially not included in analysis. In the case of the hypothetical worker, only cumulative dose received during the first, second, and third year of employment are considered in analysis. Dose for the remaining person-years are reassigned to the zero dose category. The implication is that only dose received *early* in a worker's follow-up or employment are included for analysis. This suggests that the year of hire may be an important predictor of mortality and may also be related to cumulative dose. In particular, workers hired in the early years of plant operation (before 1950) probably received higher cumulative dose than workers hired in the 1960's or 1970's. The increase in risk with increasing induction period has been noted by others. Thomas (1983) commented that exposure levels were higher in the past for many occupational settings, so subjects with high doses probably worked long ago with long follow-up, leading to a bias toward positive associations between exposure and increasing latency.

III. GROUPING OF CANCER OUTCOMES

There were thirteen cancer groupings evaluated in this analysis, which were summarized in Table 3.5. The contribution of dose adjusting for all other risk factors in the model was assessed

for each outcome using a nested-model approach. Cancer outcomes were selected in order to disentangle the relationships of solid cancers, lung cancer, and other smoking-related cancers with cumulative dose.

In four outcomes, cumulative dose significantly contributed to improvement of overall model fit at lag=0: (1) all cancers, (2) solid cancers, (3) smoking-related cancers including esophageal, (4) solid cancers excluding lung, and (4) smoking-related excluding lung.

In seven outcomes, cumulative dose did not significantly contribute to improvement of overall model fit at lag=0: (1) lung cancers, (2) smoking-related excluding esophageal, (3) all leukemias, (4) leukemias excluding chronic lymphocytic leukemia, (5) solid cancers excluding respiratory and upper digestive, (6) solid cancers excluding smoking-related, and (7) solid cancers and lung excluding other smoking-related.

From lag=0 to lag=20, the parameter estimate for cumulative dose as well as the deviance difference increased with increasing lag. One outcome, smoking-related excluding esophageal, that was not significant at lag=0 became significantly associated with cumulative dose by lag=10.

In earlier analysis of this cohort, Wing *et al.* (1991) found an association with lung cancer and cumulative dose for lag=0 and lag=10 (p=0.01 and p=0.02, respectively), using covariates agerisk, cohort, and agerisk*cohort. When adjusting for time-related variables, cumulative dose did not significantly contribute to overall model fit in the lung cancer outcome. In assessing the relationship of cumulative dose with lung cancer, neither analysis adjusted for paycode. The current analysis found that lung cancer was significantly related to duration of employment (p=0.007, lag=0), but not cumulative dose (p=0.502, lag=0). This relationship did not change with increasing lag interval. Wing *et al.* (1991) did not reflect adjustment for duration of employment. No interaction between duration of employment and dose was discovered.

To investigate further the relationship between lung cancer and cumulative dose, it was determined that duration of employment and cumulative dose were correlated (r=0.66). Instead of adding dose last to the time-related model, dose was added immediately before duration of employment, which was added last. Since these two variables were correlated, adding duration of

employment prior to dose could mask the influence of cumulative dose on mortality. After switching the order, duration of employment was still significantly associated with mortality (p=0.01, lag=0) and cumulative dose was not significantly related to lung cancer mortality (p=0.18, lag=0). This relationship was unchanged at lag=10 or lag=20.

It was thought that the relationship between lung cancer and cumulative dose may be confounded by paycode, since model fitting did not include adjustment for paycode. After adjustment for agerisk, yearrisk, and paycode, cumulative dose did not contribute to improvement in overall model fit (lag=20, p=0.4).

While lung cancer mortality was not associated with cumulative dose but was associated with duration of employment, smoking-related cancers were associated with both cumulative dose and duration of employment. Cumulative dose and duration of employment significantly contributed to improvement in overall model fit for three outcome groups: (1) smoking-related excluding esophageal, (2) smoking-related with esophageal (all EIP intervals), and (3) smoking-related excluding lung. Both variables were significantly associated with mortality in each outcome and EIP evaluated, with the exception of smoking-related excluding esophageal. At lag=0 cumulative dose was not associated with mortality for this outcome.

IV. COMPARING RESULTS USING DIFFERENT STATISTICAL MODELS

This dissertation was originally planned with the goal of comparing results between the log-linear model and the linear excess relative risk model. This comparison seemed necessary, since much controversy surrounded Wing *et al.* (1991), in part, because the analysis failed to incorporate the linear excess relative risk model.

The linear excess relative risk model has been used to analyze data from nuclear worker cohorts exposed to low-level radiation, particularly workers from the Department of Energy National Laboratories, as well as nuclear workers from the United Kingdom. The linear excess relative risk model has been used in analysis of these cohorts exposed to low-level radiation, so that

results from analysis of these cohorts would be comparable with results from follow-up studies of the atomic bomb survivor (ABS) cohort, which experienced high exposure.

The linear excess relative risk model is used to analyze data from the ABS cohort for three primary reasons. First, the linear excess relative risk model provides the best goodness-of-fit to cohort data from the ABS, compared to the log-linear or linear-quadratic models, based on published results from ABS cohort studies. The ABS cohort has been under follow-up for forty years.

Secondly, the intercept term in the linear excess relative risk model goes through zero. Since the 'true' shape of the dose-response curve at low doses is unknown in human populations, it is assumed that the dose-response curve for nuclear worker populations is linear and crosses the y-axis at zero. There is controversy about this assumption, but for purposes of radiation protection, caution is taken not to underestimate risk.

Third, cumulative dose is not transformed onto the logarithmic scale using a linear excess relative risk model, whereas the log-linear model assumes that once transformed cumulative dose is linear on the logarithmic scale. This transformation assumes that response per unit dose is the same at any point on the curve. According to some, for high doses the relative risk could be distorted using the log-linear model (Prichard, 1992). For example, if the percentage increase in mortality, say, for example 4.94%, was multiplied by 0.825 Sv (the mid-point of the highest dose category), and then exponentiated, the person exposed to 0.825 Sv is 59 times more likely to die of cancer than an unexposed person. According to Gilbert *et al.* (1989), the linear excess relative risk model is preferred over the log-linear model, because comparisons can be made to the ABS cohort data. Furthermore, Gilbert and colleagues state for lower doses the, the log-linear function $\exp(\beta z)$ is approximately equal to the linear function $1 + \beta z$. The linear excess relative risk model tends to give larger risk estimates and wider confidence interval (Gilbert *et al.*, 1989).

A. Comparing Results to Other Studies

The goal of comparing results between the linear excess relative risk model and the log-linear model cannot be completely achieved, primarily due to limitations in analytical capacity. While the log-linear model was fit using time-related factors agerisk, yearrisk, worker status, length of follow-up, duration of employment, and dose, the linear excess relative risk model adjusted for agerisk, yearrisk, and paycode. Fewer category levels of agerisk and yearrisk were allowed than in the log-linear model which had 16 agerisk categories. A complete analysis using all levels of each time-related factor was not possible since a student version of the software was available.

Comparisons between the linear excess relative risk model and the log-linear model do not completely correspond since stratification by agerisk and yearrisk were not as complete using the linear excess relative risk model. A modified comparison of these two models was performed using 8 levels of agerisk, 8 levels of yearrisk and 3 levels of paycode for the linear excess relative risk model. For the log-linear model, stratification variables included agerisk (16 levels), yearrisk (8 levels), and paycode (3 levels). This could explain why the log-linear model had a larger deviance difference, indicating that the data fits the log-linear (LL) model better than the linear excess relative risk model for solid cancers (Deviance, ERR=3.5, LL=5.8, lag=10) (Table 4.15).

Several nuclear cohort worker studies have stratified by agerisk, yearrisk, and a measure of socio-economic status, using varying levels of stratification. In analysis of the ORNL data, Gilbert *et al.* (1993) found an ERR of 1.5 (90% CI= <0, 4.0) for solid cancers with a 10 year lag, when stratifying on agerisk in single year intervals, yearrisk in five-year intervals, and paycode (three levels). Cumulative dose was divided into 10 categories. Contributory causes of cancer death were not included in that analysis. Results from analysis of the Hanford cohort using the same stratification variables above show a negative risk for mortality -0.0 (90%CI= <0,1.0) (Gilbert *et al.*, 1993, p. 414).

A combined analysis of mortality in worker cohorts from the US, United Kingdom (UK), and Canada was recently completed (IARC Study Group, 1994; Cardis *et al.*, 1995). An ERR of 1.7 (90% CI= 0.04, 4.4) was found for mortality from solid cancers at ORNL (lag=10)(Cardis *et al.*, 1995, p. 123). The approach in the IARC study included stratification by five-year agerisk and yearrisk categories as well as paycode (Cardis *et al.*, 1995, p. 120). To be eligible for membership in the IARC cohort, workers had to be employed at least six months. In this analysis eligibility was 30 days or more. In an earlier release of this same combined analysis (IARC Study Group, 1994, p.1029), the ERR for solid cancers combining three cohorts was -0.07 for lag=10 (90% CI= -0.04, 0.3).

In a Canadian study of nuclear workers, Gribbin *et al.* (1993) found an ERR of 0.049 (90% CI= -0.68, 2.17), for solid cancers with lag=10. Data were stratified by age, yearrisk, and length of follow-up in 5-year intervals. Ten dose categories were used. In the United Kingdom, Little *et al.* (1993, p. 101) found an ERR of 0.39 (90%CI= -0.23,1.16)-for solid cancers when stratifying by time since first employment (five levels), together with age, calendar time, industrial classification, and first employer.

In the current analysis, the ERR and log-linear estimates for lung cancer were 2.1 and 1.0, respectively for a 10-year lag. Gilbert *et al.* (1993), found an ERR of 0.5 (90% CI= <0.0, 6.7) in the ORNL cohort for lung cancer mortality when stratifying on agerisk in single year intervals, yearrisk in five-year intervals, and paycode (three levels). Estimates from the Hanford cohort using the same stratification scheme found an ERR of 0.1 (90% CI= <0, 1.8), where cumulative dose was divided into 10 categories. Kendall *et al.* (1992) found an ERR of 0.12 (90% CI= -0.098, 1.5) for lung cancers stratifying by age in five year intervals to age 85, calendar period (four levels), industrial classification code and first employer (Kendall *et al.*, 1992, p.223). Other sites associated with smoking were negative. Gribbin and colleagues (1993) did not evaluate lung or other smoking related cancers.

Smoking-related cancers show an association with cumulative dose in the ERR and log-linear models (5.1 and 3.0, respectively, lag=10). Earlier research found esophageal cancers and

respiratory cancers have a large impact on the overall results of mortality in the ORNL cohort. These cancers have been associated with both alcohol and smoking. Gilbert *et al.* (1993, p. 412) found an ERR of 3.0 (90% CI= 0.1, 8.1) for all smoking-linked cancers in the ORNL cohort, but when excluding lung cancer from this group found an ERR of 7.7 (90% CI= 2.1, 21). Estimates from the Hanford cohort were 0.2 (90%CI=<0,2.8) for lung cancer mortality and -0.1 (90%CI=<0, 2.3) for smoking-related cancers excluding lung. Smoking-linked cancers included respiratory, buccal cancer, and cancers of the esophagus, pancreas, and bladder (Gilbert *et al.*, 1993, p. 415). In this analysis and 13.4 and 4.7 were found for the ERR and log-linear estimates, respectively, when lung cancer was excluded from smoking-linked cancers (lag=10). Large differences between estimates of cumulative dose for smoking-related cancers excluding lung, and solid cancers suggests that the mortality burden in this cohort may be influenced by cancers associated with consumption of tobacco products.

Results from this analysis using the log-linear model are very similar to results that Gilbert and colleagues (1993) obtained using the same stratification variables, albeit with varying levels of stratification. Other differences between earlier re-analysis of the ORNL data (Gilbert *et al.* (1993)), and this analysis were inclusion of contributory causes of death and cohort eligibility requirements. Gilbert *et al.* (1993) did not include contributory causes of death and required employment for six months or more to be eligible for the study. Results from the linear excess relative risk model are slightly larger than results from the log-linear model approach, which could be due to less extensive stratification. Nevertheless, as predicted, the ERR estimates are larger than the log-linear estimates. In general, no matter what stratification variables or degree of stratification were used in the analysis of the ORNL cohort data, mortality estimates from the ORNL cohort are larger than estimates from other nuclear cohort studies.

V. HIGH DOSE OUTLIERS

Given that the overall cumulative dose in this cohort is low, it was prudent to evaluate the outliers in this cohort. As stated earlier, two cancer deaths experienced quite large cumulative dose readings (greater than 0.5 Sv) (see density distribution) that would be comparable to exposures in the ABS cohort. If these deaths are removed from the cohort, does the dose effect remain? Are these two cancer deaths that received high cumulative dose driving the results? It has been shown that the dose distribution is highly skewed to low dose and that most workers received between 10 and 50 mSv cumulative exposure (Figure 4.2). Lagging exposure would not seem to make much difference if cumulative dose at the beginning and end of follow-up were essentially the same.

Two deaths were over 0.5 Sv exposure: (1) one from esophageal cancer which received 0.52 Sv exposure, and (2) one death from laryngeal cancer with 0.82 Sv exposure. Both these workers were employed between 30-34 years (esophageal cancer), and 25-29 (laryngeal cancer) years, respectively, and both were hired in 1944. Both workers received between 10 mSv and 50 mSv cumulative exposure in the first year of employment. Cancer of these sites has been associated with both chewing tobacco and cigarette smoking, as well as alcohol consumption. Table 5.1 shows that when these two deaths (esophagus and larynx) are removed from the cohort, cumulative dose added to the log-linear model did not significantly improve overall model fit for the solid cancer grouping at lag=0 or lag=10 (p=0.33 and 0.17, respectively). It appears that these two deaths are very influential in the dose-response relationship.

Since these two death are also smoking-related, deaths were removed from the smoking-related outcome (Group II). When these two cancer deaths were removed, the association between with smoking-related cancer deaths and cumulative dose was no longer significant for any level of EIP (Table 5.2).

Smoking prevalence at ORNL was fairly high. A dissertation conducted in 1983 (Elghany, 1983) found that 86% of cancer cases smoked and 77% of controls also smoked (423 cases and 846 controls), based on a 25% random sample of the case-control study population. Given the high

smoking prevalence of male employees at ORNL, it was not surprising that an association with cumulative dose, could not be detected for lung cancers. Effects of radiation exposure may not be detectable, since cigarette smoking was such a strong risk factor for lung cancer. Fifty-three percent of the lung cancer deaths received 10 mSv or less of cumulative exposure, and 84% received less than the annual occupational limit (50 mSv) over a working lifetime. Having said that, however, it is difficult, if not impossible, to separate the contribution of smoking and radiation exposure to the cancer burden in this cohort, since recorded smoking data were not available in this analysis.

Nevertheless, the association with high cumulative exposure and esophageal cancer has precedence. Wiggs *et al.* (1994) found a dose response trend for cancer of the esophagus after controlling for exposures to plutonium in a cohort at Los Alamos National Laboratory (p=0.02). Three of the seven cases were in the unexposed group; three had cumulative dose of 10-49.9 mSv; none had cumulative dose of 50-99.9 mSv; and one death had cumulative dose of 212.1 mSv. Cancer of the esophagus has been associated with radiation in human populations exposed to high doses of therapeutic radiation. For persons exposed to radiation in the treatment of ankylosing spondylitis, more than a two-fold excess of cancer of the esophagus was observed among subjects who received very high doses to the esophagus (Wiggs *et al.*, 1994). A significant dose response for cancer of the esophagus has also been reported among the Atomic bomb survivor cohort (Shimizu *et al.*, 1990).

