

**MOTOR NEURON DISEASE/AMYOTROPHIC LATERAL SCLEROSIS:
PRELIMINARY REVIEW OF ENVIRONMENTAL RISK FACTORS AND
MORTALITY IN BEXAR COUNTY, TEXAS**

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INTRODUCTION

Several former workers from Kelly Air Force Base (AFB) and community members residing near the base have expressed concern about amyotrophic lateral sclerosis (ALS) and the possible association with environmental contaminants. Representatives from the South Texas Chapter of the ALS Association, the Air Force Institute for Environment, Safety and Occupational Risk Analysis (AFIERA), the San Antonio Metropolitan Health District (SAMHD), and the Texas Department of Health are conducting an evaluation of ALS cases with previous connections to Kelly AFB. AFIERA also is supporting a mortality study of former Kelly AFB civilian workers that will evaluate ALS among other endpoints.

To complement these efforts, the Agency for Toxic Substances and Disease Registry has prepared the following report. This report begins with a general overview of ALS, including its clinical and epidemiological characteristics. This description is followed by a review of the available literature on suspected environmental risk factors associated with the disease. Finally, this report includes a presentation of the ALS mortality experience for Bexar County in recent years. It is expected that this report will provide a useful context within which community members concerned about ALS and potential associations with Kelly Air Force Base may begin to seek answers.

GENERAL OVERVIEW OF AMYOTROPHIC LATERAL SCLEROSIS/MOTOR NEURON DISEASE

Motor neuron disease (MND) can be briefly described as a complex of conditions resulting in muscular weakness and wasting without attendant sensory changes (1). Motor neurons, grouped as lower and upper motor neurons, are nerve cells that transmit signals for movement from the brain and spinal cord to muscle tissue. The lower motor neurons project nerve impulses from the spinal cord to the skeletal muscles. The upper motor neurons project nerve impulses from the brain to the spinal cord. MND is characterized by the progressive deterioration and loss of these motor neurons. The loss of nerve stimulus to specific muscles results in atrophy and progressive weakness leading to paralysis.

Progressive muscular wasting disease was first described in 1850 by Aran, and in 1860 by Duchenne. In 1869, the French neurologist Jean-Martin Charcot described a unique condition characterized by deterioration of both lower and upper motor neurons, and this condition was termed amyotrophic lateral sclerosis (2). The Greek term *amyotrophic* translates to "no nourishment to the muscle" which leads to muscular wasting; the term *lateral* refers to an area in the spinal cord where motor neurons pathways are located; and the term *sclerosis* describes the scarring or hardening in the spinal cord that results when these motor neurons deteriorate (1). In the United States ALS is commonly referred to as Lou Gehrig's Disease after the famous baseball player who died from ALS in 1941.

Based on the current International Classification of Diseases (ICD-9), ALS is included within the more general coding for MND (335.2). Although mortality data and other studies using ICD-9 coding for disease classification are referring to this more general category, ALS accounts for 85 percent or more of all MND cases (3, 4). In addition to ALS, several other conditions are found under the general term of MND. Table 1 presents commonly diagnosed motor neuron diseases and shows a distribution of the classification of motor neuron disease based on characterization of specific neuron involvement (1). If only lower motor neuron involvement is evident, the condition may be termed *progressive muscular atrophy* (5). A lower motor neuron condition that primarily results in paralysis of muscles in the tongue and throat may be termed *progressive bulbar palsy*. If predominately upper motor neurons are involved, the condition may be characterized as *primary lateral sclerosis* (5). The majority of these conditions will ultimately progress to include both upper and lower motor neurons and will be termed ALS (3).

Clinical Features of ALS

Clinical manifestations of ALS are largely dependent on the degree to which the upper or lower motor neurons are affected. Symptoms arising from upper motor neuron dysfunction commonly include muscle stiffness, weakness, and sometimes shaking. Symptoms of lower motor neuron damage include shrinking and weakness, twitching of muscle fibers (fasciculation), and loss of tendon reflexes in the affected limbs (6). Often, patients first develop weakness and wasting in

one limb. Symptoms progress to involve other limbs and eventually, chewing, swallowing, speaking, and movement of the face and tongue also become difficult (1, 5).

