STUDIES OF AURAL NONLINEARITY AND THE MECHANISMS OF AUDITORY FATIGUE PART II: EPIDEMIOLOGIC METHODS IN NOISE-INDUCED HEARING LOSS

(Reprint)

By
John Erdreich
Linda Erdreich

Department of Otorhinolaryngology
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

SENSORY RESEARCH DIVISION

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This report is a tutorial on epidemiological methods with specific references to potential application to studying noise-induced hearing loss.
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Reviewed:

KENT A. KIMBALL, PHD
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ROGER W. WILEY, O.D., PH.D.
LTC, MSC
Chairman, Scientific Review Committee

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STUDIES OF AURAL NONLINEARITY AND THE MECHANISMS OF AUDITORY FATIGUE

FINAL REPORT

PART II.
Epidemiologic Methods in Noise-Induced Hearing Loss

by

John Erdreich and Linda S. Erdreich

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Department of Otorhinolaryngology
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma 73190

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ABSTRACT

This report is a tutorial on epidemiological methods with specific references to potential application to studying noise-induced hearing loss.
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INTRODUCTION

To most people, epidemiology conjures up the image of medical sleuths scouring the countryside for the original source of an epidemic. This is accurate only in part. A more comprehensive picture of epidemiology is the description of the distribution and dynamics of disease in large populations. With the shift in major causes of death from infectious to chronic disease, the field has similarly shifted its emphasis. In seeking the cause of disease, epidemiologists examine individual risk factors as well as external or environmental agents. Developing rigorous methods for such description is a major activity of this discipline.

The past two decades have witnessed a growth in the number of scientists concerned with the distribution of noise induced hearing loss (NIHL) in industrial populations. Studies conducted by these scientists have incorporated some of the epidemiological principles which have evolved for studying other chronic diseases; however, many available methodological and analytical techniques have been overlooked.

Behind all of these is one goal — how to obtain appropriate data and what form of analysis is used to get accurate answers to questions with a minimum of expenditure? The general questions are:

1. What rates summarize the frequency of NIHL in a population? How does one obtain and utilize these different rates?

2. What risk measures are suitable for examining the degree of association between exposure and morbidity for making population predictions or for assessment of individual risk? How do prognostic factors affect this risk?

3. What are the sampling schemes which can be employed to measure risk? What are the advantages and disadvantages of each? What control groups can be used?

4. Can one identify factors contributing to the differences in susceptibility of groups or individuals to NIHL?

Through application of tools of epidemiology we may form a picture of the causes and/or risks of NIHL which is very different from those which we have seen in the past. The purpose of this paper is to review these epidemiologic strategies and, using data from well known studies, to show how they present additional information about noise-induced deafness.

RATES

Any quantitative approach to the study of a disease is based on counting cases. The counts yield a rate for a clearly defined population within a specified time frame. Three major factors which affect a rate are methods used to find
cases, the natural duration of a disease, and frequency of death and recovery. Furthermore, if any of these factors or biases vary among populations under study, the rates will not be comparable. Two different morbidity measures, incidence and prevalence, are used to assess the frequency of disease. They have distinctly different purposes in addition to limiting the above biases. After presenting these, we shall see how they apply to the study of noise induced hearing loss.

Incidence

Incidence is frequently used in both American and British papers on noise-induced hearing loss to mean the frequency or occurrence of hearing loss. This is inconsistent with its formal epidemiologic definition. Its misuse is similar to that of the word "significant" which in certain contexts may be misinterpreted as statistical significance. Newly diagnosed cases within a given time frame are the numerator and the population at risk at that time is the denominator. If all cases can be reliably identified, incidence overcomes the bias of variable duration. It is particularly useful for infectious diseases such as polio, which legally must be reported, or for heart attacks which result in hospitalization or death. By counting only new cases the rate is not biased upward by the inclusion of long-term or recurrent chronic disease, nor is it decreased by early death or quick recovery. For conditions which require neither reporting nor hospitalization, the rate can only be obtained by longitudinal studies. hearing loss falls into this category. The Fels study (28), which is longitudinal and is based on a defined population reevaluated at regular intervals, can yield specific incidence rates such as the incidence of a defined hearing loss in fifteen year old boys. Incidence data which is specific for exposure level and/or duration would be valuable. This measure could be obtained from records of a group or company which obtained regular audiograms from its workers. With the advent of mandated hearing conservation programs such records may exist.

Incidence data is not biased by the length of disease or the recovery rate. It is particularly valuable for etiologic study. For example, an increased incidence of hearing loss in men over women strengthens the etiological association with sex. On the other hand, the increased prevalence of hearing loss in men could be either prior exposure or increased risk.

Public health planning usually requires an estimate of the number of cases which exist in a population. This is obtainable from prevalence rates. The differences in these morbidity rates is mainly in the definition of who is counted:

\[
\text{Incidence} = \frac{\text{number of newly diagnosed cases in the time period}}{\text{population at risk at that time}}.
\]

\[
\text{Prevalence} = \frac{\text{number of existing cases (old and new) within the time period}}{\text{population at risk at that time}}.
\]
Prevalence

Prevalence defines the total cases (old and new) that exists in a defined population for a given point or period in time. Prevalence estimates, as incidence estimates, may be age, race, or exposure specific. Walden's (36) prevalence study gives estimates for H-3 Hearing Profiles for U.S. Army servicemen, specific for time-in-service categories. Baughn's data, (1) after smoothing, result in prevalence estimates specific for exposure level and duration, for example, 13 cases per 100 in people exposed to 90 dB for ten years. Several points related specifically to prevalence of hearing loss as obtained from studies similar to Baughn's are important here. First, age-specific or duration-specific prevalence of hearing loss reflects to some extent the accumulation of cases. Since there is neither recovery nor death from hearing loss, it is less biased than prevalence measures for other chronic diseases such as heart disease or diabetes. Comparison of duration-specific prevalence rates (eg., hearing loss at 5 and 10 years) is biased because the population at risk (the denominator) changes. The most suitable approach to this comparison is the life table and survival data analysis which we will discuss later.