Cancers of the larynx have been observed to arise as a complication of therapeutic irradiation, after doses in the range of 30-60 Sv, but no excess has been found in the ABS cohort or in other populations exposed in the range below 1 Gy. The National Academy of Sciences concluded (1990) that the sensitivity of the larynx to radiation carcinogenesis appears to be relatively low.

Based on data presented in Tables 5.1 and 5.2, two deaths in the high dose category substantially influence the dose-response relationship in the ORNL cohort. Cumulative dose did significantly contribute to overall model fit for explaining the relationship between mortality and

exposure. This improvement in overall model fit was not found when smoking-related cancers were removed from solid cancers. There was an association with cumulative dose and smoking-related, but not when two deaths in the highest dose category were removed. When two deaths in the highest dose category were removed from the solid cancer grouping, cumulative dose did not contribute to overall improvement in fit of the time-related model after an induction period of 20 years (p=0.07). With additional follow-up, increased mortality in the ORNL cohort may be detected in the subset of cancers, independent of smoking-related cancers.

VI. INSIGHTS INTO IMPORTANT VARIABLES FOR FURTHER ANALYSIS

It has been shown that duration of employment may be an important confounder in the ORNL data. As stated earlier, paycode is also an important predictor. Some exploratory analysis was conducted in order to make more specific conclusions about the role of paycode and duration of employment as predictor variable that should be included in future analysis.

Paycode was added as a predictor variable in the log-linear model containing time-related factor: agerisk, yearrisk, worker status, length of follow-up, duration of employment, paycode, and dose. Using three cancers outcomes, it was determined that the influence of paycode was not the same for all outcomes. With solid cancers only paycode contributed to improvement of overall model fit (p=<0.00, lag=0), but cumulative dose did not. By lag=20, both paycode and duration of employment contributed significantly to overall improvement in model fit.. For lung cancers at lag=0, both paycode and duration of employment were significantly related to mortality (p=<0.00 and p=0.007, respectively), but consistent with earlier analysis, cumulative dose was not. The opposite trend was found with smoking-related cancers excluding lung. Paycode and duration of employment did not contribute to overall model fit when added as independent predictors (p=0.5 and p=0.06, respectively, lag=0), cumulative dose was associated with mortality. Mortality risk estimates for lung cancer and smoking-related excluding lung did not significantly change with

paycode included in the model than with paycode excluded. When paycode was included with solid cancers, the association between cumulative dose was reduced from 1.6 ($p=<0.04$) to 1.3 ($p=0.1$).

If paycode was assumed to be a proxy for smoking as a component of lifestyle, but there was no association between lung cancer and cumulative dose, then one would expect there to be no association between paycode and mortality. Both paycode and duration of employment appear to be important in particular subsets of cancer groupings, though not necessarily the same cancer grouping for each. Each variable is probably capturing different information. Paycode and duration of employment are not correlated with each other.

Year of hire has been indirectly suggested as an important predictor of mortality from results of empirical induction period analysis. As lagging of dose increases, x, the cumulative dose incorporated into analysis is that which was achieved x years earlier. This is why earlier exposures in follow-up time appear important.

Table 5.1

Summary of Model Fitting(a) for Solid Cancers Removing Two Cancer Deaths in Cumulative Dose Range Corresponding to Dose in Atomic Bomb Survivors by Empirical Induction Period

	Solid Cancers					
	Deaths Present (n=349)			Deaths Absent (n=347)		
EIP	Dose Coefficient(b)	Deviance(c) Difference	P-value	Dose Coefficient	Deviance Difference	P-value
Lag=0	1.6	4.2	0.04	0.9	0.9	0.33
Lag=10	2.1	6.6	<0.01	1.4	1.9	0.17
Lag=20	3.3	9.6	<0.01	2.4	3.3	0.07

Table 5.2

Summary of Model Fitting(a) for Smoking-Related Cancers Removing Two Deaths in Cumulative Dose Range Corresponding to Dose in Atomic Bomb Survivors by Empirical Induction Period

	Smoking-Related(d)					
	Deaths Present (n=144)			Deaths Absent (n=142)		
EIP	Dose Coefficient	Deviance Difference	P-value	Dose Coefficient	Deviance Difference	P-value
Lag=0	2.2	5.6	0.02	1.1	0.8	0.38
Lag=10	2.8	8.1	<0.01	1.7	1.6	0.21
Lag=20	3.8	8.2	<0.01	2.2	1.4	0.24

(a)Log-linear multiplicative model stratified by agerisk (16 levels), yearrisk(8 levels), worker status (2 levels), LOF (8 levels), and DOE (8 levels). Dose had 13 levels.
(b) Coefficient for cumulative dose per Sievert added last to time-related model.
(c) Deviance difference indicates the contribution of cumulative dose to model fit. A well-fitting variable will contribute a large deviance to overall model fit.
(d) Smoking-related includes cancers of the lung, larynx, nasopharynx, bladder, pancreas, and esophagus.

CHAPTER 6

CONCLUSIONS

The purpose of this dissertation was to determine if the risk of cancer mortality in the ORNL cohort was associated with low-level radiation exposure. The association between mortality and cumulative dose was explored by (1) grouping a variety of cancer outcomes, (2) evaluating assumptions of the empirical induction period, and (3) assessing the confounding effects of time-related factors.

The overall exposure experience of this cohort was quite low. The mean cumulative lifetime exposure in this cohort was 17.3 mSv (1.7 rem). Forty-three percent of the cancer deaths received 10 mSv (1 rem) or less of cumulative exposure. Two deaths from smoking-related cancers received 500 mSv or greater, which would be considered comparable to exposures received by survivors of the atomic bombs. Exposure of these two workers should not be considered low-dose cumulative exposure. A worker with the highest badge reading was still alive at the end of follow-up in 1984. To put these exposures into context, up to 50 mSv (5 rem) per year of cumulative exposure is permitted in occupational settings according to the National Commission on Radiation Protection (Shapiro, 1990).

Solid cancers were significantly associated with cumulative dose at each empirical induction period (lag=20, p=<0.01). The addition of cumulative dose contributed significantly to overall model fit, adjusting for time-related factors. Removal of two deaths in the highest cumulative dose group, referenced in the previous paragraph, resulted in a diminished association between solid cancer mortality and cumulative dose at each empirical induction period (Table 5.1, lag=20, p=0.07). Smoking-related cancers were associated with cumulative dose with these two cancer deaths included (Table 5.2, lag=20, p=<0.01), but cumulative dose no longer provided significant improvement in overall model fit for any level of induction period when these two deaths in the highest dose category were removed (Table 5.2, lag=20, p=0.24). When removing

smoking-related cancers from solid cancers, there was no significant association detected between cumulative dose and mortality. Cumulative dose did not contribute to overall goodness-of-fit for solid cancers with lung cancer, minus other smoking-related. Cumulative dose was not significantly associated with mortality at any empirical induction period.

The two smoking-related cancer deaths that received large amounts of cumulative exposures are strongly influential in the dose-response relationship found in these results and presumably in earlier analysis of this cohort data. Both workers were hired in 1944 and received between greater than 10 mSv and less than 50 mSv cumulative dose during the first year of employment. In the absence of these cancers, the data suggest that cumulative dose was an unlikely explanation for the observed cancer mortality at ORNL.

However, data suggest that with additional follow-up a small effect with cumulative dose may emerge independent of smoking (Table 5.1, lag=20, p=0.07). Several observations point to this conclusion. Cumulative dose was not significantly associated with solid cancers excluding smoking-related with the two high-dose cancers included. Furthermore, cumulative dose was not significantly associated with solid cancers and lung, minus smoking-related. Smoking-related cancers removing lung cancers *and* the two high dose deaths (n=38) were not significantly associated with cumulative dose. With additional follow-up, there will be more deaths and person-years, enhancing the ability to detect an association between exposure and mortality.

There are several limitations of these findings. First, paycode was not included as a covariate in log-linear analysis. Fifty-three percent (53%) of the weekly workers were deceased at the end of follow-up compared to 16.8% of the hourly workers and 30% of the monthly. This was not surprising given that 30% of the entire cohort and 63% of the cancer deaths were hired between 1943 and 1950, many of whom were short-term laborers to advance the war effort. Paycode was not related to exposure, but paycode was related to mortality in several, but not all, outcomes. There was no interaction detected between paycode and dose. Paycode was defined as the payroll category assigned when hired at ORNL: hourly, weekly or monthly. Workers who were employed by ORNL may have been promoted, and

hence, paycode may have changed from hourly to weekly or from weekly to monthly. Thus, paycode captures those who likely worked in the most exposed areas, represents previous workplace exposure, and lifestyle characteristics. Since, in general, paycode was a strong predictor of mortality, its inclusion may have precluded detecting associations with time-related factors.

Secondly, there were five covariates included in data analysis together with cumulative dose. There is a trade-off between controlling for enough risk factors to maintain validity, and the possible loss of precision resulting from control of too many variables (Kleinbaum et al., 1982, p. 278). Based on the standard error values for cumulative dose (Tables 4.12, 4.13, and 4.14), there may be over-stratification of the data (standard errors are smaller than the parameter estimates) for some outcomes. Worker status and length of follow-up do not contribute significantly to overall model fit in explaining cancer mortality, so inclusion of these variables may not have been necessary. Therefore, worker status and length of follow-up would not be relevant in future analysis of certain outcome groups.

Third, there was no information on other workplace exposures that contribute to the cancer process. Biological and/or area air monitoring was performed for many known and suspected carcinogens, such as asbestos, nickel, beryllium, carbon tetrachloride, percholoethylene and others, beginning as early as 1949 (ORAU Symposium, April, 1992). The fact that biological monitoring was performed prior to substantial knowledge about the carcinogenicity of these compound implies that exposures may have been considerable. An overestimate of cumulative dose would occur if workers with radiation exposure also were exposed to chemicals in the workplace, since no adjustment in analysis can be made for these exposures.

Fourth, there was no smoking data available for members of this cohort, so mortality risk estimates do not adjust for smoking. It is known that the smoking prevalence was high at ORNL, based on data obtained prior to employment (80%)(Elghany, 1983). It can be hypothesized that lung cancers were associated with cumulative radiation dose. However, because the contribution of smoking to the lung cancer burden masked any difference that could be detected between the

radiation exposure groups, the effect of radiation could not be detected. Assuming that lung cancer cases were smokers, the data could also suggest that the presence of radiation exposure and cigarette smoking did not enhance the risk of mortality. However, it must be said that smoking status of individuals in this cohort was unknown.

Third, it was known that radiation exposure misclassification occurred in the ORNL cohort. Early in ORNL operation, it was standard practice to record a non-detectable reading on the radiation badge as zero exposure, instead of the more conservative limit of detection. Recently, it has been determined that those which had the highest recorded dose likely received the greatest amount of unrecorded cumulative dose (Tankersley et al. in press). This suggests that results of mortality risk may be overestimated in this report.

From this analysis it is recognized that variables have different relationships with mortality depending on the outcome. The association of duration of employment quantifies not only that someone may have been exposed for a long time, but that the individual is older. The mean age of hire in the cancer mortality group was 39. The longer an individual works, the greater the probability that gamma radiation will pass through DNA, and initiate the cancer process. With more exposure, the greater the opportunity for DNA repair processes to fail. Then again, with intermittent low-level radiation exposure, the more opportunity there may be for DNA to completely repair. Duration of employment plays a role in predicting lung cancer mortality independent of cumulative dose, suggesting that duration of employment may be measuring other exposures in the workplace or may be a surrogate for cumulative dose. In future analysis, duration of employment and paycode should be considered as covariates in analysis, with the understanding that not all outcomes operate under the same combination of covariates.

The optimal empirical induction period for solid cancer development in the ORNL cohort was 20 years. The cumulative effect of low-level radiation may take longer to manifest into a cancer than acute high dose exposure such as occurred in the atomic bomb survivors. Since the optimal empirical induction period was 20 years, the empirical induction period could be

quantifying the effects of exposure occuring early in follow-up, such as during the 1940s and 1950s, when exposures where higher than in later years.

This analysis demonstrates that two smoking-related cancers deaths receiving greater than 500 mSv exposure are influential in the dose-response relationship between cancer mortality and cumulative exposure. With these two deaths removed from analysis, cancer mortality due to low-dose radiation exposure does not appear to exist in the ORNL cohort with follow-up through 1984 (lag=20, p=0.07). Additional follow-up will be necessary to more fully understand the impact of low-level radiation exposure on cancer mortality in the ORNL cohort.

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Glossary

alpha particles - an energetic helium nucleus, consisting of two neutrons and two protons. It is heavier than an electron by a factor of over 7300 and has double the charge (Shapiro, 1990, p. 33). It is commonly emitted in the active decay of uranium, thorium, radium, and polonium. Plutonium is a man-made compound that emits alpha particles. The alpha particles emitted by these compounds possess kinetic energies ranging between 4 MeV and 9 MeV. Their velocities are between 1.4 and 2.1 x 10^9 cm per second. They have a slower speed than lighter particles and impart energy at a much greater rate than lighter particles (high LET).

beta particles - high speed electrons which are emitted by nuclei of atoms as a result of energy released in a radioactive decay process involving the transformation of a neutron into a proton. Beta particles comprise one of the most important classes of directly ionizing particles. The following radionuclides emit beta particles: carbon-14, tritium, sulfur-35, calcium-45, phosphorous-32, strontium-90. Energy range is from 0.006 MeV to 1.13 MeV.

charged particles - particles that have a positive or negative charge

chromosome aberrations - a change in the shape or number of chromosome

DNA deoxyribonucleic acid is a polymer made of nucleotide units. It is what constitutes genes, and is responsible for heredity, and for carrying the information necessary for protein synthesis.

directly ionizing particles - electrons (most common in terms of exposure), alpha and beta particles, protons, and neutrons

double strand breaks - are comprised of essentially two single strand breaks, either exactly opposite t one another or in close proximity (probably not more than four bases apart). They are thought to be linearly induced with dose and are considered the most important lesion induced in irradiated cells (Bryant, 1989, p. 22).

electrons - directly ionizing radiation with a mass of 9.1 x 10-28 grams. The resting mass of an electron calculated in terms of energy content is 0.51 MeV. (E = m * v2). (Shapiro, 1990, p. 33).

excision repair - the removal of a damaged base pair by an enzyme, whereby the damaged base is cut out by an enzyme (an endonuclease), damage is broken down by exonuclease activity and DNA polymerase fills the gap with new base. Process is most well-known in non-mammalian cells and most commonly induced by UV light.

exposure - in the general sense, refers to the potential for , or actual delivery of, absorbed dose or dose equivalent; synonymous with irradiation. the condition of coming in contact with a toxicologic agent; differs from dose. (Kathren and Petersen, 1989).

fission - the chemical process of splitting the nucleus of an atom into more stable nuclei. For example, uranium has a very heavy nucleus that can be split to release energy, while the nuclei created are more stable than the original atom.

free radical - an unstable molecular fragment caused by breakage of a chemical bond in a molecule (Franks LM and Teich NM. Introduction to Molecular Biology of Cancer, second edition. Oxford Medical Publications. Oxford, England, 1991. Glossary.)

in vivo - referring to a process occuring in a living body (Stedman's Medical Dictionary)

isotope - a compound that has the same number of electrons and protons, but a different number of neutrons. An isotope is chemically equivalent to the stable form of the compound.

indirectly ionizing particles - x-rays, gamma rays, energies of the electromagnetic spectrum

ICRP - International Commission on Radiation Protection, established in 1928, sets radiation protection standards for occupational and general population exposures.

ionization - ejection of electrons from the atoms with which radiation interacts.