ALS is nearly always progressive, eventually leading to death. A common cause of death among ALS patients is respiratory failure or cardiac arrhythmias due to insufficient oxygen. Some deaths occur as a result of respiratory infection such as pneumonia. There are some rare reports of patients in whom the disease is stabilized (7), but the median length of survival in most patient populations that have been evaluated is 3 to 5 years (1, 5).

One of the unique features of this disease is the specificity with which only certain neurons involved in motor function are affected. Other functions of the nervous system are preserved, including mental and cognitive functions, sensation, and some movement coordination. Certain motor neurons are also spared, including those controlling eye movement and some neurons in the sacral spinal cord, leaving bowel and bladder control, as well as sexual function, relatively intact (1).

Epidemiology of ALS

The distribution of ALS worldwide can be described by three main groups: (1) sporadic; (2) familial; and (3) the Western Pacific variant.

Sporadic ALS

Individuals who have no family member with the condition are said to have sporadic, or classical, ALS. Sporadic ALS accounts for over 90 percent of all ALS cases. Reports from the United States and other countries indicate an annual incidence rate of 0.2 to 2.4 per 100,000 population and a prevalence of 0.8 to 7.3 per 100,000 population (3). The onset of ALS is age-related with the highest rate of onset occurring between 55 and 75 years of age (3, 8, 9). Prognosis also appears to be age-related with slightly better survival occurring among those with a younger age at onset (3). ALS is more common in males than females by a ratio of 1.5 - 2 to 1 (9, 10), but recent studies have suggested that this sex difference is decreasing over time (9, 11).

Differences in the frequency of ALS by race/ethnicity have also been observed. Mortality data in the United States indicated that the disease is more common among whites compared to non-whites (12, 13). A study in Mexico suggested that ALS prevalence was lower than in other parts of the world (14). A subsequent investigation at a Mexico City referral clinic did not support these differences, and a mortality study in Harris County, Texas showed no significant difference in mortality rates between Hispanics and non-Hispanic whites (15, 16).

Researchers have evaluated the role of genetics in the etiology of sporadic ALS. In a twin study by Graham, results showed the genetic role in sporadic ALS was substantially higher than expected. In this study, the genetic influence in the etiology of sporadic motor neuron disease

was estimated to account for 38 to 85 percent of the risk (17). However, many researchers believe that sporadic ALS may result from a combination of genetic and environmental factors (18).

Familial ALS

Familial ALS can be defined as two or more cases of ALS occurring in the same family. About five to ten percent of ALS cases are familial (5, 19, 20). Familial ALS is inherited as an autosomal dominant trait, meaning that a child of a parent with familial ALS has a 50% chance of inheriting the defective gene. Approximately 15 to 20 percent of all familial ALS cases are attributed to one of several mutations in the Cu/Zn superoxide dismutase (SOD) gene (5, 8, 21). Unlike sporadic ALS, familial ALS is distributed equally among men and women (3). Individuals with familial ALS also have a poorer prognosis than those with sporadic ALS, with a typical survival time of one to two years (3).

High Risk Foci in the Western Pacific

In certain areas of the Western Pacific, the incidence of ALS has been reported to be 50-fold to 150-fold higher than in other regions of the world (3). These high risk foci include Guam, the Kii Peninsula of Japan, and Western New Guinea. ALS patients in these areas often simultaneously acquire symptoms or pathological characteristics similar to Parkinson's disease and Alzheimer's disease. The ALS/Parkinson dementia complex (ALS/PDC) observed in these communities is clinically distinct from classical ALS. Patients who develop ALS/PDC are usually younger and live longer with the disease (mean age at onset 46 years, mean age at death 52 years for women and 50 years for men) (22). Over the past 40 years, the incidence of ALS/PDC in these high risk foci has decreased substantially to rates that are only slightly higher than other regions of the world (3). These dramatic changes in disease incidence suggest the influence of an environmental factor that has been altered over time. These foci have been investigated extensively in the hopes of identifying environmental risk factors that may account for the elevated risk among these populations.