Actually, cross-sectional, time-specific prevalence estimates can give a reasonable measure of the changing frequency over time. For example, Taylor's jute-weaver study (35) shows the often quoted increased hazard at ten to fifteen years exposure. Ideally, incidence rates would be the best measure to show this phenomenon; prevalence estimates reveal it because cases of hearing loss do not recover and do not die. This is crucial for the use to which we will put prevalence rates. Caution is necessary because the denominator population in an industrial study is not constant over time. Bias is introduced particularly if workers leave differentially due to the condition of their hearing. In a well designed and so designated prevalence study such as Walden's, the unknown factor is the loss of population after two to four years of service.

Prevalence is considered to be a function of incidence weighted by the average duration of the disease, generally expressed \( P = I \times D \). Estimates of prevalence are preferred over those of incidence for any situation where the number of existing cases is necessary for planning. Hospital beds, hearing aid services, or compensation costs are examples. These two themes, the etiologic approach of identifying and measuring the strength of risk factors, and the public health approach of measuring or predicting the impact upon the population, require different strategies for quantifying risk.

MEASURES OF RISK

Measures of risk are those statistics which measure the degree of association between an exposure and an outcome. Generally, the rate is interpreted as a conditional probability which reflects the risk under the circumstances described. Risk measures for dichotomous outcome are often based on prevalence or incidence rates and are subject to the same strengths and biases. After reviewing those measures presently used by researchers in noise-induced hearing loss, we will introduce two standard epidemiologic risk measures — attributable risk and relative risk. We will then suggest variations of these statistics which are appropriate to the problems in noise-induced hearing loss.
The last section presents statistical methods for multivariate analysis which relate the conditional probability of disease to discrete or continuous independent variables.

**Percent Risk**

The measure commonly used, percent risk or percent difference, is the difference between the percent of the exposed population with a defined hearing loss and the percent of a reference non-exposed population with that same loss. The choice of reference population has been either the non-exposed in that industrial group, or, some set of presbyacusis data. Percent risk is used in reports by Baughn (1), Burns and Robinson (26, 27), and NIOSH (24). This is the only risk measure for dichotomous outcome seen in the noise induced hearing loss literature. This statistic is the difference between two prevalence rates. The excess prevalence in the exposed compared to the non-exposed is attributed to the noise exposure. Although it is subject to the biases inherent in prevalence rates, it is not altered by death or recovery and it is the only available estimate. Other assumptions are necessary for accepting the validity of this measure: 1) for noise induced hearing loss, prevalence estimates are subject to an acceptably low level of bias due to selective loss of the population, 2) exposures are accurate and 3) the reference population is an appropriate control group. This latter requires more discussion and will be covered in more detail below. Percent risk is a functional statistic because it predicts the cumulative impact of the exposure on the population at a defined endpoint.

**Attributable Risk**

A standard epidemiologic measure similar to percent risk is derived by subtracting the incidence in the non-exposed population from the incidence in the exposed population. This statistic, attributable risk, reflects the amount of disease attributable to the specified exposure and is appropriate for establishing policies and strategies for reducing disease (20, 22). Normally, attributable risk must be calculated from incidence rates. It conveys the extent of the risk in numbers of cases, but it is dependent on background frequency so its weak-point is that it is not comparable among studies. The variation in percent risk with background frequency can be seen in the hypothetical example in Table 1. In each case the percent risk is different. Does this mean that the workers in group 1 (30 percent risk) are at greater risk for hearing loss than those in group 3 (7.5 percent risk)? The percent risk lets us answer the question of the percent of the population who will develop the disease. The strong point of percent risk is that it retains the level of the rates. This is important in order to plan to protect the population of workers or to estimate compensable cases. But what are the odds that an exposed worker will suffer a hearing loss? To answer these questions we must look at relative numbers of cases of NIHL in the exposed and non-exposed workers.
Relative Risk

When the goal is to identify an etiological factor, the desired measure is relative risk — the ratio of the incidence of disease or condition in the exposed to the incidence of disease in the non-exposed. In probability notation, relative risk is the ratio of the probability of disease (D) given the factor A to the probability of disease given the absence of A, (A)

\[
\text{Relative Risk} = \frac{P(D|A)}{P(D|\neg A)}
\]

Incidence is the preferable rate to use to estimate probability, because, as explained above, prevalence of most chronic disease is too distorted for etiologic purposes, for example, survivors may be favored. Because of the nature of hearing loss and the public health aspect of the problem, we believe the ratio of prevalence rates obtainable from available data is an acceptable measure to assess the probability of having rather than getting the defined outcome, given certain conditions. Table 1 shows this rate ratio.

The rate ratios may also be compared over several exposure levels. In the example in Table 2, 30 decibels at the same exposure duration gives the baseline cases in the non-exposed. Table 2 indicates what we know to be the case, that lower exposures for a longer time will have an effect in the population in terms of numbers of cases similar to that of high exposures for a shorter time. When using percent risk, the effects appear to be identical. In numbers of workers per hundred this is so. However, a look at the baseline prevalence shows that, when compared to eighty decibels exposure, a greater proportion of the younger cases of hearing loss have the condition due to noise exposure. Over 90% of the 32% in the 10-year group can be attributed to industrial noise exposure, where only half of the 62% in the 40-year group can be attributed to the exposure. The prevalence rate ratio, given our assumptions, conveys different information than the percent risk. The odds of a worker having hearing loss in the first case are greater than ten to one, whereas in the forty-year, ninety-five decibel case, the odds are about two to one.

In order to show the characteristics and use of the rate ratio, Table 3 uses data from the 1972 NIOSH study (24). Compare first the two different hearing level indices and 85 dB exposure. The percent difference at any age level is greater for the 1, 2, 3 kHz definition by a factor of 2 or more than that for the 0.5, 1, 2 kHz definition. The rate ratios at each level are almost identical, decreasing slightly with advancing age in each case. We interpret this to mean that 85 dB noise has the same etiologic effect on both definitions of hearing loss. Exposure to 85 dB doubles the odds of sustaining hearing loss. Impact on the population is greater at higher ages because of the varying background rate. In order to present the true picture of risk for each age group, rate ratios must be considered in addition to percent risk.

Odds Ratio

One common study design is to select cases and controls as subjects, and then assess each group for exposure to the suspected etiologic factor. The relative risk measure cannot be obtained because the total number with disease is
fixed by the method of selection. Important assumptions are, 1) that cases and controls are a representative sample of the cases and non-cases in the population of interest and, 2) the number of cases of disease in the population is small compared to the number without disease.