Joule - A Joule is the amount of energy required to set a 2-kilogram mass, at rest, into motion at the speed of 1 meter per second.

mutation - a heritable change in the genetic material. Mutations in the broadest sense include any change, from a single base pair change in the DNA to substantial deletions or rearrangements of the DNA even involving major parts or whole of chromosomes, and including chromosome translocations (Franks LM and Teich NM. Introduction to Molecular Biology of Cancer, second edition. Oxford Medical Publications. Oxford, England, 1991. Glossary).
fixation of potentially lethal lesions.

neutrons - a neutron is a common particle since it is a basic constituent of the nucleus along with the proton. Usually, a nucleus has the same number of protons and neutrons in the atom's nucleus. Unlike a proton, neutrons have no charge. There are no significant naturally occurring sources that emit neutrons. A naturally occurring nucleus that is unstable because of an excess of neutrons relative to protons will change the ratio by transformation of the neutron into a proton within the nucleus and the emission of a beta particle rather than through the emission of a neutron (Shapiro, 1990, p. 36). The most powerful sources of neutrons are nuclear-fission reactors. Approximately 2.5 neutrons are emitted per fission of uranium-235 and cause further fissions. The protection of personnel from these neutrons represents one of the more difficult problems in radiation protection.

oxidation - loss of hydrogen or loss of a electron to create a positive charge

photon - uncharged discrete packets of energy that travel through air as electromagnetic waves measured as wavelengths

protons - a naturally occuring particle that is the sole constituent of the nucleus of the hydrogen atom. The atomic number of a compound is defined by the number of protons in the nucleus. Protons has a positive charge. A proton has a mass of 1835 times the mass of an electron. Like alpha particles, they impart energy at a high rate when passing through matter (high LET). The proton is not emitted as radioactive decay like other directly ionizing particles. When the body is irradiated by neutrons, the incident energy is imparted to the protons contained in hydrogen atoms in the body, and the energetic protons become the major mechanism for transferring neutron energy to the body tissue.

photoelectric effect - experiment conducted by Einstein showing that electrons are knocked out of atoms by light beams (Gilbert, 1979, p. 249)

speed of light - the speed of light is 300,000 kilometers per second (100 kilometer = 62.1 miles)

reduction - gain of hydrogen or an electron to make the atom electronegative

radioactivity- the condition of a nucleus when it can release energy by rearranging its neutrons and protons, but it does not do it immediately. Radioactive nuclei release their energy after an almost random interval, whose time scale is set by the half-life of the particular nucleus. A nucleus that has too many

neutrons or too few for the number of protons can be unstable or radioactive. A radioactive nucleus is one that can release energy by changing itself into a different nucleus (Shapiro, 1979, p. 301).

```
/*THIS FILE IS /export/home/u1/cedrok/suzanne/results/master.sas */
options pagesize=60 linesize=80  mprint source2;
title 'pearce and checkoway person years calculation';
/*   /nutrnk/dog is the rounded version of upgen */
libname fish '/export/home/u1/cedrok/suzanne/nutrnk';
/*libname fish'/export/home/u6/cedrdv/durst/suzanne/newtrunc/upgen/Original';*/
libname bird '/export/home/u1/cedrok/suzanne/trunk/upflat';

/*********************************/
/* decimalizing dates with macro  */
/*********************************/

%macro _dateit (invar,outvar);
     yr=year(&invar);
     denom = mdy(12,31,yr) - mdy(1,1,yr) + 1;
     &outvar=(mod(yr,100)) + (mod(juldate(&invar),1000)-0.5)/denom;
%mend _dateit;

data test (keep= id type yearrisk agerisk doe lof dose pay cohort work
tse yrin yhire yrout yin yout hiredate birthdte yob agehire ageh paycode
yr start agelt year  hired  agf dose icod icod0 tsle icda8
t  follow len yrin2  yr_indx  vs_84 other_ca  dead duration
yr_rev ageterm aget agetm term termd  );

merge bird.x1upflat
       fish.dog;   /*fish.x1upgen2; for 'Original upgen'*/
      by id;
      if cum84 ne . ;
/*    if id ne 145724;
      if id ne 150230;

*/
 /*************************
  initialize cohort dates */
 /*************************/

if (_n_= 1) then do;                  /*start of follow-up*/
   sasdate=mdy(1,1,43);
   %_dateit (sasdate,start1)

   sasdate=mdy(12,31,84);             /* end of follow-up*/
   %_dateit  (sasdate,end1)

   sasend1 = mdy(12,31,84);            /* sasdate for end of follow-up*/
   onemonth = 30/365.25;              /* one month length of service*/

end;

retain start1 end1 sasend1 onemonth;

%_dateit (birthdte,yob)                /* create date of birth */

%_dateit (hiredate,yin)                /* create date of hire */

if (current = 1 or termdate > sasend1) then  /* create date of termination */
     yout = end1;
     else do;
     %_dateit (termdate, yout)
end;

if (yin >= (start1 - onemonth)) then   /* create start of follow-up*/
     yrin = yin + onemonth;
     else
     yrin = start1;

%_dateit (dlo,yrout)                   /* create end of follow-up */


icod = substr(icda8,1,3);              /* examine vital status */
icod0 = substr(other_ca,1,3);
n_icod=0;

/* Insert Outcomes to Generate 8 Death Groups */
/* Be sure to Comment-Out Outcomes not in use */


/* define death category */
%SETMYVAR;

if paycode = 'A' then pay = 0;
if paycode = 'W' then pay = 1;
if paycode = 'H' then pay = 2;

hired  = yrin;
if hired > 43.000  and hired < 45.99 then yhire = 0;
if hired >= 46 and hired  < 49.99 then yhire =  1;
if hired >= 50 and hired  < 59.99 then yhire =  2;
if hired >= 60 then  yhire = 3;

agehire =   yrin  - yob;
agelt = abs(agehire);
if yob < 100 then   agehire = agelt  ;
if (agehire < 20)  &  (agelt < 20)  then ageh = 0;

if (agehire >=20 and agehire < 30) & (agelt >=20 and agelt < 30)
       then ageh = 1;
if (agehire >=30 and agehire < 40)&(agelt  >=30 and agelt  < 40) then ageh = 2;
if (agehire >=40 and agehire < 50)&(agelt >=40 and agelt < 50) then ageh = 3;
if (agehire >=50 and agehire < 60)&(agelt  >=50 and agelt < 60) then ageh = 4;
if (agehire >=60 and agehire < 70)&(agelt  >=60 and agelt < 70) then ageh = 5;

term = yout;
if term > 43.00 and term < 45.99 then termd=0;
if term >=46 and term < 49.99 then termd =  1;
if term >=50 and term < 59.99 then termd =  2;
if term >=60 and term < 69.99 then termd =  3;
if term >=70 and term < 79.99 then termd =  4;
if term >=80 then termd =5;

ageterm = yout - yob;
agetm = abs(ageterm);
if yob < 100 then ageterm = agetm ; /* sometimes ageterm is negative */
if (ageterm >=15 and ageterm < 19.99) & (agetm >= 15 and agetm < 19.99)
       then aget = 0;
if (ageterm >=20 and ageterm < 39.99) & (agetm >=20 and agetm < 39.99)
       then aget = 1;
if (ageterm >=40 and ageterm < 59.99) & (agetm >= 40 and agetm < 59.99)
       then aget = 2;
if (ageterm >=60 and ageterm < 80.0) & (agetm >=60 and agetm < 80.0)
       then aget = 3;

tsle = yrout - yout;     /*time since last employment 3.30.95 */
if tsle < 0 then tse = 0;
if tsle >= 0 and tsle < 10 then tse = 1;
if tsle >=10 and tsle < 20 then tse = 2;
if tsle >=20 and tsle < 30 then tse = 3;
if tsle >=30 and tsle <=  41  then tse =  4;
```

```
/*frcyrs= (1, (yrout - (yrin + yr -1)); */
doe=yout-yin;
start=43;

/* define lagyears and latency  */

%LAGLAT;
monlag=0;

/*generate person years*/

  type=0;
  follow=(floor(yrout-yrin + 0.5)) ;

 if follow  < 1 then follow =1;  /*PREVENTS ROUNDING PERSON-YEARS TO 0*/
                                 /*new added 4.17.95 */
 if follow < latency + 1 then delete;  /*removes pyrs*/

  array cum_dose (yr_indx) cum43-cum84;
  array dose_a (yr_inda) dose43-dose84;

  do yr= latency + 1 to follow; /*removes pys then lags-added 6.15.95*/
  dose=0;
    yr_indx = floor(yr + yrin + 0.5 - start)-lagyears;
    if (yr_indx) > 0 then do;
       if cum_dose > 0 and cum_dose <1000 then dose = 1;
       else if cum_dose >= 1000  and cum_dose <5000 then dose = 2;
       else if cum_dose >= 5000  and cum_dose  <10000 then dose = 3;
       else if cum_dose >= 10000 and cum_dose <15000 then dose = 4;
       else if cum_dose >= 15000 and cum_dose < 20000 then dose = 5;
       else if cum_dose >= 20000 and cum_dose < 25000 then dose = 6;
       else if cum_dose >= 25000 and cum_dose < 30000 then dose = 7;
       else if cum_dose >= 30000 and cum_dose < 35000 then dose = 8;
       else if cum_dose >=35000  and cum_dose < 40000 then dose = 9;
       else if cum_dose >=40000  and cum_dose < 45000 then dose = 10;
       else if cum_dose >=45000  and cum_dose < 50000 then dose = 11;
       else if cum_dose >=50000 then dose = 12;
       end;

/*For removing two deaths in highest dose catetory 8/8/95
        else if cum_dose >=50000 then delete;
        end;
*/

     yr_inda=yr_indx + lagyears;
     if dose_a > . then work = 1; else work = 0;
     do i = 1 to 2;
       if work = 0 then do;
         yr_inda = yr_inda - 1;
         if yr_inda > 0 then if dose_a > . then work = 1;
       end;
     end;

     year=yrin + yr;  /* changed from yrin + yr -0.5 5.10.95*/
     t=year - yob;
     if (t<0) then t=t + 100;
     agerisk = 5 * floor(t/5);

     if (yob <60) then yob = yob + 100;  /* revised cohort 4.2.95 */
     if yob <= 90.999  then cohort = 0;
     if 91  <= yob <=  100.999  then cohort = 1;
     if 101 <= yob <=  110.999  then cohort = 2;
     if 111 <= yob <=  120.999  then cohort = 3;
     if 121 <= yob <=  130.999  then cohort = 4;
     if 131 <= yob <=  140.999  then cohort = 5;
     if 141 <= yob <=  150.999  then cohort = 6;
     if 151 <= yob <=  160.999  then cohort = 7;

     doe=5 * min(floor((year-yin)/5), floor((yout-yin)/5));
     lof= 5  * floor((year-yrin)/5);
         if year < 45 then year =45;      /*original W code -- added 3.22.95*/
     yearrisk=(5 * floor((year-5)/5))+5;
     /*frcyrs= (1, ( yrout - (yrin + yr -1));
     weight frcyrs; */
     output test;
   end;

/*generate deaths - repeat algorithm for multiple outcomes*/

   if (dead = 1) then do;
      type=1;
      dose=0;
if dead = 1 & follow < latency + 1 then delete; /*remove deaths 6.17.95*/
 yr_indx=floor(yrout+1-start )-lagyears;
   if (yr_indx > 0)  then do;
        if cum_dose > 0 and cum_dose <1000 then dose = 1;
        else if cum_dose >= 1000  and cum_dose <5000 then dose = 2;
        else if cum_dose >= 5000  and cum_dose  <10000 then dose = 3;
        else if cum_dose >= 10000 and  cum_dose <15000 then dose = 4;
        else if cum_dose >= 15000 and cum_dose < 20000 then dose = 5;
        else if cum_dose >= 20000 and cum_dose < 25000 then dose = 6;
        else if cum_dose >= 25000 and cum_dose < 30000 then dose = 7;
        else if cum_dose >= 30000 and cum_dose < 35000 then dose = 8;
        else if cum_dose >=35000  and cum_dose < 40000 then dose = 9;
        else if cum_dose >=40000  and cum_dose < 45000 then dose = 10;
        else if cum_dose >=45000  and cum_dose < 50000 then dose = 11;

        else if cum_dose >=50000 then dose = 12;
        end;


/* For removing two deaths from highest dose category 8/8/95
         else if cum_dose >=50000 then delete;
         end;

*/

      yr_inda=yr_indx + lagyears;
      if dose_a > . then work = 1; else work = 0;
      do i = 1 to 2;
        if work = 0 then do;
          yr_inda = yr_inda - 1;
        if yr_inda > 0 then if dose_a > . then work=1;
         end;
      end;

      year=yrin + yr ; /* changed from yrin + yr - 0.5 -- don't need rounding */
      t = yrout - yob;
      if (t<0) then t=t + 100;
      agerisk = 5 * floor(t/5);

      if (yob <60) then yob = yob + 100;  /* revised cohort 4.2.95 */
      if yob <= 90.999 then cohort = 0;
      if 91  <= yob <=  100.999  then cohort = 1;
      if 101 <= yob <=  110.999  then cohort = 2;
      if 111 <= yob <=  120.999  then cohort = 3;
      if 121 <= yob <=  130.999  then cohort = 4;
```

```
    if 131 <= yob <=  140.999  then cohort = 5;
    if 141 <= yob <=  150.999  then cohort = 6;
    if 151 <= yob <=  160.999  then cohort = 7;

     doe=5 * floor((yout-yin)/5);
     if yrout < yrin then yrout = yrin; /* added 5.10.95 -- negative yrout*/
       /*yrout is mid-year, and yrin is mid-month== sometimes negative*/
     lof=5 * floor((yrout-yrin)/5);
        if yrout < 45 then yrout =45; /* original W code added 3.22.95 */
    yearrisk=(5 * floor((yrout-5)/5 ))+5;
 output test;

  end;


/* output count by variables listed*/

%SETBL;
```

Appendix 2

File generated from running SAS program is composed of two parts.
When type=0, column headings are:

```
------------
type, agerisk, yearrisk, work, lof, doe, dose, person-years
0 15 45 0 0 0 0 0
0 15 45 0 0 0 1 0
0 15 45 0 0 0 2 0
0 15 45 0 0 0 3 0
0 15 45 0 0 0 4 0
0 15 45 0 0 0 5 0
0 15 45 0 0 0 6 0
0 15 45 0 0 0 7 0
0 15 45 0 0 0 8 0
0 15 45 0 0 0 9 0
```

When type=1, column headings are:

```
-----------
type, agerisk, yearrisk, work, lof, doe, dose, deaths
1 15 45 0 0 0 0 0
1 15 45 0 0 0 1 0
1 15 45 0 0 0 2 0
1 15 45 0 0 0 3 0
1 15 45 0 0 0 4 0
1 15 45 0 0 0 5 0
1 15 45 0 0 0 6 0
1 15 45 0 0 0 7 0
1 15 45 0 0 0 8 0
1 15 45 0 0 0 9 0
```

The file has been cut in half. Person-years and deaths
are in the last two columns.