Table 1 Classification of Motor Neuron Disorders

SPORADIC
<ul style="list-style-type: none"> Upper and lower motor neurons <ul style="list-style-type: none"> Amyotrophic lateral sclerosis Predominately upper motor neurons <ul style="list-style-type: none"> Primary lateral sclerosis Pseudobulbar palsy Predominately lower motor neurons <ul style="list-style-type: none"> Progressive muscular atrophy (Bulbar palsy and Spinal muscular atrophy) Multifocal motor neuropathy with conduction block Motor neuropathy with paraproteinemia Motor-predominant peripheral neuropathies Other <ul style="list-style-type: none"> Associated with other degenerative disorders <ul style="list-style-type: none"> Olivopontocerebellar atrophy Azorean (Machado-Joseph) disease Secondary motor neuron disorders
FAMILIAL
<ul style="list-style-type: none"> Familial amyotrophic lateral sclerosis <ul style="list-style-type: none"> Autosomal dominant Autosomal recessive (juvenile) Spinal muscular atrophies (SMA) <ul style="list-style-type: none"> SMA I: Infantile: Werdnig-Hoffman disease SMA II: Childhood onset SMA III: Adolescent onset: Wohlfart-Kugelberg-Welander disease Familial spastic paraparesis (FSP) <ul style="list-style-type: none"> Familial HTLV-I myelopathy Isolated FSP Complicated FSP Hereditary biochemical disorders <ul style="list-style-type: none"> Superoxidase dismutase deficiency Androgen receptor mutation (Kennedy's syndrome) Miscellaneous <ul style="list-style-type: none"> Arthrogryposis multiplex xongentia Progressive juvenile bulbar palsy (Fazio-Londe)
ALS/PARKINSON-DEMENTIA COMPLEX
Western Pacific Foci (Three foci: Guam, Western New Guinea, and Kii Peninsula)

Adapted from Harrison's Principles of Internal Medicine, 13th edition, 1994 (p 2282).

ENVIRONMENTAL RISK FACTORS FOR MND/ALS

The purpose of this review is to present information found in scientific literature on human studies of motor neuron disease/amyotrophic lateral sclerosis (MND/ALS), and to discuss suspected environmental risk factors associated with this disease. The general categories of possible environmental risk factors that have been investigated and will be evaluated in this review are heavy metals, trace elements, solvents and other volatile organic chemicals, radiation, and agricultural chemicals. Several other potential risk factors have been evaluated in the scientific literature including infectious agents, smoking, nutritional intake, physical exertion, trauma, and contact with domestic animals. These factors will not be considered in this review of environmental agents, with the exception of electric shock as a type of trauma because it is relevant to the discussion of non-ionizing radiation as a potential risk factor. Appendix A summarizes the studies discussed in this review.

Heavy Metals

Metals such as lead and mercury are known to have neurotoxic properties. Heavy exposure to lead is associated with neurological disturbances such as encephalopathy and neuropathy, and there are a few reports of a lead-induced syndrome similar to MND (23, 24). These observations initiated speculation that lead or other heavy metals may play a role in MND etiology.

Some case-control studies have suggested an association between exposure to heavy metals, particularly lead and mercury, and risk of MND, but this has not been consistently observed. Based on few observations, self-reported heavy exposure to lead was three times more common among a group of MND patients from medical centers in England compared with non-MND controls from the same medical centers who were matched for age and sex (25). An equal number of MND and non-MND patients reported slight exposure to lead (25). The relevance of the observed association of heavy exposure to lead and risk of MND is difficult to interpret as the exposed cases expressed predominantly lower motor neuron involvement and an atypical, slow form of the disease (25). A study in Sweden also found the association with past occupational exposure to heavy metals to be stronger among cases with predominantly lower motor neuron involvement, but this association was not evident when restricting the case definition to those with both upper and lower motor neuron symptoms (26). Another investigation found an elevation in risk among ALS patients from a Texas clinic who had frequent contact with lead or mercury compared to patients with various non-ALS neurological diseases (27). These investigators conducted a follow-up investigation with a different and larger population of MND patients and observed significantly more cases reporting exposure to lead and mercury than neighborhood-matched controls (28). Two studies from the Mayo Clinic found a higher proportion of ALS cases with previous exposure to heavy metals compared with controls (29, 30). In one of these studies, a composite variable was calculated for occupational and recreational sources of lead, and the risk estimate for lifetime cumulative exposure to lead of 200 hours or more was 5.5 (95% confidence interval 1.44, 21.0) (30). Finally a MND study in

Scotland of 103 matched case-control pairs found 17 pairs in which only the case reported past exposure to lead compared with 3 pairs in which only the patient control reported lead exposure, yielding an odds ratio of 5.7 (95% confidence interval 1.6, 30) (31).