An appropriate statistic to measure risk is the estimated odds ratio (9) defined as,

odds ratio = \frac{odds for exposure factor given hearing loss}{odds for exposure factor given no hearing loss} = \frac{P(A | D)/P(A | D')}{P(A | D)/P(A | D')}

= \frac{P(A | D)P(A | D')}{P(A | D)P(A | D')}

This is also called the cross-product ratio because it can be derived from a four-cell table (two exposure groups and two outcome groups) by multiplying the diagonals. It approximates relative risk.

The chi-square test for four-fold tables can be used to test whether the difference in the frequencies is due to chance alone.

Choosing a Risk Measure for Binary Outcome

Both the method of measuring the frequency of disease and the type of risk measure must be considered when using these estimates as decision guidelines. The risk measure should be structured to suit the goal of the study.

Percent risk gives the number of cases expected in a population given the specified conditions. It can be interpreted as the risk attributable to exposure. An increase in this statistic often reflects an increase in background risk, and the choice of reference group is crucial. This measure is most accurate when obtained as the difference between two incidence rates.

We have suggested that the ratio of the prevalence rates be used as a risk index for noise-induced hearing loss provided the indicated assumptions are met. The prevalence ratio describes an important relationship between outcome and exposure, so we believe that it or, ideally, relative risk obtained from incidence rates, should be considered in setting damage risk criteria. Incidence data and relative risks are needed to study the basic mechanism of the effect and to accurately indicate dose-response relationships. Table 4 gives an illustration of the different kinds of information presented by relative risk and attributable risk. The question is the effect of smoking on death rates for lung cancer and coronary artery disease. (Mortality rates are not subject to the biases of prevalence rates so they can be used to form the risk measures). If we look at the attributable risk, more coronary artery disease deaths per 100,000 are attributed to smoking than to lung cancer. This is due to the high rate of coronary artery disease in the population. The relative risk on the other hand shows the lung cancer rate to be multiplied more than 10 times in the smokers while coronary artery disease is not quite doubled.
The high relative risk can be ascribed to the etiology of lung cancer. Alternatively stated, smokers have a 10.8 times greater risk of lung cancer than non-smokers because smoking is an important causal agent for the disease. Smoking is not the major cause of coronary artery disease although it doubles the risk. However, the high background rate makes this increase of great public health significance.

The derivation, characteristics, and applications of various risk measures are summarized in Table 5. This table lists another way of obtaining an odds ratio: a multivariable method called logistic regression.

Logistic Regression and the Probability of Disease

Frequently several different independent variables are considered as risk factors for a disease or condition. For example, one may wish to determine the risk for some defined exposure level, exposure duration, age, or sex; or an investigator may wish to explore the possibility that a certain factor such as smoking, hypertension, or eye color, increases the risk for hearing loss given a defined exposure. Individual comparisons for several factors at several levels are tedious and do not describe the simultaneous effect of the variables. A multivariate method is needed to describe the risk of the outcome.

Logistic regression is a probability model which relates the independent variables to the natural logarithm of the odds for the disease. Probability of outcome, say, hearing loss, can be calculated for the simultaneous effect of a set of suspected risk factors (19). This model is suitable for studies of NIHL because it is distribution-free. Dichotomous, categorical, or continuous variables can be included. Those variables which show a significant relationship to the outcome under univariate analysis are included in the regression.

One of the first epidemiologic applications of the model was in the Framingham study of coronary heart disease relating risk factors such as age, blood pressure, serum cholesterol, and cigarette consumption to heart disease. The method is based on the fact that the logarithm of the ratio of the probability of the event, \( P_i \), to the probability of it not occurring, \( 1 - P_i \), is a simple linear function of the individual values of the independent variables \( X_{ij} \) (19). The log of this odds ratio is called the logistic transform of \( P_i \) for \( n \) individuals and \( p \) independent variables. The linear logistic model is

\[
\log_e \frac{P_i}{1-P_i} = \sum_{j=1}^{p} b_j X_{ij}
\]

It is analogous to the regression model for normally distributed data. The fitted equation can then be used to compute probabilities, or odds, for various combinations of risk factors or, as with multiple regression, for different groups by sex or type of exposure, or level of hearing loss. Odds ratio can also be
obtained by comparing the computed odds for two sets of variables such as different exposure levels. Transformations or interaction terms may also be included.

The analysis for matched case control studies is also developed for outcomes with more than 2 categories, or for subgroups (3, 13). One published example using an adaptation of Cox's model in the area of noise-induced hearing loss shows separate analyses for the effect of age and the effect of exposure (29). After characterizing an individual by noise exposure, age, and sex they calculate the probability that an individual will fall into one of the hearing loss categories.

**Estimates of NIPTS as Risk Statistics**

Each of the risk statistics discussed heretofore requires both definition of an exposed and non-exposed (control) population and definition of a dichotomous outcome for "hearing loss." Forcing a cutoff for the definition of hearing loss does not cause particular problems when studying etiology but may be problematic if the results are to be used for setting standards of acceptable noise exposure.

Robinson's (26) approach to assessing risk obviates the problem of non-continuous hearing loss estimates. Based on measurements in an otologically controlled, non-pathological population, Robinson derived an empirical method for predicting the hearing level of a percentage of the exposed population. Robinson's method corrects for age (which is assumed proportional to duration of exposure) and for exposure level. Robinson's estimated hearing loss is not, however, a risk measure. The measure of risk is the difference between the percentage of the exposed population with a particular loss and the percentage of the control population with the same loss. As such, the only major difference between Robinson's noise risk estimates and percent risk as used by Baughn and others is that Robinson's estimate is based on continuous distributions of age, noise, and hearing loss. Johnson (16) uses this measure in preparing tables to summarize the effects of noise exposure on hearing threshold levels of a population.

We must emphasize that because the Burns and Robinson data is derived from a geographically specific population, extension of the predictions to other groups must be viewed with caution. After dealing extensively with data from many studies and various populations, Johnson (16) concludes that "the better the two groups are matched, the better the NIPTS data".

**SELECTION OF CONTROL POPULATIONS: INTERNAL OR REPRESENTATIVE?**

The usefulness of any of the risk measures we have discussed is critically dependent on the profile of the population selected to serve as the "non-exposed" reference. Two approaches may be taken in selecting the reference population: either take a random sample of the entire population designed to be representative of those exposed to noise or select individuals as controls who are
similar to the study group with respect to the factors which may be related to
NIHL. Choosing the first alternative, representativity, may seem a logical
choice, especially to those of who are trained to randomize all conditions to
avoid bias. However, in this context it most likely leads to serious biases itself
because the exposed population is not similarly randomized (15).