The column heading are:

```
type, agerisk, yearrisk, work, lof, doe, dose, person-years, deaths
0 15 45 1 0 0 0 60 0
0 15 45 1 0 0 1 74 0
0 15 45 1 0 0 2 5 0
0 15 50 1 0 0 0 5 0
0 15 50 1 0 0 1 5 0
0 15 55 1 0 0 0 22 0
0 15 55 1 0 0 1 19 0
0 15 55 1 0 0 2 1 0
0 15 60 1 0 0 0 3 0
0 15 60 1 0 0 1 11 0
```

```
# THIS FILE IS TO FIT THE FOLLOWING VARIALBES:
# USING 8 OUTCOMES AND 4 LAG/LATENCY COMBINATIONS

#=============================================================================
#                        Checks on the dataframe
# ============================================================================

# Check on dataframes should be repeated for 26 unique dataframes.
# See /export/home/ul/cedrok/suzanne/results/ForSplus/M1/naming.files.for.SAU

  dat.fil <- matrix(scan("fo5ml5e"), ncol=9, byrow=T)
  dat.fil <- as.data.frame(dat.fil)
  names(dat.fil)_c("type","agerisk","yearrisk","work","lof","doe","dose",
  "per","dead")

cat( "\n")
cat("Column headings for ALL LEUKEMIA , MODEL 1
are:\n",
  names(dat.fil), "\n" )
  cat("Total number of person-years are", sum(dat.fil$per),"\n")

  cat("Total number of deaths are", sum(dat.fil$dead),"\n" )
  cat("Latency=0 and Lag=0") ; cat( "\n")
  attach(dat.fil)
#                     Data Input and Variable Revision
# ============================================================================
#
#     Variable    Unique values.
#     --------    --------------
#        type          (0, 1)
#      agerisk         (0, 1, 2, 3, ...., 16)
#      yearrisk        (0, 1, 2, 3, ...., 7 )
#      work            (0, 1)
#      lof             (0, 1, 2, 3, ...., 9 )
#      doe             (0, 1, 2, 3, ...., 9 )
#      dose            (0, 1, 2, 3, ...., 13)
#      per             ...
#      dead            ...

# Variable revision.
# ------------------
   cat("In order to get positive values for (offset(log(pys)))  0.001
   was added to the variable for person-years." ) ; cat( "\n")
#  1.  Person year units:  100000 person-years -> 1.
      pys _ per + 0.001  / 100000
      cat("The sum of pys is", sum(pys), "\n" )
#  2.  Reassign Dose: (0, 1, 2, 3, ...., 12 ) --> (0, 0.5, 2.5, 7.5, 12.5,
#      17.5, 22.5, 27.5, 32.5, 37.5, 42.5, 47.5, 82.5)
      mdose_c(0, 0.5, 2.5, 7.5, 12.5, 17.5, 22.5, 27.5, 32.5, 37.5,
              42.5, 47.5, 82.5) [ dose + 1  ]
# ============================================================================
#                              Model fitting
# ============================================================================

# Function to display model fit.
# ------------------------------
  display.fit _ function( fit.out,  per, dead, mdose , T  ) {
     est.dead _ fit.out$fitted.values
     X _ cbind(per, dead, est.dead)
     mat _ apply( X, MARGIN=2, FUN=function(i) (tapply(i,mdose,sum)) )
     rate_ mat[,2)/mat[,1] *100000
     est.rate _ mat[,3]/mat[,1]  * 100000
     mat _ round( cbind(mat, rate, est.rate ), 3)
     Tper _ sum(per) ; Td_ sum(dead)  ; Testd_round(sum(est.dead),3)
     Totals_ cbind(Tper, Td, Testd )
     cat( paste( c("\n",rep("-",30),"\n") ) )
     print(my.summary( fit.out,    correlation=F ) ) ; cat( "\n" )
     print( mat  ) ; cat( "\n" )
     cat("Total number of person-years, deaths, and estimated deaths are \n",
     Totals  ) ; cat( "\n" )
     invisible(mat) )


# Estimate factor effects relative to 1st level.
# 'Contrasts' mean that all the linear combinations are contrasts of levels.
# 'contr.treatment' means that coding in model assumes that the first level
# is the reference group. This also means that the coefficient for this
# level is zero.  'contrast.poly' assumes that factors are equally
# spaced and ordered (p. 34-36, Chambers and Hastie, 1993).
# 'options' changes the default contrast.
# ----------------------------------------------------------
  options( contrasts=c("contr.treatment","contr.poly") )


# Model 1:  (intercept only)
# ----------------------------------------------------------------------------
  fit.out.1 _ glm( dead ~ offset(log(pys)), family=poisson,
  control=glm.control(maxit=20))
  display.fit( fit.out.1, per, dead, mdose )

# 'offset' means that deaths are weighted by person-years. The log is used
# to keep offset values positive.

# Model 2: agerisk
# ----------------------------------------------------------------------------
  fit.out.2 _ glm( dead ~ offset(log(pys)) + agerisk, family=poisson,
control=glm.control(maxit=20) )
  display.fit( fit.out.2, per, dead, mdose )
  diff.dev.1_ deviance(fit.out.1) - deviance(fit.out.2) # deviance
  diff.df.1 _ fit.out.1$df.residual - fit.out.2$df.residual # dfs for deviance
  sign.age_1-pchisq(diff.dev.1,diff.df.1 ) # p-value for chi-sq distribution
# P-value for reduction in deviance with addition of variable
  cat("\nP-value for reduction in deviance with addition of variable is",
          sign.age, sep=" "  , fill=T )

# Test for Heterogeneity between SMRs for k mdose groups.
# HO: SMR for mdose groups k=2,3..,12 equals 1. There are 12 dfs since there
# are 13-1 mdose groups.
# QUESTION: should we be using equation 3.12 in B&D, Vol. II, which tests for
# trend (p. 96).
  # est.dead_ fit.out.2$fitted.values
   #sed_sum((dead-est.dead)**2/est.dead)
   #sed_round(sed, 3)

#cat("\nPearson chi-square is" , sed, sep=" ", fill=T)
#  diff.sed.2_ round(1-pchisq(sed, 12 ), 3)
#  cat("\nP-value for test of heterogeneity that a SMR for at least one mdose
#  group is significantly different from 1 is", diff.sed.2 , sep=" " )


#  Model 3: agerisk  + yearrisk
# ----------------------------------------------------------------------------
  fit.out.3 _ glm( dead ~ offset(log(pys)) + agerisk + yearrisk,
                   family=poisson, control=glm.control(maxit=20))
  display.fit( fit.out.3, per, dead, mdose )
  diff.dev.2_ deviance(fit.out.2) - deviance(fit.out.3)
  diff.df.2 _ fit.out.2$df.residual - fit.out.3$df.residual
```

```
  sign.yr_ round(1-pchisq(diff.dev.2,diff.df.2) ,3)

# P-value for reduction in deviance with addition of variable
  cat("\nP-value for reduction in deviance with addition of variable is",
          sign.yr, sep=" "  , fill=T )

# Test for Heterogeneity between Relative Risks for
# each mdose group. HO: SMR for dose groups k=2,3..,12 equals 1.
# QUESTION: should we be using equation 3.12 in B&D, Vol. II, which tests for
# trend (p. 96). There are 12 dfs since there are 8-1 mdose groups.

#  est.dead_ fit.out.3$fitted.values
#  sed_  sum((dead-est.dead)**2/est.dead)
#  sed_round( sed, 3)
#cat("\nPearson chi-square is" , sed, sep=" ", fill=T)
#  diff.sed.3_ round( 1-pchisq(sed, 12), 3)
#cat("\nP-value for test of heterogeneity that a SMR for at least one mdose
#group differs from 1 is", diff.sed.3 , sep=" " )


#  Model 4:  agerisk + yearrisk + work
#-------------------------------------------------------------------------------
   fit.out.4 _ glm( dead ~ offset(log(pys)) +  agerisk  + yearrisk + work,
         family=poisson, control=glm.control(maxit=20))
  display.fit( fit.out.4, per, dead, mdose)
  diff.dev.3_ deviance(fit.out.3) - deviance(fit.out.4)
  diff.df.3 _ fit.out.3$df.residual - fit.out.4$df.residual
  sign.work_ round(1-pchisq(diff.dev.3,diff.df.3), 3)

# P-value for reduction in deviance with addition of variable
  cat("\nP-value for reduction in deviance with addition of variable is",
          sign.work, sep=" "  , fill=T )

#  Model 5:  agerisk  + yearrisk + work + lof
#-------------------------------------------------------------------------------

  fit.out.5 _ glm( dead ~ offset(log(pys)) + agerisk + yearrisk +
        work + lof , family=poisson, control=glm.control(maxit=20))
  display.fit( fit.out.5, per, dead, mdose )
  diff.dev.4_ deviance(fit.out.4) - deviance(fit.out.5)
   diff.df.4 _ fit.out.4$df.residual - fit.out.5$df.residual
  sign.lof_ round( 1-pchisq(diff.dev.4,diff.df.4), 3)

# P-value for reduction in deviance with addition of variable
  cat("\nP-value for reduction in deviance with addition of variable is",
          sign.lof, sep=" "  , fill=T )


#  Model 6:  agerisk  + yearrisk + work + lof + doe
#-------------------------------------------------------------------------------
  fit.out.6 _ glm( dead ~ offset( log(pys) ) + agerisk + yearrisk +
        work + lof + doe, family=poisson, control=glm.control(maxit=20)  )
  display.fit( fit.out.6, per, dead, mdose )
  diff.dev.5_ deviance(fit.out.5) - deviance(fit.out.6)
   diff.df.5 _ fit.out.5$df.residual - fit.out.6$df.residual
  sign.doe_ round(1-pchisq(diff.dev.5,diff.df.5), 3)

# P-value for reduction in deviance with addition of variable
  cat("\nP-value for reduction in deviance with addition of variable is",
          sign.doe, sep=" "  , fill=T )


# Model 7: agerisk  + yearrisk + work + lof + doe + mdose
#-------------------------------------------------------------------------------

fit.out.7_glm( dead ~ offset( log(pys) ) + agerisk + yearrisk + work +
 lof + doe + mdose, family=poisson, control=glm.control(maxit=20))

display.fit( fit.out.7, per, dead, mdose )
diff.dev.6_deviance(fit.out.6) - deviance(fit.out.7)
diff.df.6 _ fit.out.6$df.residual - fit.out.7$df.residual
sign.mdose_ round(1-pchisq(diff.dev.6,diff.df.6), 3)

# P-value for reduction in deviance with addition of variable
  cat("\nP-value for reduction in deviance with addition of variable is",
          sign.mdose, sep=" "  , fill=T )


# Model 8: agerisk  + yearrisk + work + lof + doe + mdose + mdose*agerisk
#fit.out.8_glm( dead ~ offset( log(pys) ) + agerisk + yearrisk + work +
#jh lof + doe +  mdose + mdose:agerisk, family=poisson,
#j control=glm.control(maxit=20))
#display.fit( fit.out.8, per, dead, mdose )
#diff.dev.7_deviance(fit.out.7) - deviance(fit.out.8)
#diff.df.7 _ fit.out.7$df.residual - fit.out.8$df.residual
#sign.doag_ round(1-pchisq(diff.dev.7,diff.df.7), 3)

# P-value for reduction in deviance with addition of variable
#  cat("\nP-value for reduction in deviance with addition of variable is",
#          sign.doag, sep=" "  , fill=T )


# Model 9: agerisk  + yearrisk + work + lof + doe + mdose + mdose:agerisk
# + doe:work
#-------------------------------------------------------------------------------

#fit.out.9_glm( dead ~ offset( log(pys) ) + agerisk + yearrisk + work +
#j lof + doe +  mdose + mdose:agerisk+ doe:work, family=poisson,
# control=glm.control(maxit=20))
#display.fit( fit.out.9, per, dead, mdose )
#diff.dev.8_deviance(fit.out.8) - deviance(fit.out.9)
#diff.df.8 _ fit.out.8$df.residual - fit.out.9$df.residual
#sign.dowk_ round(1-pchisq(diff.dev.8,diff.df.8), 3)

# P-value for reduction in deviance with addition of variable
#  cat("\nP-value for reduction in deviance with addition of variable is",
#          sign.dowk, sep=" "  , fill=T )


# Model 10: agerisk  + yearrisk + work + lof + doe + mdose + mdose:agerisk
# + doe:work + mdose:doe
#-------------------------------------------------------------------------------

#fit.out.10_glm( dead ~ offset( log(pys) ) + agerisk + yearrisk + work +
# lof + doe +  mdose + mdose:agerisk + doe:work + mdose:doe, family=poisson,
# control=glm.control(maxit=20))
#display.fit( fit.out.10, per, dead, mdose )
#diff.dev.9_deviance(fit.out.9) - deviance(fit.out.10)
#diff.df.9 _ fit.out.9$df.residual - fit.out.10$df.residual
#sign.dsdo_ round(1-pchisq(diff.dev.9,diff.df.9), 3)

# P-value for reduction in deviance with addition of variable
#  cat("\nP-value for reduction in deviance with addition of variable is",
#          sign.dsdo, sep=" "  , fill=T )


# Model 11: agerisk  + yearrisk + work + lof + doe + mdose + mdose:agerisk
```

```
# + doe:work + mdose:doe + mdose:lof
#-------------------------------------------------------------------------------

#fit.out.11_glm( dead ~ offset( log(pys) ) + agerisk + yearrisk + work +
# lof + doe +  mdose + mdose:agerisk + doe:work + mdose:doe + mdose:lof,
# family=poisson,  control=glm.control(maxit=20))
#jdisplay.fit( fit.out.11, per, dead, mdose )
#diff.dev.10_deviance(fit.out.10) - deviance(fit.out.11)
#diff.df.10 _ fit.out.10$df.residual - fit.out.11$df.residual
#sign.dslf_ round(1-pchisq(diff.dev.10,diff.df.10), 3)

# P-value for reduction in deviance with addition of variable
#  cat("\nP-value for reduction in deviance with addition of variable is",
#           sign.dslf, sep=" "  , fill=T )

# Model 12: agerisk  + yearrisk + work + lof + doe + mdose + mdose:agerisk
# + doe:work + mdose:doe + mdose:lof + lof:doe
#-------------------------------------------------------------------------------

#fit.out.12_glm( dead ~ offset( log(pys) ) + agerisk + yearrisk + work +
# lof + doe +  mdose + mdose:agerisk + doe:work + mdose:doe + mdose:lof +
# lof:doe , family=poisson, control=glm.control(maxit=20))
#display.fit( fit.out.12, per, dead, mdose )
#diff.dev.11_deviance(fit.out.11) - deviance(fit.out.12)
#diff.df.11 _ fit.out.11$df.residual - fit.out.12$df.residual
#jsign.dolf_ round(1-pchisq(diff.dev.11,diff.df.11), 3)

# P-value for reduction in deviance with addition of variable
#  cat("\nP-value for reduction in deviance with addition of variable is",
#           sign.dolf, sep=" "  , fill=T )


cat( "\n")
# Analysis of Variance Table Testing Significance of Terms Added Sequentially
cat( "\n")
cc_anova(fit.out.7, test="Chisq")
round(cc,3)
```