Other case-control studies have failed to find a statistically significant association between past metals exposure and risk of ALS (32-37). One of these studies illustrated the potential for recall bias that may inflate the frequency of reported exposure among cases. McGuire et al. (35) presented risk estimates based upon individuals' self-reported exposure to metals and based upon exposure assessment by a four-member expert panel evaluating job history information. The findings indicated an elevated risk of ALS for self-reported metals exposure (odds ratio = 1.6 for both sexes combined; 2.3 for females), but this elevation in risk was no longer evident when exposure was based upon the expert panel assessment (1.2 for both sexes combined; 0.5 for females) (35).

Evaluations of the distribution of MND incidence and mortality have not contributed any consistent evidence for an association between this disease and exposure to lead or other heavy metals. ALS incidence in a ceramics district of northern Italy with known elevations in environmental lead levels was slightly higher than surrounding districts, but the difference was not significant (38). A similar evaluation of an adjacent district with a similar concentration of ceramics industries and known lead pollution found ALS incidence rates equivalent to the remainder of its respective province (39). Finally, a comparison of United States MND mortality rates found an inverse relationship between MND mortality and the percentage of county residents employed in the metal industry, and mortality rates in counties with lead-smelting operations were not different from the national average (40).

Specific occupations associated with metal exposures also have been investigated as risk factors for ALS. Three case-control studies have found welders to be over-represented among ALS patients (26, 30, 41), but another study failed to observe an association with welding (42). No significant associations were observed between ALS and other metal-related industries, such as metal working and metal casting (17, 43, 44). One of these studies found an odds ratio of 2.5 for MND cases previously employed in the metal manufacturing/fitting industry, but this estimate was imprecise and based on only five cases and two controls in these occupations (17).

Several studies have examined the concentration of lead and other heavy metals in the spinal cord, muscle, and biological fluids of ALS patients, but the findings have been inconclusive (45, 46). Further, when elevated levels of certain metals in biological media have been observed, it is difficult to discern if these elevations indicate causality or if they are a consequence of the disease process.

Chromium, and more specifically hexavalent chromium, is a potential environmental exposure identified from past air emission data at Kelly AFB. There have been no evaluations of chromium, as a potential risk factor for MND. However, there is no evidence that chromium exposure adversely affects the nervous system, and there are no reports in either animals or

humans of musculoskeletal effects or chronic neurological effects following inhalation exposure to hexavalent chromium (47).

In summary, there have been several investigations of heavy metal exposure, particularly lead, as a risk factor for ALS. Some case-control studies demonstrated a positive association between past exposure to heavy metals and risk of ALS, but this has not been consistently observed. Many of the previous studies have relied on self-reporting of past exposure to heavy metals, thus allowing the potential introduction of recall bias that may artificially inflate risk estimates. Future investigations of heavy metals as a risk factor for ALS should include objective evaluations of past exposures.

Dietary Exposures to Trace Elements

Observations from areas of high ALS incidence in the Western Pacific have led to hypotheses regarding trace elements. In these areas, there have been reports of high environmental levels of aluminum and variations in the environmental levels of calcium and magnesium (48), but the dietary patterns of some of these populations do not support the calcium deficiency theory (49). Moreover, no evidence exists to support these associations among individuals with sporadic, or classical, forms of the disease (46). Muscle aluminum levels in 21 patients with classical ALS showed no differences from a control population (50). In a population-based case-control study, a food frequency questionnaire was used to evaluate the association between ALS and essential metals among other dietary factors. Calcium intake was not associated with the risk of ALS, nor was the intake of copper, lead, or zinc (51). Another study of dietary factors observed no association with calcium intake, but dietary magnesium was found to be protective for ALS (52). These dietary studies together with inconsistent observations of metal content in tissue from ALS patients do not lend strong support to the role for trace elements and essential metals, but these factors have not been adequately studied among classical ALS cases.