A basic approach to many epidemiologic studies is to describe variations in
the occurrence of disease as a function of geography, or of time, or of personal
factors such as age, race, or sex. Variation in rates for groups so defined often
provide important clues to etiology. Cancer rates are, for example, examined by
sex, race, and even by state to yield clues to causes of disease. Studies by Coso,
Royster et al, Robinson show variations in hearing loss when populations vary in personal factors. Kryter, Guignard, and Johnson discuss this in their reviews. Rosen's work suggests that risk factors for coronary heart disease, which vary geographically, may account for some population differences in hearing loss. Selecting an external control population (i.e., one from a population different from the exposed) can result in erroneous risk measures and, therefore, in misinterpretation of the etiology of disease. When determining a risk measure, the control population must be comparable to the exposed study population, not to the potential exposed population.

Baughn argues that for data to be meaningful, they must be
representative of the population-at-large. On this basis, he did not eliminate
those workers who suffered from or had a history of auditory pathology from his
data base.

Choosing an internally consistent population, however, reduces variability.
Burns and Robinson report that they screened each of their subjects and,
if the response was positive for pathology, the worker was eliminated from the
study. Not surprisingly, the British ears of Burns and Robinson generally have
lower thresholds than the ears in the studies which do not select to minimize
these confounding variables. The effect that this screening has on the measured
distribution of NIHL is not known. However, we can illustrate the effect of
selection of the reference population by looking at a study of lung cancer of the
steel workers of Allegheny County, Pennsylvania.

Morbidity studies of these workers included consideration of increased
cancer rates. If the interest is in cancer rates in these workers, it is logical to
compare them to workers of similar age, sex, and socio-economic status
elsewhere in the United States. Redmond and Breslin compare mortality in
Allegheny County steel workers to the rate in the entire United States population
and show that the steel workers have a statistically significant higher lung cancer
mortality than does the general population. Does this mean that the steel worker
is at greater risk than his non-steel worker neighbor? This analysis cannot answer
that question.

When the analysis is repeated using only the population of Allegheny County
as the reference, Redmond and Breslin showed that the steel worker is at no
greater risk for lung cancer than his neighbors. The excess cancer rate obtained
in the first comparison then cannot be attributed to working in the steel mill. It
is clear that the choice of a control group is critical to the derivation of risk measures. When factors which increase or decrease rates can be identified, they can be controlled by matching, stratification, or by screening (8, 13, 19). When these risk factors cannot be identified or measured, a reasonable solution to the problem is to aim for a similar distribution in the two groups by the selection of internal controls: workers similar to the study group in every respect except the exposure factor (7).

Epidemiologic experience supports the idea that a control group must be selected and screened in a manner similar to that of the experimental group and must be from the same geographic area and the same era. For NIHL studies inter- or intra-industry controls are suggested due to the lack of identification of risk factors for NIHL and the selection for health for working populations. This selection is believed to be higher for long-term chronic conditions (7, 22) than short-term, quickly fatal diseases. With appropriate attention to selection of control populations, we can approach other problems such as identification of risk factors for NIHL. It is our contention that epidemiologic methods are available which would facilitate identification of suspected individual risk factors for noise-induced hearing loss. Another reason to identify the individual who is more susceptible to noise-induced hearing loss is that these risk factors could be used to increase the efficiency of study design. The inter-individual variability often noted (e.g., 4, 5, 30, 31, 32) could be reduced by stratification and other control methods. It would be equally useful to identify risk factors which explain hearing loss in non-exposed populations, that is, to study the risk factors for presbyacusis as several researchers have already suggested (6, 11, 12). Animal studies provide some plausible direction. For example, Borg's (2) study in rats suggests hypertension as a risk factor.

Our goal in the next section is to introduce various sampling schemes, analytic methods, and guidelines for sample size determination for future epidemiologic studies. We will introduce methods to handle the variable of survival time — time from beginning exposure to first hearing loss — which we believe is an important consideration in comparing the effect of various levels of exposures or effect of individual risk factors.

SAMPLING SCHEMES AND OTHER FACTORS IN STUDY DESIGN

This section will discuss the three basic sampling schemes used in human population studies: cross-sectional, case-control, and cohort. We will show how each of these is designed and analyzed and will summarize the advantages and disadvantages of each. The overall goal in selecting an approach is to acquire the necessary information in a manner least costly in time, money, and resources. For each scheme we present the information necessary to make this decision: method of sample size calculations, appropriate analytic techniques, and types of risk measures and other statistics which may be obtained.
Cross-Sectional Study

In the cross-sectional approach, a population such as workers in an industry or admission to a hospital is defined first. Each individual is then categorized on both the disease factor and the exposure factor. For simplicity consider binary outcome which yields a four-cell table (consisting of all combinations of disease and exposure), although in fact several levels may be considered. Since the population is defined first, a case of the condition may be either newly diagnosed or existing; thus, this approach yields prevalence data. It is often called a prevalence study, and often determination of that rate is its major purpose. Baughn's study (1) is an example since he first identified his study population as those in the industry with audiograms. Results can be presented either as the proportion of cases with the exposure factor or the proportion of those exposed who have the disease. For either approach, data may be stratified for any specific risk factor such as age, race, or sex. A chi-square test of association may be performed. This is a test of whether the relative risk is significantly different from one at a specified alpha level. The statistical power and precision of the chi-square is the weakest for this of the three sampling schemes (9). The bias of using prevalence rather than incidence data can, in some instances, be overcome by stratification on duration, or by multivariate methods such as the logistic which can incorporate the time parameter.

For continuous data such as decibel level, multiple regression methods are suitable but again, all biases for prevalence data apply.

Case-Control Studies

Another sampling approach involves selection of cases and of suitable controls. Cases and controls are then classified on the presence or absence or level of the exposure factor, such as noise or cigarette smoking. Selection is based on the existence of the condition, and exposure to the risk factor is assessed for the time prior to the development of the disease. Thus, this design has been referred to as a retrospective. The major drawbacks are selective recall and temporal bias. For example, recall of diet or trauma to the head in the past is less certain than a documented work history. Temporal bias is the greatest potential disadvantage of the retrospective study.