Outcome 1 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING FOR ALL CANCERS,
UNDERLYING AND CONTRIBUTORY CAUSES OF DEATH,
BY LATENCY AND LAG COMBINATIONS

Outcome 1: All Cancers (n=379)

Total number of person-years are 213950
Total number of deaths are 379
Latency=0 and Lag=0

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6359	2367.949				
agerisk	1	693.036	6358	1674.913	0.000	0.102	0.004	0
yearrisk	1	0.170	6357	1674.743	0.680	-0.003	0.006	0.678
work	1	0.319	6356	1674.424	0.572	0.072	0.127	0.568
lof	1	0.595	6355	1673.829	0.441	0.008	0.010	0.440
doe	1	2.501	6354	1671.328	0.114	0.011	0.007	0.110
mdose	1	4.093	6353	1667.235	0.043	0.015	0.006	0.021

Outcome 1: All Cancers (n=359)

Total number of person-years are 173398
Total number of deaths are 359
Latency=5 and Lag=5

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5103	2169.804				
agerisk	1	621.106	5102	1548.698	0.000	0.105	0.004	0
yearrisk	1	0.001	5101	1548.697	0.969	0.000	0.007	0.969
work	1	0.104	5100	1548.593	0.747	0.043	0.134	0.746
lof	1	1.050	5099	1547.544	0.306	0.010	0.010	0.307
doe	1	3.978	5098	1543.565	0.046	0.014	0.007	0.043
mdose	1	6.359	5097	1537.206	0.012	0.020	0.007	0.003

Outcome 1: All Cancers (n=379)

Total number of person-years are 213950
Total number of deaths are 379
Latency=0 and Lag=10

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5254	2299.864				
agerisk	1	693.036	5253	1606.828	0.000	0.102	0.004	0
yearrisk	1	0.170	5252	1606.658	0.680	-0.003	0.006	0.679
work	1	0.319	5251	1606.339	0.572	0.072	0.127	0.570
lof	1	0.595	5250	1605.744	0.441	0.008	0.010	0.441
doe	1	2.501	5249	1603.243	0.114	0.011	0.007	0.111
mdose	1	6.693	5248	1596.550	0.010	0.021	0.007	0.002

Outcome 1: All Cancers (n=359)

Total number of person-years are 173398
Total number of deaths are 359
Latency=5 and Lag=15

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3688	2249.808				
agerisk	1	621.104	3687	1628.704	0.000	0.105	0.004	0
yearrisk	1	0.001	3686	1628.703	0.971	0.000	0.007	0.969
work	1	0.102	3685	1628.600	0.749	0.043	0.134	0.746
lof	1	1.053	3684	1627.548	0.305	0.010	0.010	0.308
doe	1	3.978	3683	1623.569	0.046	0.014	0.007	0.043
mdose	1	9.587	3682	1613.982	0.002	0.032	0.008	0.000

Outcome 1: All Cancers (n=379)

Total number of person-years are 213950
Total number of deaths are 379
Latency=0 and Lag=20

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3838	2379.711				
agerisk	1	693.036	3837	1686.675	0.000	0.102	0.004	0
yearrisk	1	0.170	3836	1686.506	0.680	-0.003	0.006	0.679
work	1	0.318	3835	1686.187	0.573	0.072	0.128	0.571
lof	1	0.594	3834	1685.593	0.441	0.008	0.010	0.442
doe	1	2.500	3833	1683.093	0.114	0.011	0.007	0.111
mdose	1	10.506	3832	1672.587	0.001	0.033	0.008	0.000

Outcome 2 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING FOR ALL CANCERS EXCLUDING LEUKEMIA
UNDERLYING AND CONTRIBUTORY CAUSES OF DEATH
BY LATENCY AND LAG COMBINATIONS

Latency = 0 and Lag = 0

Total number of person-years are 213950
Total number of deaths are 349

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			6359	2281.926					
agerisk	1	652.548	6358	1629.378	0.000	0.103	0.004	0	0.103
yearrisk	1	0.332	6357	1629.046	0.564	-0.004	0.007	0.56	-0.008
work	1	0.122	6356	1628.923	0.727	0.047	0.133	0.723	-0.114
lof	1	0.393	6355	1628.530	0.531	0.006	0.010	0.530	0.001
doe	1	1.990	6354	1626.540	0.158	0.010	0.007	0.154	0.006
mdose	1	4.205	6353	1622.335	0.040	0.016	0.007	0.019	0.016

Latency=5 and Lag=5

Total number of person-years are 173398
Total number of deaths are 331

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5103	2099.829				
agerisk	1	588.110	5102	1511.718	0.000	0.106	0.004	0
yearrisk	1	0.012	5101	1511.706	0.911	-0.001	0.007	0.911
work	1	0.003	5100	1511.703	0.959	0.007	0.141	0.958
lof	1	0.688	5099	1511.016	0.407	0.009	0.011	0.407
doe	1	3.555	5098	1507.460	0.059	0.014	0.007	0.056
mdose	1	6.243	5097	1501.218	0.012	0.021	0.007	0.003

Latency=0 and Lag=10

Total number of person-years are 213950
Total number of deaths are 349

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf.
NULL			5254	2221.753					
agerisk	1	652.548	5253	1569.205	0.000	0.103	0.004	0	0.103
yearrisk	1	0.332	5252	1568.873	0.564	-0.004	0.007	0.562	-0.008
work	1	0.122	5251	1568.751	0.727	0.047	0.133	0.725	-0.089
lof	1	0.393	5250	1568.357	0.531	0.006	0.010	0.531	0.000
doe	1	1.990	5249	1566.367	0.158	0.010	0.007	0.154	0.005
mdose	1	6.625	5248	1559.742	0.010	0.021	0.007	0.002	0.021

Latency=5 and Lag=15

Total number of person-years are 173398
Total number of deaths are 331

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3687	2129.749				
agerisk	1	588.108	3686	1541.641	0.000	0.106	0.004	0
yearrisk	1	0.012	3685	1541.629	0.913	-0.001	0.007	0.911
work	1	0.006	3684	1541.624	0.941	0.007	0.141	0.959
lof	1	0.688	3683	1540.936	0.407	0.009	0.011	0.408
doe	1	3.555	3682	1537.380	0.059	0.014	0.007	0.056
mdose	1	8.655	3681	1528.725	0.003	0.032	0.009	0.000

Latency=0 and Lag=20

Total number of person-years are 213950
Total number of deaths are 349

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			3837	2251.516					
agerisk	1	652.548	3836	1598.969	0.000	0.103	0.004	0	0.103
yearrisk	1	0.332	3835	1598.637	0.565	-0.004	0.007	0.563	-0.008
work	1	0.122	3834	1598.515	0.727	0.047	0.134	0.726	-0.078
lof	1	0.393	3833	1598.123	0.531	0.006	0.010	0.531	-0.001
doe	1	1.993	3832	1596.130	0.158	0.010	0.007	0.155	0.005
mdose	1	9.578	3831	1586.552	0.002	0.033	0.008	0.000	0.033

Outcome 3 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING FOR LUNG CANCERS,
UNDERLYING AND CONTRIBUTORY CAUSES OF DEATH,
BY LATENCY AND LAG COMBINATIONS

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 104

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			6353	894.159					
agerisk	1	187.002	6352	707.156	0.000	0.101	0.008	0	0.096
yearrisk	1	0.040	6351	707.117	0.842	-0.002	0.012	0.841	-0.018
work	1	0.043	6350	707.073	0.835	0.051	0.244	0.835	-0.494
lof	1	1.198	6349	705.875	0.274	0.021	0.019	0.279	0.003
doe	1	7.331	6348	698.544	0.007	0.035	0.013	0.006	0.033
mdose	1	0.450	6347	698.094	0.502	0.009	0.013	0.453	0.009

Latency=5 and Lag=5

Total number of person-years are 173398
Total number of deaths are 100

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5097	820.472				
agerisk	1	155.766	5096	664.707	0.000	0.099	0.008	0
yearrisk	1	0.002	5095	664.704	0.962	-0.001	0.013	0.962
work	1	0.045	5094	664.659	0.832	0.053	0.247	0.830
lof	1	1.351	5093	663.308	0.245	0.023	0.020	0.248
doe	1	7.592	5092	655.717	0.006	0.037	0.013	0.005
mdose	1	0.961	5091	654.756	0.327	0.015	0.013	0.268

Latency=0 and Lag=10

Total number of person-years are 213950
Total number of deaths are 104

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose.

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			5248	870.672					
agerisk	1	187.002	5247	683.669	0.000	0.101	0.008	0	0.097
yearrisk	1	0.040	5246	683.629	0.842	-0.002	0.012	0.841	-0.018
work	1	0.043	5245	683.586	0.835	0.051	0.242	0.833	-0.478
lof	1	1.198	5244	682.388	0.274	0.021	0.019	0.276	0.002
doe	1	7.331	5243	675.057	0.007	0.035	0.013	0.006	0.032
mdose	1	1.018	5242	674.039	0.313	0.015	0.013	0.253	0.015

Latency=5 and Lag=15

Total number of person-years are 173398
Total number of deaths are 100

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3679	860.102				
agerisk	1	155.764	3678	704.338	0.000	0.099	0.008	0
yearrisk	1	0.002	3677	704.336	0.961	-0.001	0.013	0.962
work	1	0.045	3676	704.291	0.832	0.053	0.249	0.831
lof	1	1.352	3675	702.939	0.245	0.023	0.020	0.250
doe	1	7.591	3674	695.348	0.006	0.037	0.013	0.005
mdose	1	0.234	3673	695.114	0.629	0.012	0.022	0.593

Latency=0 and Lag=20

Total number of person-years are 213950
Total number of deaths are 104

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose.

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			3829	910.301					
agerisk	1	187.001	3828	723.300	0.000	0.101	0.008	0	0.096
yearrisk	1	0.040	3827	723.261	0.842	-0.002	0.012	0.841	-0.018
work	1	0.043	3826	723.217	0.835	0.051	0.243	0.834	-0.481
lof	1	1.198	3825	722.019	0.274	0.021	0.019	0.279	0.002
doe	1	7.331	3824	714.688	0.007	0.035	0.013	0.006	0.034
mdose	1	0.285	3823	714.403	0.593	0.013	0.021	0.553	0.013

Outcome 4 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING FOR

SOLID CANCERS MINUS LUNG, UNDERLYING AND CONTRIBUTORY CAUSES OF DEATH,

BY LATENCY AND LAG COMBINATIONS (other smoking related included)

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 245

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6357	1748.455				
agerisk	1	465.655	6356	1282.799	0.000	0.104	0.005	0
yearrisk	1	0.311	6355	1282.488	0.577	-0.004	0.008	0.575
work	1	0.079	6354	1282.409	0.778	0.045	0.160	0.777
lof	1	0.002	6353	1282.407	0.968	0.000	0.012	0.968
doe	1	0.017	6352	1282.390	0.896	-0.001	0.009	0.896
mdose	1	4.145	6351	1278.245	0.042	0.019	0.008	0.018

Latency=5 and Lag=10

Total number of person-years are 173398
Total number of deaths are 231

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5101	1612.106				
agerisk	1	433.409	5100	1178.698	0.000	0.109	0.005	0
yearrisk	1	0.010	5099	1178.688	0.920	-0.001	0.009	0.92
work	1	0.006	5098	1178.682	0.937	-0.014	0.172	0.937
lof	1	0.056	5097	1178.626	0.814	0.003	0.013	0.814
doe	1	0.178	5096	1178.448	0.673	0.004	0.009	0.672
mdose	1	5.616	5095	1172.832	0.018	0.024	0.008	0.004

Latency=0 and Lag=10

Total number of person-years are 213950
Total number of deaths are 245

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5252	1703.451				
agerisk	1	465.656	5251	1237.795	0.000	0.104	0.005	0
yearrisk	1	0.311	5250	1237.484	0.577	-0.004	0.008	0.573
work	1	0.079	5249	1237.405	0.778	0.045	0.159	0.775
lof	1	0.002	5248	1237.403	0.968	0.000	0.012	0.969
doe	1	0.017	5247	1237.386	0.896	-0.001	0.009	0.896
mdose	1	5.964	5246	1231.422	0.015	0.024	0.008	0.003

Latency=5 and Lag=20

Total number of person-years are 173398
Total number of deaths are 231

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3683	1608.989				
agerisk	1	433.409	3682	1175.580	0.000	0.109	0.005	0
yearrisk	1	0.010	3681	1175.570	0.920	-0.001	0.009	0.92
work	1	0.006	3680	1175.563	0.937	-0.014	0.171	0.937
lof	1	0.056	3679	1175.508	0.813	0.003	0.013	0.813
doe	1	0.178	3678	1175.330	0.673	0.004	0.009	0.671
mdose	1	10.043	3677	1165.288	0.002	0.039	0.009	0.000

Latency=0 and Lag=20

Total number of person-years are 213950
Total number of deaths are 245

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3833	1700.176				
agerisk	1	465.656	3832	1234.520	0.000	0.104	0.005	0
yearrisk	1	0.311	3831	1234.209	0.577	-0.004	0.008	0.575
work	1	0.079	3830	1234.130	0.778	0.045	0.160	0.777
lof	1	0.002	3829	1234.128	0.968	0.000	0.012	0.968
doe	1	0.017	3828	1234.111	0.896	-0.001	0.009	0.896
mdose	1	10.966	3827	1223.145	0.001	0.040	0.009	0.000

Outcome 5 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING FOR

SOLID CANCER, MINUS SMOKING RELATED*, UNDERLYING AND CONTRIBUTORY CAUUSES

BY LATENCY AND LAG COMBINATIONS

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 205

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose.

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			6356	1477.833					
agerisk	1	360.712	6355	1117.121	0.000	0.100	0.005	0	0.103
yearrisk	1	0.404	6354	1116.717	0.525	-0.006	0.009	0.52	-0.001
work	1	0.220	6353	1116.498	0.639	0.081	0.172	0.638	0.246
lof	1	0.097	6352	1116.401	0.756	-0.004	0.013	0.755	0.000
doe	1	1.144	6351	1115.256	0.285	-0.011	0.010	0.289	-0.012
mdose	1	0.137	6350	1115.120	0.711	0.005	0.012	0.694	0.005

Latency=5 and Lag=5

Total number of person-years are 173398
Total number of deaths are 191

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5100	1357.651				
agerisk	1	340.941	5099	1016.709	0.000	0.106	0.006	0
yearrisk	1	0.000	5098	1016.709	0.987	0.000	0.010	0.988
work	1	0.001	5097	1016.708	0.970	0.007	0.186	0.971
lof	1	0.004	5096	1016.704	0.949	-0.001	0.014	0.949
doe	1	0.197	5095	1016.507	0.657	-0.005	0.010	0.659
mdose	1	0.192	5094	1016.315	0.661	0.007	0.014	0.642

Latency=0 and Lag=10

Total number of person-years are 213950
Total number of deaths are 205

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose.