Selenium was evaluated as a potential dietary factor associated with MND following a report of four ALS cases in a sparsely populated area of South Dakota with high levels of environmental selenium (53). However, elevated urinary selenium was found in only one of the cases, and previous evaluations of ALS death rates in the United States are not consistent with the heterogeneity of selenium soil content that is observed across the country (54-56). In a small region of Italy that had been accidentally exposed to high levels of selenium in drinking water, four ALS cases were found when fewer than one case would have been expected according to the population size and age distribution (57). Finally, selenium measurements in blood and tissue samples were elevated in ALS patients compared to controls (58, 59), but this has not been consistently observed (60-62).

Exposure to solvents and other non-agricultural chemicals

Numerous solvents and other industrial chemicals have neurotoxic properties, but past exposure to these agents is difficult to quantify and validate. Several case-control studies have evaluated the risk of ALS among those reporting past occupational exposure to solvents (31, 32, 35, 63). A study in Scotland comparing MND cases with non-MND patient controls found a three-fold elevation in risk among those reporting that they "ever had an occupation with exposure to solvents or chemicals" (31). Two studies in Italy reported a doubling in risk of MND among those who reported "direct or indirect exposure to organic solvents" and "continual exposure to organic solvents," but neither of these elevations in risk was statistically significant (32, 63). A case-control study in England found a significantly elevated risk for MND among those previously exposed to fumes and dust, but the actual exposure is not well-described by the investigators (64).

A study in the United States reported a small but statistically significant elevated risk of ALS among those who self-reported solvent exposure (odds ratio and 95% CI 1.6 (1.1, 2.5)), but the investigators found no elevated risk when overall solvent exposure was assessed by an expert panel review of occupational histories (35). However, the expert panel assessment of occupational exposure to more specific groups of chemicals found elevated risk estimates for alcohols or ketones; benzene, toluene, or xylene; and cleaning solvents or degreasers (35). This is the only study that evaluated the risk of ALS from exposure to individual, specifically identified, volatile organic compounds.

Three other studies that evaluated solvent or chemical exposure did not observe consistent associations between past exposure and risk of MND (26, 41, 65). Twenty-five patients from a Minnesota ALS clinic were compared to patients with other neuromuscular diseases and another set of controls selected from the residential neighborhoods of the ALS cases (41). These findings indicated a positive association with occupational exposure to organic solvents when comparing ALS cases to the patient controls, but no similar association was found when comparing cases to the neighborhood-matched controls (41). A large study in Japan also found no difference in the proportion of MND cases and neighborhood-matched controls reporting occupational exposure to chemicals (65). It could be argued that controls matched to cases by neighborhood could have similar occupational exposures thus masking associations, but the investigators did not provide enough information to assess this possibility. Finally, a study in Sweden comparing MND cases and non-MND controls found no overall elevated risk for MND among those with past occupational exposure to solvents, but the investigators did observe an elevated risk among men with a family history of neurodegenerative diseases who had previous contact with solvents (26). The same study did not find any association between MND and reported occupational exposure to petroleum products, aromatic hydrocarbons, halogenated hydrocarbons, or mixed volatile hydrocarbons (26).

In summary, the epidemiologic literature offers some support for an association between ALS and past exposure to organic solvents. Other than the study in Japan (65), these studies have

found either a weak association between exposure to organic solvents and risk of ALS, or a mixture of positive and negative results which varied by exposure classification, control group selection, or the sub-group of cases evaluated. Most of these studies suffer from deficiencies with regard to exposure characterization and chemical specificity.