One must exercise care in designating a study "retrospective" since some sampling schemes look back in time but are not case-control studies. Selecting noise-exposed individuals prior to evaluating thresholds is not a retrospective design. A retrospective study would identify cases of hearing loss and a suitable reference population prior to evaluating exposure.

Although the case control study is a classical, efficient, and frequently used approach (13, 20, 21, 22) it has been attacked for its biases (8). However, responders to this criticism have emphasized that it is not the technique itself but its misuse which is the problem. A comprehensive review of this controversy can be found in the Journal of Chronic Disease (14). Case control studies are especially useful for rare diseases since only this approach yields sufficient cases for analysis. They are substantially less expensive and time consuming than cohort studies because existing records can be used and little follow-up is
involved. They are often used to find leads and associations which may provide the basis for larger, more definitive studies of cause and effect. An example is the question of the association between noise-induced hearing loss and hypertension. If case control studies show no association between noise-induced hearing loss and hypertension then long-term studies are not needed.

A well designed case-control study can give an estimate of the relative risk (the odds ratio) and can provide more power and precision for the test of this association than either the cross-sectional or the cohort study (9). Furthermore, the effect can usually be obtained with smaller sample size that is needed for longitudinal studies. Tables are available for determining the least significant relative risk obtainable with a sample of predetermined size (37).

The Cohort Study and Survival Data Analysis

Cohort studies follow a group or cohort over time, counting cases of the outcome of interest which have developed by the endpoint. This type of study is also referred to as longitudinal, incidence, follow-up, or prospective. This approach is usually defined by a sampling scheme in which subjects are selected on the basis of exposure to the etiologic factor of interest. The groups of exposed and non-exposed are followed or traced and categorized for presence or absence of the disease.

Cohort studies can also be non-concurrent if the period of observation starts in the past, but individuals are first identified by the exposure factor. The availability of records is important in this approach and, typically, special groups such as industrial populations are studied. Many studies of noise-induced hearing loss are of this type, for example, Taylor (35) selected jute-weavers for various exposure groups, and school teachers and office workers to form the non-exposed. It is difficult to get incidence data for chronic conditions from this approach because the onset of the condition cannot be pinpointed in time. The Fels study of hearing in children (28) is a concurrent cohort study which will yield incidence rates as new cases of hearing loss are identified. Since neither exposure nor presence of disease were criteria for inclusion at any point in time, it may be analyzed either way as appropriate for a cross-sectional study. A summary of the main types of study design is given in Table 6.

A potential bias in cohort studies is loss to follow-up. All cases in the original cohort of exposed and non-exposed should be accounted for whether or not they have developed the condition or are lost to follow-up. Another problem in this type of study is censoring; that is, when the observation time varies among subjects at the end of the study or cannot be determined because they have been lost to follow-up. Although standard univariate and multivariate statistical methods are appropriate for cohort studies the problems of loss to follow-up, withdrawal, and censoring constitute a source of bias. A complication of longitudinal studies is that at the end of the study subjects have been observed for different lengths of time because of loss to follow-up, withdrawal, or termination of the study before the event occurs to all. Also, in some circumstances it is more efficient for subjects to enter observation at different times.
One method to compute rates in longitudinal studies is to use person-years of observation as the denominator. Thus, 5 people observed for 10 years constitute 50 person-years. The number to whom the event occurred is the numerator. The disadvantage of this method is that it assumes constant risk over the time period of observation. This would make this method more acceptable for short-term rather than long-term studies. The statistical method which is best suited to handle these problems in cohort studies is the clinical life table (19, 22).

The familiar population life table uses terms such as alive or dead. The life table is a technique for survival data analysis in which time to event is the important parameter. The familiar population life table uses public health statistics such as age-specific mortality rates for a population, whereas the clinical trial model accepts subjects at different times in order to increase the sample size for rare occurrences. This results in two types of censoring. Singly censored data is obtained when all subjects begin at the same time, are followed for the same amount of time, but are lost to follow-up or "alive" (without the event) at the end of the study. Progressive censoring occurs when subjects enter at different times. At termination of the study follow-up times vary.

The ability of the life table method to handle censoring means that the investigator can use information on subjects up to the point at which they are lost or withdrawn, and can account for those who survive at term of study.

A requirement for applying a life table is that each acceptable subject has a well defined starting point that can be determined objectively such as date of employment. The frequency of follow-up must be carefully specified to determine the intervals in the table. It is also assumed that, within the time-frame of the study, the event is independent of calendar time. The end-point must be clearly defined and dichotomous.

It is obvious that the method is well suited to studies of noise-induced hearing loss, yet it has not been used. Any definition of hearing loss or threshold increment would serve as the outcome. The structure of the life table is shown in Table 7. The life table method, often called survival data analysis, is based on estimating mortality rates for each time interval. It yields the following three major functions where \( t \) is the interval \( t_{i-1} < t < t_i, i = 1, 2, \ldots, n \).

1. Survivorship function: the cumulative survivor rate at time \( t \), a usual life table estimate, \( S(t) \). It is the probability that an individual survives longer than time "\( t \)" and can be plotted as a survival curve.

2. Probability density function: probability, \( f(t) \), of dying in a specified interval per unit width.

3. Hazard function or conditional failure rate: the probability of failure in the interval given that the individual has survived to that interval, \( h(t) \).

The only information needed for survival data analysis is, for each interval, the number to whom the event occurred, the number withdrawn, the loss to follow-up and the number without the event. All the other information can be calculated from this.
The usual adjustment for those who are lost or withdrawn alive during an interval is to credit each with half the length of the interval. Assuming uniform distribution of the losses throughout the interval the number exposed to risk during the $i + h$ interval $n_i$ is

$$n_i = n_i - \frac{1}{2} (l_i + w_i)$$

where $n_i$ is the number who enter the interval, $l_i$ the number lost to follow-up and $w_i$ the number withdrawn.

Standard errors can be obtained for each of these functions so that significance tests can be performed or confidence limits obtained. This means that we can compare estimates in two intervals of the life table, or between the same time interval for two different life tables (usually two treatments or exposures or different groups with same exposure).

While the life table is especially useful for large numbers, hence the grouping of the data, another method is available for small samples. The Kaplan-Meier Product-Limit estimate of the cumulative proportion surviving is obtained by ordering the observations. For details see Gross and Clark (10) or Lee (19).