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			5251	1437.968					
agerisk	1	360.714	5250	1077.255	0.000	0.100	0.005	0	0.103
yearrisk	1	0.404	5249	1076.851	0.525	-0.006	0.009	0.523	-0.001
work	1	0.220	5248	1076.631	0.639	0.081	0.172	0.638	0.255
lof	1	0.097	5247	1076.534	0.756	-0.004	0.013	0.755	0.000
doe	1	1.144	5246	1075.391	0.285	-0.011	0.010	0.289	-0.013
mdose	1	0.286	5245	1075.104	0.593	0.008	0.014	0.566	0.008

Latency=5 and Lag=15

Total number of person-years are 173398
Total number of deaths are 191

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3681	1327.317				
agerisk	1	340.942	3680	986.375	0.000	0.106	0.006	0
yearrisk	1	0.000	3679	986.375	0.988	0.000	0.010	0.988
work	1	0.001	3678	986.374	0.971	0.007	0.184	0.970
lof	1	0.004	3677	986.369	0.949	-0.001	0.014	0.948
doe	1	0.196	3676	986.173	0.658	-0.005	0.010	0.658
mdose	1	1.258	3675	984.915	0.262	0.022	0.016	0.170

Latency=0 and Lag=20

Total number of person-years are 213950
Total number of deaths are 205

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			3831	1407.477					
agerisk	1	360.714	3830	1046.763	0.000	0.100	0.005	0	0.103
yearrisk	1	0.404	3829	1046.360	0.525	-0.006	0.009	0.522	-0.001
work	1	0.220	3828	1046.140	0.639	0.081	0.171	0.636	0.270
lof	1	0.097	3827	1046.043	0.756	-0.004	0.013	0.754	-0.001
doe	1	1.144	3826	1044.899	0.285	-0.011	0.010	0.287	-0.015
mdose	1	1.747	3825	1043.153	0.186	0.025	0.015	0.102	0.025

* Smoking-related cancers exluded are lung (162-163) n=104; larynx (161) n=4; nasopharnyx (147) n=1; bladder (188) n=3; pancreas (157) n=26; esophagus (150) n=6.

Outcome 6 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING

SOLID CANCERS AND LUNG CANCER, EXCLUDING OTHER SMOKING-RELATED*

UNDERLYING AND CONTRIBUTORY CAUSES OF DEATH,

BY LATENCY AND LAG COMBINATIONS

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 309

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6358	2024.076				
agerisk	1	547.701	6357	1476.375	0.000	0.100	0.004	0
yearrisk	1	0.402	6356	1475.973	0.526	-0.004	0.007	0.524
work	1	0.253	6355	1475.720	0.615	0.071	0.141	0.614
lof	1	0.141	6354	1475.579	0.707	0.004	0.011	0.708
doe	1	0.609	6353	1474.970	0.435	0.006	0.008	0.432
mdose	1	0.525	6352	1474.445	0.469	0.007	0.009	0.412

Latency=5 and Lag=5

Total number of person-years are 173398
Total number of deaths are 291

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5102	1658.790				
agerisk	1	496.186	5101	1362.604	0.000	0.104	0.005	0
yearrisk	1	0.002	5100	1362.603	0.967	0.000	0.008	0.967
work	1	0.024	5099	1362.579	0.877	0.023	0.148	0.875
lof	1	0.389	5098	1362.190	0.533	0.007	0.011	0.532
doe	1	1.699	5097	1360.491	0.192	0.011	0.008	0.187
mdose	1	0.998	5096	1359.493	0.318	0.011	0.010	0.266

Latency=0 and Lag=10

Total number of person-years are 213950
Total number of deaths are 309

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5253	1969.041				
agerisk	1	547.701	5252	1421.340	0.000	0.100	0.004	0
yearrisk	1	0.402	5251	1420.939	0.526	-0.004	0.007	0.523
work	1	0.253	5250	1420.686	0.615	0.071	0.140	0.611
lof	1	0.141	5249	1420.545	0.707	0.004	0.011	0.707
doe	1	0.609	5248	1419.936	0.435	0.006	0.008	0.432
mdose	1	1.187	5247	1418.748	0.276	0.012	0.010	0.222

Latency=5 and Lag=15

Total number of person-years are 173398
Total number of deaths are 291

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3685	1868.086				
agerisk	1	496.186	3684	1371.900	0.000	0.104	0.005	0
yearrisk	1	0.002	3683	1371.899	0.967	0.000	0.008	0.967
work	1	0.024	3682	1371.875	0.877	0.023	0.149	0.876
lof	1	0.389	3681	1371.486	0.533	0.007	0.011	0.533
doe	1	1.699	3680	1369.787	0.192	0.011	0.008	0.188
mdose	1	1.376	3679	1368.411	0.241	0.018	0.013	0.177

Latency=0 and Lag=20

Total number of person-years are 213950
Total number of deaths are 309

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3835	1978.180				
agerisk	1	547.699	3834	1430.481	0.000	0.100	0.004	0
yearrisk	1	0.401	3833	1430.080	0.527	-0.004	0.007	0.524
work	1	0.256	3832	1429.824	0.613	0.071	0.140	0.613
lof	1	0.141	3831	1429.683	0.707	0.004	0.011	0.707
doe	1	0.609	3830	1429.074	0.435	0.006	0.008	0.432
mdose	1	1.883	3829	1427.191	0.170	0.020	0.013	0.109

* Smoking related cancers exluded are: larynx 161 n=4; nasopharnyx 147 n=1; esophagus 150 n=6; bladder 188 n=3; and pancreas 157 n=26.

Outcome 7 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING FOR SOLID CANCER EXCLUDING SMOKING-RELATED GROUP 1, RESPIRATORY AND UPPER DIGESTIVE, UNDERLYING AND CONTRIBUTORY CAUSES OF DEATH, BY LATENCY AND LAG COMBINATIONS

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 232

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6357	1663.232				
agerisk	1	431.464	6356	1231.768	0.000	0.103	0.005	0
yearrisk	1	0.117	6355	1231.651	0.732	-0.003	0.008	0.731
work	1	0.335	6354	1231.315	0.563	0.095	0.163	0.560
lof	1	0.033	6353	1231.282	0.855	-0.002	0.012	0.855
doe	1	0.889	6352	1230.394	0.346	-0.009	0.010	0.350
mdose	1	0.143	6351	1230.251	0.705	0.005	0.012	0.690

Latency=5 and Lag=5

Total number of person-years are 173398
Total number of deaths are 218

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	Std.Err	P-val
NULL			5101	1530.938				
agerisk	1	403.359	5100	1127.579	0.000	0.108	0.005	0
yearrisk	1	0.038	5099	1127.541	0.846	0.002	0.009	0.846
work	1	0.040	5098	1127.502	0.842	0.035	0.175	0.842
lof	1	0.000	5097	1127.501	0.985	0.000	0.013	0.985
doe	1	0.141	5096	1127.361	0.708	-0.004	0.010	0.709
mdose	1	0.249	5095	1127.112	0.618	0.007	0.013	0.598

Latency=0 and Lag=10

Total number of person-years are 213950
Total number of deaths are 232

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5252	1618.612				
agerisk	1	431.465	5251	1187.147	0.000	0.103	0.005	0
yearrisk	1	0.117	5250	1187.030	0.732	-0.003	0.008	0.731
work	1	0.335	5249	1186.694	0.563	0.095	0.163	0.561
lof	1	0.033	5248	1186.661	0.855	0.095	0.163	0.561
doe	1	0.888	5247	1185.773	0.346	-0.009	0.009	0.346
mdose	1	0.341	5246	1185.432	0.559	0.008	0.013	0.533

Latency=5 and Lag=15

Total number of person-years are 173398
Total number of deaths are 218

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3683	1528.687				
agerisk	1	403.359	3682	1125.328	0.000	0.108	0.005	0
yearrisk	1	0.038	3681	1125.290	0.846	0.002	0.009	0.845
work	1	0.040	3680	1125.250	0.842	0.035	0.174	0.840
lof	1	0.000	3679	1125.250	0.985	0.000	0.013	0.985
doe	1	0.141	3678	1125.109	0.708	-0.004	0.010	0.708
mdose	1	1.831	3677	1123.278	0.176	0.023	0.014	0.104

Latency=0 and Lag=20

Total number of person-years are 213950
Total number of deaths are 232

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3833	1616.203				
agerisk	1	431.465	3832	1184.738	0.000	0.103	0.005	0
yearrisk	1	0.117	3831	1184.621	0.732	-0.003	0.008	0.731
work	1	0.335	3830	1184.286	0.563	0.095	0.162	0.559
lof	1	0.033	3829	1184.253	0.855	-0.002	0.012	0.854
doe	1	0.888	3828	1183.364	0.346	-0.009	0.010	0.348
mdose	1	2.339	3827	1181.025	0.126	0.026	0.014	0.062

Outcome 8 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING FOR RESPIRATORY RELATED CANCERS,
UNDERLYING AND CONTRIBUTORY CAUSES OF DEATH, NO ESOPHAGUS
BY LATENCY AND LAG COMBINATIONS

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 138

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6354	1159.802				
agerisk	1	274.730	6353	885.072	0.000	0.106	0.007	0
yearrisk	1	0.011	6352	885.061	0.916	-0.001	0.011	0.915
work	1	0.046	6351	885.014	0.830	0.047	0.214	0.828
lof	1	1.665	6350	883.349	0.197	0.021	0.017	0.200
doe	1	6.938	6349	876.411	0.008	0.030	0.011	0.007
mdose	1	2.362	6348	874.049	0.124	0.017	0.009	0.078

Latency=5 and Lag=5

Total number of person-years are 173398
Total number of deaths are 134

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5098	1067.785				
agerisk	1	231.382	5097	836.404	0.000	0.105	0.007	0
yearrisk	1	0.012	5096	836.392	0.914	-0.001	0.012	0.914
work	1	0.072	5095	836.320	0.788	0.059	0.218	0.786
lof	1	1.656	5094	834.664	0.198	0.022	0.017	0.203
doe	1	6.913	5093	827.751	0.009	0.030	0.011	0.007
mdose	1	3.776	5092	823.975	0.052	0.022	0.010	0.021

Latency=0 and Lag=10

Total number of person-years are 213950
Total number of deaths are 138

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5249	1129.342				
agerisk	1	274.730	5248	854.612	0.000	0.106	0.007	0
yearrisk	1	0.011	5247	854.601	0.916	-0.001	0.011	0.915
work	1	0.046	5246	854.555	0.830	0.047	0.215	0.829
lof	1	1.665	5245	852.889	0.197	0.021	0.017	0.201
doe	1	6.938	5244	845.952	0.008	0.030	0.011	0.007
mdose	1	3.844	5243	842.107	0.050	0.023	0.010	0.020

Latency=5 and Lag=15

Total number of person-years are 173398
Total number of deaths are 134

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3681	1129.057				
agerisk	1	231.381	3680	897.676	0.000	0.105	0.007	0
yearrisk	1	0.012	3679	897.664	0.914	-0.001	0.012	0.914
work	1	0.072	3678	897.592	0.788	0.059	0.219	0.787
lof	1	1.656	3677	895.936	0.198	0.022	0.017	0.204
doe	1	6.913	3676	889.024	0.009	0.030	0.011	0.007
mdose	1	4.507	3675	884.516	0.034	0.032	0.012	0.007

Latency=0 and Lag=20

Total number of person-years are 213950
Total number of deaths are 138

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	SrdErr.	P-val
NULL			3831	1190.614				
agerisk	1	274.730	3830	915.884	0.000	0.106	0.007	0
yearrisk	1	0.011	3829	915.873	0.916	-0.001	0.011	0.916
work	1	0.046	3828	915.827	0.830	0.047	0.216	0.829
lof	1	1.665	3827	914.161	0.197	0.021	0.017	0.202
doe	1	6.938	3826	907.224	0.008	0.030	0.011	0.007
mdose	1	4.583	3825	902.641	0.032	0.033	0.012	0.007

Outcome 9 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING FOR SMOKING RELATED CANCERS,
WITH ESOPHAGEAL UNDERLYING AND CONTRIBUTORY CAUSES OF DEATH,
BY LATENCY AND LAG COMBINATIONS (outcome 4a)

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 144

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose.

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			6354	1214.782					
agerisk	1	292.717	6353	922.065	0.000	0.107	0.006	0	0.103
yearrisk	1	0.017	6352	922.048	0.896	-0.001	0.011	0.895	-0.018
work	1	0.000	6351	922.048	0.983	-0.004	0.212	0.983	-0.562
lof	1	1.871	6350	920.177	0.171	0.022	0.016	0.174	0.003
doe	1	10.841	6349	909.336	0.001	0.036	0.011	0.001	0.029
mdose	1	5.608	6348	903.728	0.018	0.022	0.008	0.005	0.022

Latency=5 and Lag=5

Total number of person-years are 173398
Total number of deaths are 140

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr	P-val
NULL			5098	1122.424				
agerisk	1	247.173	5097	875.251	0.000	0.106	0.007	0
yearrisk	1	0.023	5096	875.228	0.878	-0.002	0.011	0.878
work	1	0.001	5095	875.226	0.971	0.008	0.217	0.971
lof	1	1.854	5094	873.373	0.173	0.023	0.017	0.178
doe	1	10.894	5093	862.479	0.001	0.036	0.011	0.001
mdose	1	7.966	5092	854.513	0.005	0.028	0.008	0.000

Latency=0 and Lag=10

Total number of person-years are 213950
Total number of deaths are 144

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose.

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			5249	1186.157					
agerisk	1	292.717	5248	893.440	0.000	0.107	0.006	0	0.103
yearrisk	1	0.017	5247	893.423	0.896	-0.001	0.011	0.896	-0.018
work	1	0.000	5246	893.423	0.983	-0.004	0.213	0.983	-0.526
lof	1	1.871	5245	891.551	0.171	0.022	0.016	0.176	0.002
doe	1	10.841	5244	880.710	0.001	0.036	0.011	0.001	0.028
mdose	1	8.073	5243	872.638	0.004	0.028	0.008	0.000	0.028

Latency=5 and Lag=15

Total number of person-years are 173398
Total number of deaths are 140

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3681	1182.678				
agerisk	1	247.173	3680	935.505	0.000	0.106	0.007	0
yearrisk	1	0.023	3679	935.482	0.878	-0.002	0.011	0.878
work	1	0.001	3678	935.480	0.971	0.008	0.217	0.971
lof	1	1.854	3677	933.627	0.173	0.023	0.017	0.179
doe	1	10.894	3676	922.733	0.001	0.036	0.011	0.001
mdose	1	8.138	3675	914.595	0.004	0.038	0.010	0.000

Latency=0 and Lag=20

Total number of person-years are 213950
Total number of deaths are 144

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose.