Occupations as a surrogate measure for past exposure to solvents or other chemicals

Past occupations have been used as a surrogate for solvent or chemical exposures, but the occupations and chemicals involved have varied. A review of mortality data in England and Wales found a greater number of deaths among leather workers than expected (66, 67). Leather workers included tanners, shoemakers and repairers, cutters, lasters, sewers, and other leather product makers (67). Although these mortality studies were unable to evaluate specific exposures, it has been hypothesized that solvent exposures in these industries may be associated with the observed elevation in ALS risk. The most potentially neurotoxic solvents currently used in the leather and shoe industries are toluene, methyl-ethyl-ketone, and ethyl acetate. Chemicals previously used in these industries include tri-chloroethylene, carbon tetrachloride, benzene, tri-ortho-cresyl phosphate, and n-hexane (68). A review of medical records in Italy also found a greater proportion of cases than controls with the occupation of tanners (69).

However, an association between leather work and ALS has not been consistently reported (70-73). No former leather workers were observed among 161 MND patients in a region of Scotland, but based on the distribution of occupations in the general population less than one former leather worker would have been expected among the patients (70). A review of deaths among 3,830 workers in the boot and shoe industry in England found no excess mortality from MND (71). In Sweden, shoemakers and tanners were not found to be overrepresented among ALS cases when compared with the occupational experience of a non-ALS comparison group (73).

Risk for MND among individuals occupationally exposed to paints has also been evaluated with the assumption that these individuals are more likely to have been exposed to solvents. A study in England of twin pairs discordant for disease found three to four times greater risk for MND among those with previous occupational paint usage (17). A case-control study in Italy, observed 11 of 512 MND cases with a previous occupation of house painter and only 4 of 512 non-MND patient controls with the same occupation, yielding a statistically significant risk estimate for this occupation (69). A review of all United States MND deaths, 1982-1991, reported a greater proportion of cases among white women employed in the broad category of painters, sculptors, or craft artists (44). However, a large population-based case-control study in Sweden found no excess risk for ALS among painters (26). A smaller U.S. study with limited statistical power also failed to observe an association between individuals employed in the manufacture of paints and pigments and risk of ALS (41). Finally, studies in the United Kingdom did not find a greater proportion of MND cases with the occupation of painters and decorators when compared with the proportion of people with these occupations in the general population (67, 70).

Communities near Kelly AFB have expressed concern over possible past exposure to jet fuel. No investigations of jet fuel as a risk factor for MND were found in the literature. A study of U.S. deaths in 24 states found a significant two-fold increase in death due to MND among commercial pilots (74). The same investigators surveyed over 10,000 commercial airline pilots in the United States and Canada and found a higher than expected number of pilots reporting motor neuron disease (75). The authors of these studies do not identify jet fuel as a potential exposure for commercial pilots, and these investigations were not designed to identify specific exposures to which disease risk can be attributed. Investigations in the United States and Sweden found slightly elevated risk estimates for MND cases employed in the petroleum industry and as gas station attendants, but these findings were based on few observations and did not achieve statistical significance (41, 73).

Various other occupations with likely exposure to solvents or other chemicals have been evaluated, but any findings related to these occupations have been weak, imprecise, and/or inconsistent. An analysis of U.S. death certificates indicated a greater than expected proportion of deaths among white males employed as chemical engineers (44). This occupation has not been evaluated in other studies, but case-control studies in Sweden and Japan did not find a significantly elevated risk for ALS among individuals previously employed in the chemical manufacturing industry (17, 43, 65). Previous occupation in the plastics manufacturing industry was observed among 11 of 518 ALS patients compared to three of 518 friends, neighbors, or workmates identified by the cases, yielding a statistically significant elevation in risk (34). No other studies have reported on work in the plastics industry as a risk factor for MND. Investigators in Italy reported a non-statistically significant doubling in risk for MND among individuals previously employed in the rubber industry (69). Other case-control studies in Sweden and Japan did not observe an elevation in risk for individuals in the rubber manufacturing industry (65, 70, 73). In a large case-control investigation in Sweden a weak, imprecise elevated risk for ALS was found among printers (43), but studies in the United Kingdom and Japan found no difference in the proportion of ALS cases and non-ALS controls reporting previous occupation in printing or related industries (65, 72). A study in Italy found that six of 512 cases were employed as hairdressers compared with only one of 512 non-MND patients (69). This occupation, with potential exposures to dyes and varnishes, was also found to be over-represented among black women in a review of MND deaths in the United States (44). Finally, investigators from one region in Israel reported that five out of eleven ALS cases were employed in textiles, an industry that employed approximately 3000 individuals in the region (76). However, several case-control studies in Sweden, Italy, and Japan and comparisons of the proportional distribution of cases employed in the textile industry in the United Kingdom did not support an association between MND and occupation in this industry (43, 65, 67, 69, 70).