It is often helpful to draw graphs for each of these functions. The resulting curves can be used to find the 50th percentile, or median, and to compare survival data from two or more groups. From these the peak interval of risk or the points of decreasing hazard can be identified.

Basic life table methods can be found in a basic biostatistics texts. More advanced methods of modelling and testing can be found in books devoted to these techniques (10, 19). Some examples of the potential use of survival data analysis in studies of NIHL are to compare the survival time (time to hearing loss) for two groups such as 85 vs 95 decibel exposure, comparing groups using two different hearing protectors or comparing different levels of impulse noise exposure. Groups with similar exposures but different individual risk factors could be compared to identify prognostic factors.

We believe that methods used in survival data analysis provide an ideal approach to the study of noise-induced hearing loss. The data is less biased than prevalence data and the probability density function can be considered a very specific incidence rate. Problems such as time to event, loss to follow-up and censoring which complicate analysis, are handled by this method. This approach could be used to identify prognostic factors and this information will increase the precision of further survival studies. Methods exist for identifying and incorporating prognostic factors into the analysis (19). Packaged programs such as BMDP incorporate several of the techniques.

**SAMPLE SIZE REQUIREMENTS**

In order to determine sample size for either cohort or case control study, the desired level of type I or type II errors (alpha and beta errors) must be specified. The minimum difference worth detecting in terms of the relative risk

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must also be specified. Sample size requirements for these two different sampling schemes will vary due to the different factors which enter into the calculations for each approach (33).

To ascertain sample size for cohort studies, the necessary information is the incidence of disease among the non-exposed. This is to insure that adequate numbers of cases will be included to reach the required statistical significance level. It follows then that more rare diseases require larger sample sizes. Case-control studies select on outcome and then ascertain exposure so the required information is the proportion of the study population which was exposed to the factor of interest.

The accumulative experience in studies of noise-induced hearing loss provides excellent data to make these estimates from available tables (9, 33, 37). The type I and type II errors can be selected to suit the seriousness of the outcome and the cost of prevention. For questions with political or legal implications, relative risk estimate inevitability will involve value judgements. This approach does, however, enable investigators and agencies to specify goals and tailor a study to meet them. An equal number of subjects in each group is efficient, but if costs of each differ, guidelines exist to select unequal sample sizes to increase power for a fixed total cost (23).

It is possible that the study of the factors which make individuals vary in their susceptibility to noise damage may involve more difficulties in finding subjects who meet both the exposure criteria and possess another risk factor, such as smoking or high cholesterol. In occupational settings the temporal biases may be reduced if company records are available and work history is documented. Since non-concurrent prospective studies may involve some of the same biases as case-control studies, it behooves us to look at the case-control design for economy. Preliminary examination of sample size needs could determine in advance what study design goals are efficient and feasible.

We could hypothesize, for example, that high serum cholesterol is a risk factor to noise-induced hearing loss and decide to limit our study to ten to fifteen years of exposure. To test this hypothesis we need an established population of individuals who have been exposed to a measurable common noise level for ten to fifteen years. The risk factor or exposure under study is high cholesterol. For cohort design, we would select from this pool of noise exposed those with and without high cholesterol and then categorize them with respect to the outcome, hearing loss.

Let us assume a type I error of .05, and a type II error of .10 (90% power) is acceptable. A reasonable estimate of the background frequency for 15 decibel loss is 4% (1, 24). Table 8 shows sample size requirements for each group of the cohort study; that is, the total sample size is obtained by doubling the table entries (33). For a case-control design we would select from the same pool cases of hearing loss and controls with no hearing loss. The sample size is determined by the prevalence of the exposure or risk factor of interest, high cholesterol, which we estimate from other published studies to be about 10% or 15% depending on age (17). Table 8 shows sample sizes for various circumstances by using these
estimates with Schlesselman's tables (33). Values for an exposure prevalence of 30% as for cigarette smoking are also given in Table 8. The case-control study requires considerably fewer subjects than the cohort study. Several adjustments can be made to reduce this number even further: (1) increase the type II error to reduce the possibility of detecting small unimportant differences, (2) look at a population with a higher rate of the exposure prevalence, for example, older workers with a greater rate of high cholesterol, (3) raise the relative risk level considered important. An important alternative which could be very fruitful for etiological questions is to take these subjects and use logistic regression, which does not have astringent requirements for sample size and which could incorporate various exposure levels as a variable.

Rather than detect a difference in the proportion of the population with the outcome as relative risk does, an alternative goal could be to detect a certain percent difference or percent risk for a given population, \( P_2 - P_1 \). While this is not comparable among studies, it would be appropriate for a specified group. Suppose, for example, that we want to verify that a 10% difference in hearing loss exists between men and women. To determine the necessary sample size from tables for absolute differences, the proportions in the two groups need to be hypothesized as well as the two errors (9). For a 10% increase over a background rate of 5% \( P_2 - P_1 = .10 \) we find that the required size of group 1 is 125. To test a 15% increase the sample size needed is 125.

It is possible to convert between the proportions and the odds ratio if only one of these is available. For example, to reproduce a study under circumstances with different background rates \( P_1 \) one can simply find \( P_2 \) for the given odds ratio regardless of whether the research design is case-control or cohort.

**EPILOGUE: CAN WE USE THE DATA?**

We speak of identifying the risk factors of noise-induced hearing loss without really considering how this information will be used. Gathering information for its own sake is an activity which, in these times, is becoming an undertaking few are willing to support. The use of data such as we have discussed as a basis for noise standards and legislation is recognized and we need not dwell on it here except to reiterate that homogeneity of the experimental units, the people, is as important for reducing variability and increasing precision as is homogeneity of the noise exposure. One way of obtaining homogeneity is to incorporate the risk factors in the analysis. In certain situations one can assume that the risk factors are randomized. The other alternative to overcoming the problem of individual differences is to randomize the subjects to the exposure — an unfeasible approach. However, another question of far-reaching consequence must be addressed if we are to consider the identification of risk factors for NIHL. The question, simply, is, how can the information be applied to protect both the worker and his employer?