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			3831	1246.411					
agerisk	1	292.717	3830	953.694	0.000	0.107	0.006	0	0.103
yearrisk	1	0.017	3829	953.677	0.896	-0.001	0.011	0.896	-0.019
work	1	0.000	3828	953.677	0.983	-0.004	0.214	0.983	-0.519
lof	1	1.871	3827	951.805	0.171	0.022	0.016	0.177	0.001
doe	1	10.841	3826	940.964	0.001	0.036	0.011	0.001	0.029
mdose	1	8.252	3825	932.712	0.004	0.038	0.010	0.000	0.038

Outcome 10 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING FOR

SMOKING-RELATED CANCERS (Group II)*, MINUS LUNG CANCER;

UNDERLYING AND CONTRIBUTORY CAUSES OF DEATH

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 40

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			6352	469.285					
agerisk	1	108.653	6351	360.632	0.000	0.126	0.013	0	0.121
yearrisk	1	0.012	6350	360.620	0.912	0.002	0.021	0.912	-0.018
work	1	0.164	6349	360.456	0.686	-0.181	0.452	0.689	-0.786
lof	1	0.761	6348	359.695	0.383	0.027	0.032	0.391	0.005
doe	1	3.686	6347	356.009	0.055	0.038	0.019	0.050	0.023
mdose	1	8.612	6346	347.398	0.003	0.039	0.010	0.000	0.039

Latency=5 and Lag=5

Total number of person-years are 173398
Total number of deaths are 40

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5096	447.966				
agerisk	1	93.785	5095	354.180	0.000	0.123	0.013	0
yearrisk	1	0.041	5094	354.140	0.840	-0.004	0.022	0.838
work	1	0.077	5093	354.062	0.781	-0.123	0.440	0.780
lof	1	0.572	5092	353.490	0.449	0.024	0.032	0.452
doe	1	3.388	5091	350.101	0.066	0.037	0.019	0.059
mdose	1	10.448	5090	339.654	0.001	0.045	0.010	0.000

Latency=0 and Lag=10

Total number of person-years are 213950
Total number of deaths are 40

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose.

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			5247	464.147					
agerisk	1	108.653	5246	355.494	0.000	0.126	0.013	0	0.121
yearrisk	1	0.012	5245	355.481	0.911	0.002	0.021	0.911	-0.019
work	1	0.164	5244	355.318	0.686	-0.180	0.444	0.685	-0.708
lof	1	0.761	5243	354.557	0.383	0.027	0.032	0.386	0.004
doe	1	3.686	5242	350.871	0.055	0.038	0.019	0.050	0.020
mdose	1	10.389	5241	340.482	0.001	0.045	0.010	0.000	0.045

Latency=5 and Lag=15

Total number of person-years are 173398
Total number of deaths are 40

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3677	475.182				
agerisk	1	93.785	3676	381.396	0.000	0.123	0.013	0
yearrisk	1	0.041	3675	381.356	0.840	-0.004	0.022	0.839
work	1	0.076	3674	381.280	0.783	-0.123	0.444	0.782
lof	1	0.573	3673	380.707	0.449	0.024	0.032	0.455
doe	1	3.389	3672	377.318	0.066	0.037	0.019	0.060
mdose	1	12.797	3671	364.521	0.000	0.060	0.011	0.000

Latency=0 and Lag=20

Total number of person-years are 213950
Total number of deaths are 40

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last) Last col. is coef with dose.

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val	Conf
NULL			3827	491.363					
agerisk	1	108.653	3826	382.710	0.000	0.126	0.013	0	0.122
yearrisk	1	0.011	3825	382.699	0.918	0.002	0.021	0.911	-0.020
work	1	0.164	3824	382.535	0.686	-0.181	0.450	0.688	-0.720
lof	1	0.761	3823	381.774	0.383	0.027	0.032	0.390	0.000
doe	1	3.686	3822	378.088	0.055	0.038	0.019	0.050	0.022
mdose	1	12.585	3821	365.503	0.000	0.059	0.011	0.000	0.059

* smoking-related cancers (n=40) include: larynx 161 (n=4); nasopharnyx 147 (n=1); esophagus 150 (n=6); bladder 188 (n=3); pancrease 157 (n=26).

Outcome 11 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING FOR ALL LEUKEMIAS,
UNDERLYING AND CONTRIBUTORY CAUSES OF DEATH,
BY LATENCY AND LAG COMBINATIONS

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 30

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6351	269.258				
agerisk	1	41.539	6350	227.719	0.000	0.088	0.014	0
yearrisk	1	0.253	6349	227.467	0.615	0.012	0.023	0.619
work	1	0.621	6348	226.846	0.431	0.337	0.422	0.424
lof	1	0.420	6347	226.426	0.517	0.022	0.035	0.522
doe	1	0.627	6346	225.799	0.429	0.020	0.025	0.424
mdose	1	0.045	6345	225.754	0.831	0.006	0.025	0.823

Latency=0 and Lag=2

Total number of person-years are 213950
Total number of deaths are 30

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6257	267.890				
agerisk	1	41.539	6256	226.352	0.000	0.088	0.014	0
yearrisk	1	0.253	6255	226.099	0.615	0.012	0.023	0.619
work	1	0.621	6254	225.478	0.431	0.337	0.422	0.425
lof	1	0.420	6253	225.058	0.517	0.022	0.035	0.522
doe	1	0.627	6252	224.432	0.429	0.020	0.025	0.424
mdose	1	0.048	6251	224.383	0.826	0.006	0.026	0.818

Latency=5 and Lag=2

Total number of person-years are 173398
Total number of deaths are 28

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5540	245.840				
agerisk	1	34.335	5539	211.504	0.000	0.088	0.015	0
yearrisk	1	0.275	5538	211.230	0.600	0.013	0.026	0.605
work	1	0.850	5537	210.379	0.356	0.406	0.433	0.348
lof	1	0.748	5536	209.631	0.387	0.031	0.037	0.395
doe	1	0.402	5535	209.229	0.526	0.017	0.026	0.520
mdose	1	0.072	5534	209.157	0.788	0.008	0.026	0.763

Latency=5 and Lag=5

Total number of person-years are 173398
Total number of deaths are 28

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			4846	243.890				
agerisk	1	34.335	4845	209.554	0.000	0.088	0.015	0
yearrisk	1	0.275	4844	209.280	0.600	0.013	0.026	0.602
work	1	0.850	4843	208.430	0.356	0.406	0.429	0.344
lof	1	0.748	4842	207.681	0.387	0.031	0.037	0.391
doe	1	0.402	4841	207.279	0.526	0.017	0.026	0.520
mdose	1	0.292	4840	206.988	0.589	0.016	0.025	0.536

Latency=0 and Lag=10

Total number of person-years are 213950
Total number of deaths are 30

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5246	265.845				
agerisk	1	41.539	5245	224.306	0.000	0.088	0.014	0
yearrisk	1	0.253	5244	224.053	0.615	0.012	0.023	0.616
work	1	0.621	5243	223.432	0.431	0.337	0.418	0.421
lof	1	0.420	5242	223.012	0.517	0.022	0.034	0.519
doe	1	0.627	5241	222.386	0.429	0.020	0.025	0.423
mdose	1	0.182	5240	222.204	0.670	0.012	0.025	0.629

Latency=5 and Lag=15

Total number of person-years are 173398
Total number of deaths are 28

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3676	287.401				
agerisk	1	34.335	3675	253.066	0.000	0.088	0.015	0
yearrisk	1	0.275	3674	252.791	0.600	0.013	0.026	0.604
work	1	0.850	3673	251.941	0.356	0.406	0.431	0.346
lof	1	0.748	3672	251.193	0.387	0.031	0.037	0.394
doe	1	0.401	3671	250.792	0.527	0.017	0.026	0.521
mdose	1	0.901	3670	249.891	0.343	0.030	0.026	0.233

Outcome 12 from Table 3.5

SUMMARY OF LOG-LINEAR MODEL FITTING FOR ALL LEUKEMIAS, EXCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA, UNDERLYING AND CONTRIBUTORY CAUSES OF DEATH, BY LATENCY AND LAG COMBINATIONS

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 23

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6351	209.831				
agerisk	1	24.583	6350	185.248	0.000	0.077	0.016	0
yearrisk	1	0.277	6349	184.971	0.599	0.014	0.026	0.603
work	1	0.013	6348	184.958	0.911	0.054	0.485	0.911
lof	1	0.364	6347	184.594	0.546	0.023	0.039	0.550
doe	1	1.211	6346	183.382	0.271	0.032	0.029	0.264
mdose	1	0.187	6345	183.196	0.665	0.012	0.025	0.634

Latency=0 and Lag=2

Total number of person-years are 213950
Total number of deaths are 23

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6257	209.991				
agerisk	1	24.583	6256	185.408	0.000	0.077	0.016	0
yearrisk	1	0.277	6255	185.131	0.599	0.014	0.026	0.604
work	1	0.013	6254	185.119	0.911	0.054	0.485	0.911
lof	1	0.364	6253	184.754	0.546	0.023	0.039	0.550
doe	1	1.211	6252	183.543	0.271	0.032	0.029	0.264
mdose	1	0.233	6251	183.310	0.629	0.013	0.025	0.591

Latency=5 and Lag=2

Total number of person-years are 173398
Total number of deaths are 22

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			5540	195.271				
agerisk	1	18.685	5539	176.586	0.000	0.073	0.017	0
yearrisk	1	0.045	5538	176.541	0.832	0.006	0.028	0.833
work	1	0.233	5537	176.308	0.629	0.235	0.481	0.625
lof	1	0.604	5536	175.703	0.437	0.032	0.042	0.444
doe	1	0.625	5535	175.078	0.429	0.024	0.030	0.422
mdose	1	0.234	5534	174.845	0.629	0.014	0.025	0.573

Latency=0 and Lag=10

Total number of person-years are 213950
Total number of deaths are 23

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6257	209.991				
agerisk	1	24.583	6256	185.408	0.000	0.077	0.016	0
yearrisk	1	0.277	6255	185.131	0.599	0.014	0.026	0.604
work	1	0.013	6254	185.119	0.911	0.054	0.485	0.911
lof	1	0.364	6253	184.754	0.546	0.023	0.039	0.550
doe	1	1.211	6252	183.543	0.271	0.032	0.029	0.264
mdose	1	0.233	6251	183.310	0.629	0.013	0.025	0.591

Latency=5 and Lag=15

Total number of person-years are 173398
Total number of deaths are 22

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			3676	237.044				
agerisk	1	18.685	3675	218.360	0.000	0.073	0.017	0
yearrisk	1	0.045	3674	218.315	0.832	0.006	0.028	0.833
work	1	0.233	3673	218.082	0.629	0.235	0.478	0.623
lof	1	0.604	3672	217.477	0.437	0.032	0.041	0.442
doe	1	0.625	3671	216.852	0.429	0.024	0.030	0.421
mdose	1	1.325	3670	215.527	0.250	0.037	0.025	0.128

NON CANCER OUTCOMES, EXCLUDED CANCERS AND EXTERNAL CAUSES OF DEATH

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 972

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6363	4702.784				
agerisk	1	1967.786	6362	2734.997	0.000	0.107	0.002	0
yearrisk	1	45.940	6361	2689.057	0.000	-0.026	0.004	0
work	1	33.813	6360	2655.244	0.000	-0.506	0.090	0
lof	1	2.198	6359	2653.046	0.138	0.009	0.006	0.14
doe	1	12.350	6358	2640.696	0.000	0.016	0.004	0.000
mdose	1	3.007	6357	2637.689	0.083	0.010	0.005	0.060

ALL CAUSES OF DEATH

Latency=0 and Lag=0

Total number of person-years are 213950
Total number of deaths are 1523

Analysis of Deviance Table

Poisson model

Response: dead

Terms added sequentially (first to last)

	Df	Deviance	Resid. Df	Resid. Dev	Pr(Chi)	Coef.	StdErr.	P-val
NULL			6369	5945.888				
agerisk	1	2419.893	6368	3525.994	0.000	0.094	0.002	0
yearrisk	1	37.401	6367	3488.593	0.000	-0.019	0.003	0
work	1	32.321	6366	3456.273	0.000	-0.372	0.067	0
lof	1	1.153	6365	3455.119	0.283	0.005	0.005	0.283
doe	1	7.494	6364	3447.625	0.006	0.010	0.004	0.006
mdose	1	5.741	6363	3441.883	0.017	0.011	0.004	0.008

Appendix 5: EXCESS RELATIVE RISK* AT 1 SIEVERT EXPOSURE TO GAMMA RADIATION
BY LEVELS OF STRATIFICATION AND LAG INTERVAL (EIP)
SOLID CANCERS -- LEUKEMIAS EXCLUDED, UNDERLYING & CONTRIBUTORY CAUSES (n=349)

STRATA	EIP	ERR(1 Sv)	95% CI	Std. Err.	Null Deviance	Null DF	Deviance	Likelihood#	LR P-value
Agerisk(1)	Lag=0	3.01	0.08, 5.9	1.5	1579.3	6352	1573.3	6.1	0.01
8 levels	Lag=10	4.01	0.43, 8.0	1.2	1519.2	5247	1511.1	8	0.01
	Lag=20	7.8	1.7, 13.9	3.1	1530.5	3830	1518.6	11.9	<0.00
Yearrisk(2)	Lag=0	6.1	2.2, 9.9	2.0	2135.3	6352	2120.0	14.4	< 0.00
8 levels	Lag=10	13.0	6.6, 19.3	3.3	2075.1	5247	2046.1	28.9	<0.00
	Lag=20	43.2	26.3, 60.2	8.7	2086.5	3830	2031.0	55.5	<0.00
LOF(3)	Lag=0	1.1	-0.87, 3.11	1.1	1927.3	6352	1925.9	1.4	0.23
8 levels	Lag=10	2.0	-0.6, 4.6	1.3	1867.0	5247	1864.0	3.1	0.08
	Lag=20	4.9	0.06, 9.8	2.5	1878.5	3830	1872.0	6.3	0.01
DOE(4)	Lag=0	1.7	-0.85, 4.2	1.3	2195.0	6352	2192.9	2.2	0.14
8 levels	Lag=10	15.5	5.5, 23.7	4.6	2134.9	5247	2116.5	18.4	<0.0
	Lag=20	207.0	140.5, 273	33.9	2146.2	3830	2041.0	105.2	<0.0
Work(5)	Lag=0	24.6	14.09, 35.06	5.4	2191.3	6358	2139.4	51.9	<0.00
2 levels	Lag=10	43.6	28.5, 58.7	7.7	2131.1	5253	2045.0	86.1	<0.00
	Lag=20	111.2	79.5, 143	16.2	2142.0	3836	2005.4	137.1	<0.00
Agerisk,	Lag=0	3.0	0.02, 5.9	1.5	1536.2	6299	1530.4	5.8	0.02
Yearrisk	Lag=10	4.1	0.4, 7.8	1.9	1476.0	5194	1468.0	8.1	<0.00
	Lag=20	8.3	1.7, 14.9	3.4	1487.4	3777	1475.5	11.9	<0.00
Agerisk, (6)	Lag=0	2.8	-0.08, 5.7	1.5	1546.0	6301	1540.6	5.3	0.02
Yearrisk, (7)	Lag=10	3.9	0.31, 7.6	1.9	1485.8	5196	1478.2	7.6	<0.00
LOF (8)	Lag=20	8.8	1.8, 15.7	3.5	1497.1	3779	1484.9	12.2	<0.00

Appendix 5: EXCESS RELATIVE RISK* AT 1 SIEVERT EXPOSURE TO GAMMA RADIATION
BY LEVELS OF STRATIFICATION AND LAG INTERVAL (EIP)
SOLID CANCERS -- LEUKEMIAS EXCLUDED (continued)

STRATA	EIP	ERR(1 Sv)	ERR 95% CI	Std. Err.	Null Deviance	Null DF	Deviance	Likelihood#	LR P-value
Agerisk,	Lag=0	2.9	-0.48, 6.4	1.8	1555.2	6302	1551.0	4.6	0.03
Yearrisk,	Lag=10	4.2	-0.19, 8.7	2.3	1495.0	5197	1488.3	6.6	0.01
DOE(9)	Lag=20	10.6	1.8, 19.5	4.5	1506.3	3780	1493.8	12.5	<0.00
Agerisk,	Lag=0	3.4	0.12, 6.6	1.7	1559.5	6323	1553.0	6.3	0.01
Yearrisk,	Lag=10	4.5	0.51, 8.5	2.0	1499.0	5218	1490.0	8.4	<0.00
Work	Lag=20	9.0	2.0, 16.0	3.5	1510.0	3801	1498.0	12.6	<0.00

* Excess relative risk of mortality increases (or decreases) with 1 Sv change in exposure. Alternatively, the ERR increases (or decreases) by N percent with 10 mSv change in exposure, where N is ERR.