There are several limitations that must be acknowledged when using occupational studies to identify environmental risk factors for MND. First, given the uncertainties with regard to the timing between exposure and the onset of MND, it is unclear when the relevant exposure may have taken place. Many of the occupational studies cited above do not have the degree of specificity required to characterize timing and duration of exposure. Second, occupational

studies, particularly those focusing on job title or industry as the risk factor, are unable to identify specific substances that may be causally related to MND. Third, it is difficult to compare occupational studies from different areas or different time periods, as exposures to specific agents could vary by time and job titles and categories could vary by country. Finally, exposures encountered in the occupational setting are often of a different nature, intensity, and duration than exposures encountered in the environmental setting.

Radiation

Exposure to ionizing radiation has not been extensively studied as a potential risk factor for MND. In a study from Japan past occupational exposure to ionizing radiation, primarily in the medical or paramedical professions, was observed in only two of 103 MND cases and five of 104 controls (65). The same publication reporting on a separate case-control study found the same proportion of cases and controls who had survived atomic bombings in Hiroshima or Nagasaki (65). Another investigator observed a correlation between Japanese ALS mortality rates and data on nuclear fallout from nuclear weapons testing conducted in the 1950s and 1960s in the Pacific Islands (77). However, the fallout from these weapons tests include a variety of radiation products, and such studies are relatively limited in their ability to establish a causal linkage between specific exposures and disease.

Non-ionizing radiation, particularly from power frequency electric and magnetic fields, has also been evaluated as a risk factor for MND. Previous reports suggested an association between amyotrophic lateral sclerosis and occupations with potential electromagnetic field exposure. Reviews of cohorts in both the United States and Denmark found a greater risk for MND among electrical utility employees that would have opportunities for exposure to electromagnetic fields (78-80). A clinic-based study in Sweden found elevated risks for ALS among individuals with the highest magnetic field exposure (81). Other case-control studies in the United States and Sweden also observed significantly elevated risk for MND among individuals employed in electrically-related occupations (26, 34, 65, 82). Finally, a survey in Scotland found a higher proportion of electrical and electronic workers among MND cases when compared with the distribution of occupations in the general population (70). The observed cases with these occupations were too small to make valid statistical comparisons, and a similar review of occupations among MND deaths in England and Wales did not find a greater than expected proportion of electrical and electronic workers (67, 70).

Individuals with electrical occupations, however, may have greater potential for electric shock events. Several case-control studies reported history of electrical shock as a specific trauma associated with MND (34, 63, 83-85), although studies in Japan and Sweden did not observe associations between electrical injuries and MND (26, 65). Thus, despite the relatively consistent observations for occupational exposure to non-ionizing radiation and risk of MND, it remains possible that electric shock or another unidentified variable associated with electrical occupations, rather than electromagnetic fields, is the more relevant exposure.

The studies described above focus primarily on occupational exposure to non-ionizing radiation. There have been no investigations of residential exposure to power frequency electromagnetic fields or exposure to microwave or radio frequency emissions from communications equipment.

Agricultural chemicals

Observations of an association between farming and risk of MND has led to speculation that agricultural chemicals may be a risk factor. Case-control studies in Italy, Greece, and Sweden have found weak, but statistically significant, associations between agricultural work and rural residence and risk of MND (43, 69, 86, 87). Community-based surveys in Sweden and Scotland found twice the proportion of agricultural workers among MND patients as compared to the general population (88, 89). A review of death certificates in the United States found a positive association between county MND mortality and the percentage of the county population living on rural farms (40).