We believe that it is feasible to identify these risk factors and to ultimately develop a profile of susceptibility to NIHL. The causes of NIHL are fairly well documented and the cost of reducing this noise has also been estimated.
The questions which must be asked are:

On whom is the burden of prevention to fall? Shall the employer be held totally responsible for the welfare of the worker or can all or some of the burden be placed on the employee?

By what methods may prevention of NHL be accomplished? Is noise reduction the ultimate and only acceptable solution? If we can identify the hypersensitive employee may we exclude this person from a noisy occupation?

The answer to the first question, we believe, is fairly well accepted. The burden of prevention is primarily on the employer. The OSHA Act of 1973 mandates workplace safety standards which provide some degree of protection for the worker. Additionally, the Act provides formal mechanisms by which the employee may seek investigation and correction of perceived safety hazards. In general, a worker must endure the hazard and file a grievance to insure that he suffers no reprisals for leaving the work place.

If this seems to put the worker in an untenable position, the employer is placed in an equally awkward position.

If the worker is exposed to hazardous conditions even though they are within acceptable limits and the employer can identify the worker as a susceptible individual, then the employer may be liable for injuries sustained by the employee. On the other hand, if the employer, after identifying the susceptible worker, then reassigns the person to some other job, he may be liable for damages as a consequence of discrimination against the "handicapped" (34).

There are several solutions to this dilemma:

1. We can abandon all attempts to identify risk factors for occupational disease and thereby remain complacent.

2. We can identify risk factors and conservatively exclude hypersensitive workers from jobs which entail noise exposure. With this approach, we effectively place the burden of solutions to the problem on the courts. Eventually, there will emerge from the morass of litigation a practice which dictates the procedure to be employed.

3. Perhaps the most acceptable solution is one which involves both the worker and the employer in reducing occupational hazards. As a model, the 1974 agreement between U.S. Steel and the United Steel Workers provides for pay incentives to workers who help reduce toxic emissions.

The political climate is beginning to change to favor positive solutions to problems such as this. Issues of environment are coming to be viewed not simply
in terms of production vs protection nor jobs vs safety but in terms of the need to plan for and anticipate the consequences of our decisions. If we, the scientific community are able to present our work in this considered framework we will be better able to educate both labor and management to the meaning of our work and to the consequences of their decisions. In this way, we will be able to gain acceptance of what we do and see it reach its full impact.
REFERENCES


ACKNOWLEDGEMENTS

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Table 1

Effect of Background Frequency of Disease On Summary Statistics

<table>
<thead>
<tr>
<th>Prevalence in Exposed</th>
<th>Prevalence in Non-Exposed</th>
<th>Percent Risk</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>30</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>15</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>7.5</td>
<td>7.5</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

These hypothetical data show that percent risk varies with the background frequency, whereas the ratio of the rates is the same.
Table 2
Summary Statistics for Various Exposure Levels and Duration

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Prevalence in exposed</th>
<th>Prevalence in non-exposed</th>
<th>Percent Risk</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 dB$_A$, 10 Years</td>
<td>32</td>
<td>3</td>
<td>29</td>
<td>10.7</td>
</tr>
<tr>
<td>95 dB$_A$, 40 Years</td>
<td>62</td>
<td>33</td>
<td>29</td>
<td>1.9</td>
</tr>
</tbody>
</table>

The source of the data is Baughn (1). The percent risks are the same, but the rate ratios are quite different.
Table 3
RELATIONSHIP OF HEARING IMPAIRMENT TO AGE AND NOISE EXPOSURE*

A. Hearing Level Index = 0.5, 1, 2 KHz

<table>
<thead>
<tr>
<th>Age</th>
<th>Percent Impaired</th>
<th>Percent Difference</th>
<th>Rate Ratio</th>
<th>Percent Impaired</th>
<th>Percent Difference</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-35</td>
<td>6.8</td>
<td>3.5</td>
<td>2.1</td>
<td>11.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36-45</td>
<td>9.7</td>
<td>4.7</td>
<td>1.9</td>
<td>15.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46-54</td>
<td>16.6</td>
<td>7.2</td>
<td>1.8</td>
<td>24.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-70</td>
<td>31.0</td>
<td>11.0</td>
<td>1.6</td>
<td>41.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Hearing Level Index = 1, 2, 3 KHz

<table>
<thead>
<tr>
<th>Age</th>
<th>Percent Impaired</th>
<th>Percent Difference</th>
<th>Rate Ratio</th>
<th>Percent Impaired</th>
<th>Percent Difference</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-35</td>
<td>17.6</td>
<td>9.7</td>
<td>2.2</td>
<td>29.7</td>
<td>21.8</td>
<td>3.8</td>
</tr>
<tr>
<td>36-45</td>
<td>19.2</td>
<td>10.4</td>
<td>2.2</td>
<td>31.9</td>
<td>23.1</td>
<td>3.6</td>
</tr>
<tr>
<td>46-54</td>
<td>32.9</td>
<td>15.1</td>
<td>1.8</td>
<td>48.3</td>
<td>30.5</td>
<td>2.7</td>
</tr>
<tr>
<td>55-70</td>
<td>45.7</td>
<td>18.1</td>
<td>1.7</td>
<td>61.6</td>
<td>34.0</td>
<td>2.2</td>
</tr>
</tbody>
</table>

The relationship of percent difference and rate ratio is clouded by the bias inherent in prevalence estimates. Percent difference is based on cumulative disease cases. Rate ratio, however, is normalized to the population and shows little change with age. The decreasing trend with age is explained by the fact that other factors contribute to hearing loss.

* Source of data: Criteria for a Recommended Standard for Occupational Exposure to Noise, NIOSH, 1972.
Table 4

Illustration of the Different Information Presented

by Relative Risk and Attributable Risk

<table>
<thead>
<tr>
<th></th>
<th>Rate in Smokers&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Rate in Non-Smokers</th>
<th>Relative Risk</th>
<th>Attributable Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>48.33</td>
<td>4.49</td>
<td>10.8</td>
<td>43.84</td>
</tr>
<tr>
<td>Coronary Artery</td>
<td>294.6</td>
<td>169.54</td>
<td>1.7</td>
<td>125.13</td>
</tr>
</tbody>
</table>

This higher relative risk of smokers for lung cancer than for coronary artery disease indicates that smoking is a more important factor for that disease. The high attributable risk for coronary artery disease indicates that a greater number of these deaths are attributable to the smoking factor than are lung cancer deaths.