Likelihood ratio test (LR) compares the contribution of adding Sv to the stratified null model, by comparing the difference between the null deviance and deviance of the current model. The degrees of freedom for the test are computed as the difference in the number of free parameters in the current model and the number in the null model, i.e. 1 df. LR is same as 'Deviance' in Table 4.12.

(1) agerisk -- 8 levels, (<45, 45-49, 50-54, 55-59, 60-64, 65-70, 70-74, 75+)

(2) yearrisk -- 8 levels, (1945-49, 1950-54, 1955-59, 1960-64, 1965-69,1970-75, 1975-79, 1980-1984)

(3) length of follow-up (lof) (years) -- 8 levels (0-4, 5-9,10-14, 15-19, 20-24, 25-29, 30-34, 35-41)

(4) duration of employment (doe) (years) -- 8 levels (0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-40)

(5) worker status -- 2 levels (0,1)

(6) agerisk -- 5 levels, (<45, 45-54, 55-64, 65-74, 75-92)

(7) yearrisk -- 4 levels, (1945-54, 1955-64, 1965-74,1975-1984)

(8) lof -- 4 levels (<10, 10-19, 20-29, 30-41)

(9) doe -- 4 levels (<10, 10-19, 20-29, 30-41)

Appendix 5: EXCESS RELATIVE RISK* AT 1 SEIVERT EXPOSURE TO GAMMA RADIATION
BY LEVELS OF STRATIFICATION AND LAG INTERVAL (EIP)
LEUKEMIAS EXCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA (n=23)

STRATA	EIP	ERR(1 Sv)	ERR 95% CI	Std. Err.	Null Deviance	Null DF	Deviance	Likelihood#	LR P-value
Agerisk(1)	Lag=0	3.1	-7.5, 13.7	5.4	174.4	6344	173.8	0.5	0.48
8 levels	Lag=2	3.6	-7.8, 14.9	5.8	174.5	6250	173.9	0.6	0.44
	Lag=10	3.6	-7.8, 14.9	5.8	174.5	6250	173.9	0.6	0.44
Yearrisk(2)	Lag=0	7.0	-8.7, 22.7	8.0	186.4	6344	185.1	1.3	0.25
8 levels	Lag=2	8.1	-8.9, 25.1	8.7	186.6	6250	185.0	1.5	0.20
	Lag=10	8.1	-8.9, 25.1	8.7	186.6	6250	185.0	1.5	0.21
LOF(3)	Lag=0	2.4	-7.1, 11.9	4.8	185.8	6344	185.4	0.4	0.55
8 levels	Lag=2	2.8	-7.3, 12.9	5.2	185.9	6250	185.5	0.4	0.51
	Lag=10	2.8	-7.3, 12.9	5.2	185.9	6250	185.5	0.4	0.51
DOE(4)	Lag=0	1.3	-7.3, 9.8	4.3	193.8	6344	193.6	0.1	0.73
8 levels	Lag=2	1.9	-8.0, 11.9	5.1	193.9	6250	193.6	0.2	0.63
	Lag=10	1.9	-8.0, 11.9	50.0	193.9	6250	193.7	0.2	0.64
Work(5)	Lag=0	26.0	-15.7, 67.7	21.3	207.9	6350	204.0	3.8	0.05
2 levels	Lag=2	31.3	-15.8, 78.3	24.0	208.1	6256	20.35	4.6	0.03
	Lag=10	31.3	-15.8, 78.3	24.0	208.0	6256	20.35	4.5	0.03
Agerisk,	Lag=0	2.1	-6.9, 11.15	4.6	135.5	6291	135.2	0.2	0.6
Yearrisk	Lag=2	2.4	-7.2, 12.0	4.9	135.6	6197	135.3	0.4	0.55
	Lag=10	2.4	-7.2, 11.9	4.9	135.6	6197	135.3	0.4	0.55
Agerisk, (6)	Lag=0	3.2	-7.9, 14.4	5.7	154.8	6293	154.3	0.5	0.47
Yearrisk, (7)	Lag=2	3.6	-8.1, 15.3	6.0	154.9	6199	154.4	0.6	0.40
LOF (8)	Lag=10	3.6	-8.1, 15.3	6.0	154.9	6199	154.4	0.6	0.40

Appendix 5: EXCESS RELATIVE RISK AT 1 SIEVERT EXPOSURE TO GAMMA RADIATION
BY LEVELS OF STRATIFICATION AND LAG INTERVAL (EIP)
LEUKEMIAS EXCLUDING CHRONIC LYMPHOCYTIC LEUKEMIA (n=23) (continued)

STRATA	EIP	ERR(1 Sv)	95% CI	Std. Err.	Null Deviance	DF	Deviance	Likelihood	P-VALUE
Agerisk,	Lag=0	2.4	-8.9, 13.8	5.8	151.4	6294	151.1	0.3	0.60
Yearrisk,	Lag=2	2.9	-9.3, 15.12	6.2	151.5	6200	151.1	0.4	0.54
DOE (9)	Lag=10	2.9	-9.4, 15.12	6.2	151.5	6200	151.1	0.4	0.54
Agerisk,	Lag=0	2.9	-8.3, 14.14	5.7	158.7	6315	158.3	0.4	0.50
Yearrisk,	Lag=2	3.4	-8.6, 15.3	6.0	158.9	6221	158.3	0.5	0.47
Work	Lag=10	3.4	-8.6, 15.33	6.0	158.9	6221	158.4	0.5	0.47

* Excess relative risk of mortality increases (or decreases) with 1 Sv change in exposure. Alternatively, the ERR increases (or decreases) by N percent with 10 mSv change in exposure, where N is the ERR.
# Likelihood ratio test (LR) compares the contribution of adding Sv to the stratified null model, by comparing the difference between the null deviance and deviance of the current model.
The degrees of freedom (DF) for the test are computed as the difference in the number of free parameters in the current model and the number in the null model, i.e. 1 DF. LR is the same as 'Deviance' in Table 4.12.
(1) agerisk -- 8 levels, (<45, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75+)
(2) yearrisk -- 8 levels, (1945-49,1950-54,1955-59,1960-64,1965-69,1970-74, 1975-79,1980-84)
(3) length of follow-up (lof) (years) -- 8 levels (0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-41)
(4) duration of employment (doe) (years) -- (0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-41)
(5) worker status -- 2 levels (0,1)
(6) agerisk -- 5 levels (<45, 45-54, 55-64, 65-74, 75-90)
(7) yearrisk -- 4 levels (1945-54, 1955-64, 1965-74, 1975-84)
(8) lof -- 4 levels (<10, 10-19, 20-29, 30-41)
(9) doe -- 4 levels (<10, 10-19, 20-29, 30-41)

Appendix 5: EXCESS RELATIVE RISK* AT 1 SIEVERT EXPOSURE TO GAMMA RADIATION
BY LEVELS OF STRATIFICATION AND LAG INTERVAL (EIP)
SOLID CANCERS EXCLUDING SMOKING-RELATED* (n=205)

STRATA	EIP	ERR(1 Sv)	95% CI	Std. Err.	Null Deviance	Null DF	Deviance	Likelihood#	LR P-value
Agerisk(1)	Lag=0	0.3	-2.39, 2.99	1.4	1078.0	6349	1078.0	0.04	0.84
8 levels	Lag=10	0.4	-2.80, 3.53	1.6	1038.2	5244	5243.0	0.04	0.83
	Lag=20	3.0	3.15, 9.18	3.2	1003.1	3824	1001.9	1.2	0.28
Yearrisk(2)	Lag=0	1.80	-1.67, 5.21	1.8	1391.8	6349	1390.0	0.9	0.33
8 levels	Lag=10	4.6	-0.78, 10.01	2.8	1351.9	5244	1348.0	3.2	0.08
	Lag=20	22.6	7.72, 37.4	7.6	1316.9	3824	1303.6	13.2	<0.00
LOF(3)	Lag=0	-0.9	-2.14, 0.34	0.6	1284.2	6349	1283.6	0.7	0.42
8 levels	Lag=10	-0.8	-2.48, 0.83	0.9	1244.4	5244	1244.0	0.4	0.53
	Lag=20	0.6	-3.48, 4.75	2.1	1209.3	3824	1209.2	0.8	0.78
DOE(4)	Lag=0	-0.2	-2.43,1.94	1.10	1437.00	6349	1437.0	0.03	0.87
8 levels	Lag=10	4.8	-1.73, 11.43	3.4	1397.2	5244	1395.1	2.1	0.15
	Lag=20	168.0	93.72, 242.2	37.9	1362.1	3824	1318.5	43.6	<0.00
Work(5)	Lag=0	10.9	2.531, 19.23	4.2	1427.7	6355	1417.8	9.8	0.01
2 levels	Lag=10	21.5	8.89, 34.06	6.4	1387.8	5250	1368.4	19.4	<0.00
	Lag=20	75.6	44.07, 107.20	16.1	1352.7	3830	1305.2	47.5	<0.00
Agerisk,	Lag=0	0.3	2.42, 2.90	1.4	1025.6	6296	1025.6	0.03	0.86
Yearrisk	Lag=10	0.4	-2.81, 3.65	1.7	985.8	5191	985.7	0.06	0.08
	Lag=20	2.9	-3.46, 9.17	3.2	950.7	3771	949.7	1.0	0.32
Agerisk, (6)	Lag=0	0.01	2.43, 2.43	1.2	1065.8	6298	1065.8	<0.00	0.99
Yearrisk, (7)	Lag=10	0.02	-2.80, 3.16	1.5	1025.9	5193	1025.9	0.01	0.91
LOF (8)	Lag=20	3.1	-3.39, 9.63	3.3	990.8	3773	989.8	1.1	0.29

Appendix 5: EXCESS RELATIVE RISK AT 1 SEIVERT EXPOSURE TO GAMMA RADIATION
BY LEVELS OF STRATIFICATION AND LAG INTERVAL (EIP)
SOLID CANCERS EXCLUDING LEUKEMIAS AND RESPIRATORY (n=232) (continued)

STRATA	EIP	ERR(1 SV)	ERR 95% CI	Std. Err.	Null Deviance	Null DF	Deviance	LR (1df)#	LR P-value
Agerisk,	Lag=0	0.53	(-2.4, 3.5)	1.5	1116.6	6247	1116.4	0.1	0.75
Yearrisk,	Lag=10	0.9	(-2.8, 4.6)	1.9	1072	5142	1071.7	0.2	0.6
DOE	Lag=20	7.16	(-2.4, 16.7)	4.9	1060.3	3723	1056.8	3.5	0.06
Agerisk,	Lag=0	0.13	(-2.3, 2.3)	1.2	1164	6305	1164	0.006	0.98
Yearrisk,	Lag=10	0.3	(-2.6, 3.2)	1.5	1119.4	5200	1119.3	0.03	0.85
Work	Lag=20	3.6	(-2.6, 9.9)	3.2	1107.7	3781	1106	1.7	0.19

* Excess relative risk of mortality increases (or decreases) with 1 Sv change in exposure.
Alternatively, the ERR increases (or decreases) by N percent with 1 mSv change in exposure, where N is ERR.
** Respiratory cancers are the following: hypopharynx (1), ill-defined lip (1), trachea, bronchus, lung(104), larynx (4), nasopharynx (1), esophagus (6).
# Likelihood ratio test (LR) compares the contribution of adding Sv to the stratified null model, by comparing the difference between the null deviance and deviance of the current model. The degrees of freedom for the test are computed as the difference in the number of free parameters in the current model and the number in the designated null model, i.e. 1 df.
(1) agerisk -- 7 levels, (<45, 45-49, 50-54, 55-59, 60-64, 65-74, 75+)
(2) yearrisk -- 4 levels, (1945-54, 1955-64, 1965-74,1975-84)
(3) length of follow-up (lof) (years) -- 6 levels (0-9, 10-19, 20-24, 25-29, 30-34, 35-41)
(4)duration of employment (doe) (years) -- (0-4, 5-9, 10-19, 20-29, 30-41)
(5) worker status -- 2 levels (0,1)

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Appendix 6: CUMULATIVE DOSE by Person-Years for One Individual Comparing Two Approaches: (1) No Induction Assumed and (2) Latency=0, Lag=20

Lag=0, Latency=0 Person-years=23

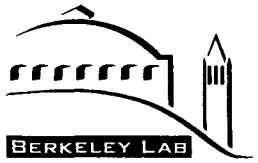
PYs	ID	STATUS	AGE	CUMDOSE
1	41075	alive	44	1 rem
2	41075	alive	45	1 rem
3	41075	alive	46	1 rem
4	41075	alive	47	1 rem
5	41075	alive	48	1 rem
6	41075	alive	49	1 rem
7	41075	alive	50	3 rem
8	41075	alive	51	5 rem
9	41075	alive	52	11 rem
10	41075	alive	53	19.4 rem
11	41075	alive	54	19.4 rem
12	41075	alive	55	19.4 rem
13	41075	alive	56	19.4 rem
14	41075	alive	57	19.4 rem
15	41075	alive	58	19.4 rem
16	41075	alive	59	19.4 rem
17	41075	alive	60	19.4 rem
18	41075	alive	61	19.4 rem
19	41075	alive	62	19.4 rem
20	41075	alive	63	19.4 rem
21	41075	alive	64	19.4 rem
22	41075	alive	65	19.4 rem
23	41075	death	66	19.4 rem

NOTE:
A worker's total exposure profile from date of hire until death.

Lag=20, Latency=0 Person-years=23

PYs	ID	STATUS	AGE	CUMDOSE
1	41075	alive	44	0 rem
2	41075	alive	45	0 rem
3	41075	alive	46	0 rem
4	41075	alive	47	0 rem
5	41075	alive	48	0 rem
6	41075	alive	49	0 rem
7	41075	alive	50	0 rem
8	41075	alive	51	0 rem
9	41075	alive	52	0 rem
10	41075	alive	53	0 rem
11	41075	alive	54	0 rem
12	41075	alive	55	0 rem
13	41075	alive	56	0 rem
14	41075	alive	57	0 rem
15	41075	alive	58	0 rem
16	41075	alive	59	0 rem
17	41075	alive	60	0 rem
18	41075	alive	61	0 rem
19	41075	alive	62	0 rem
20	41075	alive	63	0 rem
21	41075	alive	64	1 rem
22	41075	alive	65	1 rem
23	41075	death	66	1 rem

NOTE:
Cumulative dose is pushed forward by the number of years represented in the lag interval. The last 20 years of real-time exposures are omitted. Dose equals 1 rem over a working lifetime. The assumption here is that exposures in the interval immediately prior to disease are not relevant to an evaluation of dose-response.



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