<sup>a</sup> Mortality rates per 100,000 population.
Table 5

Summary of Available
Risk Measures for Discrete Outcome

<table>
<thead>
<tr>
<th>Risk Measures</th>
<th>Derivation</th>
<th>Characteristics</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attributable risk</td>
<td>Difference between incidence of disease in exposed and in reference population.</td>
<td>Retains level of rates. Varies with background frequency. Not obtainable from case-control studies.</td>
<td>Policy decisions</td>
</tr>
<tr>
<td>Relative risk</td>
<td>Ratio of incidence of disease in exposed to incidence in reference population.</td>
<td>Invariant to background frequency. Does not retain level of rates. Does not vary with study design.</td>
<td>Etiology</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>Cross product ratio from case-control studies. Logistic regression</td>
<td>Approximates relative risk if disease is rare. Used as relative risk.</td>
<td>Etiology</td>
</tr>
<tr>
<td>Prevalence ratio for NIHL</td>
<td>Ratio of prevalence of disease in exposed to prevalence in reference population</td>
<td>Biases of prevalence data reduced due to nature of hearing loss and occupational studies. Available from existing data. Does not vary with background frequency. Does not retain level of rates.</td>
<td>Etiology</td>
</tr>
<tr>
<td>Type</td>
<td>Sampling Basis</td>
<td>Obtainable Outcome Measures</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------</td>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>Exposure</td>
<td>Prevalence or Incidence (Relative Risk)</td>
<td></td>
</tr>
<tr>
<td>(Prospective or Longitudinal)</td>
<td></td>
<td>Survival functions</td>
<td></td>
</tr>
<tr>
<td>Case-Control (Retrospective)</td>
<td>Disease</td>
<td>Odds Ratio</td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>Population at Risk</td>
<td>Prevalence</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Randomly Assigned treatment or exposure</td>
<td>Odds Ratio</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incidence (Relative Risk)</td>
<td></td>
</tr>
</tbody>
</table>
Table 7

Format of a Life Table

Showing Information Necessary and Rates Obtained

<table>
<thead>
<tr>
<th>Survival time t</th>
<th>Number lost to follow-up</th>
<th>Number with *</th>
<th>Number entering interval i</th>
<th>Number exposed to risk</th>
<th>Cumulative survival rate</th>
<th>Probability of failure</th>
<th>Conditional failure (Hazard)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 3</td>
<td>l</td>
<td>w</td>
<td>d</td>
<td>n_i</td>
<td>s(t)</td>
<td>f(t)</td>
<td>h(t)</td>
</tr>
<tr>
<td>4 - 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 - 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 - 12</td>
<td>S(t)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 - 15</td>
<td>S(t) = number of patients surviving longer than t / total number of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Survivorship Functions Estimated From Life Tables

\[ f(t) = \frac{\text{number of patients dying in the interval beginning at time } t}{(\text{total number of patients}) \times (\text{interval width})} \]

\[ h(t) = \frac{\text{number of subjects dying per unit time in the interval}}{\text{number of patients surviving at } t} \]

* "Alive" and "dead" refer to the event, which could also be defined as hearing loss. Survival time refers, then, to time free of the defined hearing loss.
Table 8
SAMPLE SIZE REQUIREMENTS:

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Cohort Sample Size</th>
<th>Case Control Sample Size for Various Exposure Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>1.5</td>
<td>2491</td>
<td>1217</td>
</tr>
<tr>
<td>2</td>
<td>738</td>
<td>378</td>
</tr>
<tr>
<td>3</td>
<td>239</td>
<td>133</td>
</tr>
<tr>
<td>4</td>
<td>129</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>54</td>
</tr>
</tbody>
</table>

Illustrated for studies of the condition that has an incidence of 49% in those not exposed to the risk factor.
Commander
US Army Medical Research Institute of Chemical Defense
Aberdeen Proving Ground
21010

HQ, First United States Army
ATTN: AFKA-MD (Surgeon's Ofc)
Fort George G. Meade, MD 20755

Director
Ballistic Research Laboratory
ATTN: DRDAR-TSB-S (STINFO)
Aberdeen Proving Ground, MD 21010

US Army Research & Development Technical Support Activity
Fort Monmouth, NJ 07703

Commander/Director
US Army Combat Surveillance & Target Acquisition Laboratory
ATTN: DELECS-0
Fort Monmouth, NJ 07703

US Army Avionics R&D Activity
ATTN: DAFAA-O
Fort Monmouth, NJ 07703

US Army White Sands Missile Range Technical Library Division
White Sands Missile Range
New Mexico 88002

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Propulsion Laboratory MS 77-5
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Cleveland, OH 44135

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Dugway, UT 84022

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ATTN: DRCSG
5001 Eisenhower Avenue
Alexandria, VA 22333

US Army Foreign Science & Technology Center
ATTN: DRXST-1S1
220 7th St., NE
Charlottesville, VA 22901

Commander
US Army Training and Doctrine Command
ATTN: ATCD
Fort Monroe, VA 23651

US Army Avionics R&D Activity
ATTN: DAFAA-O
Fort Monmouth, NJ 07703

US Army White Sands Missile Range Technical Library Division
White Sands Missile Range
New Mexico 88002

Chief
Benet Weapons Laboratory
LCWSL, USA ARRADCOM
ATTN: DRDAR-LCB-TL
Watervliet Arsenal
Watervliet, NY 12189

US Army Research & Technology Labs
US Army Research & Technology Laboratories
ATTN: Technical Librarian
Natick, MA 01760
<table>
<thead>
<tr>
<th>Director</th>
<th>Commanding Officer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naval Biosciences Laboratory</td>
<td>Naval Biodynamics Laboratory</td>
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<td>Oklahoma City, OK 73125</td>
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<td>Naval Air Development Center</td>
<td>ATTN: Ms. Carmen Kinj</td>
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<td>Technical Information Division</td>
<td>288 Bloor Street West</td>
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<td>Box 36, US Embassy</td>
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<td>MAJ J. Soutendam (Ret.)</td>
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<td>1133 Sheppard Avenue West</td>
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<td>Director of Biological &amp; Medical Sciences Division</td>
<td>Dr. E. Hendler</td>
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<td>Office of Naval Research</td>
<td>Code 6003</td>
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<td>Naval Air Development Center</td>
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<td>Arlington, VA 22217</td>
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