Despite the observations described above, an equal number of studies have found no association between farming or rural living and MND (30, 36, 41, 42, 65, 67, 70, 85). Investigations in the United States and Japan found no differences in the proportion of MND cases and non-MND controls reporting previous agricultural work (41, 42, 65). Additional case-control studies in the United States and Italy found no association between rural residence and risk of MND (30, 36, 85). Analyses in Finland and the United States found no indication that a rural place of birth was associated with ALS (90, 91). Finally, evaluations of the proportional distribution of occupations among MND cases in the United Kingdom did not find an excess number of cases who had previously been employed in the broad occupational grouping of farmers, foresters, and fishermen (67, 70).

Case-control studies investigating the association between exposure to agricultural chemicals and risk of ALS also have yielded inconsistent results. The strongest support for such an association was a population-based study in the United States which found that men with past exposure to agricultural chemicals were at greater risk for ALS (OR and 95% CI = 2.4 (1.2, 4.8)) (35). An exposure-response trend was observed when an expert panel of industrial hygienists grouped exposed individuals into low and high categories (35). Two previous case-control studies in the United States and Italy have found two- to three-fold increases in risk of ALS associated with exposure to agricultural chemicals, but these risk estimates were imprecise and not statistically significant (34, 63). Other studies have not observed an association between reported exposure to agricultural chemicals and risk of ALS (26, 31, 32). Comparisons of MND cases with non-MND controls in Scotland and Sweden found no elevated risk among the few subjects who had reported past occupational exposure to pesticides (26, 31). Another case-control study in Italy did not find an association between MND and self-reported exposure to agricultural chemical substances, despite having found a statistically significant weak elevation in risk for rural residence (32).

Finally, a retrospective cohort mortality study of over 40,000 employees from a chemical company found three ALS deaths among employees involved in the manufacture of 2,4-dichlorophenoxyacetic acid (92). This was found to be more than three times the number of ALS deaths expected from among this cohort. Although each of the cases were involved in the manufacture of 2,4-D, the authors indicate that their respective employment occurred during different years and for durations ranging from 1.3 to 12.5 years (92). There are no additional studies supporting an association between 2,4-D or phenoxy herbicides in the risk of ALS.

Summary of Investigated Environmental Risk Factors Relevant to Kelly AFB

ALS is a complex disease of unknown etiology. Several environmental risk factors have been investigated for a causal linkage, but the cumulative evidence for specific factors is limited and inconsistent.

Some heavy metals have been investigated because they are known to be associated with certain neurological symptoms that are similar to symptoms experienced by individuals with ALS. To date, the evidence linking metals exposure to ALS is inconclusive. Future investigations of heavy metals exposure and the risk of ALS would benefit from well-characterized evaluation of past exposures.

Organic chemicals are also among the potential contaminants of concern at Kelly AFB. Several studies support an hypothesized association between organic solvents and risk of ALS. Some of these studies have demonstrated mixed results that were dependent upon control group selection or the sub-group of cases evaluated. As with the investigations of lead and heavy metals, most of the studies evaluating organic chemicals as a potential risk factor for ALS suffer from deficiencies in exposure assessment.

Radiation exposures have been described among some occupational groups at Kelly AFB. No clear evidence exists for an association between radiation exposures and ALS. However, previous studies had evaluated radiation exposures that could be different from potential exposures at Kelly AFB in terms of product and duration.

Finally, it is worth noting that the U.S. Department of Veteran Affairs recently issued a news release declaring that veterans that served in the Gulf War were nearly twice as likely to develop ALS as their non-deployed counterparts (93). The full report on these findings is not yet available, so we are unable to discuss the potential reasons for this observation or to comment upon the risk factors associated with ALS among Gulf War veterans and such risk factors that may be common to Kelly AFB. These recent findings differ from a previous analysis by the U.S. Department of Defense which found that Gulf War veterans were not at increased risk for hospitalization due to ALS in the years 1991 through 1997 (94).

EVALUATION OF MND MORTALITY IN BEXAR COUNTY, TX

Purpose

As with other neurological diseases, there is no active surveillance system to monitor ALS disease occurrence. Because ALS is a distinctive and usually fatal disease, mortality data has often been used to indicate the occurrence of this disease in a community or larger region (13). Although the frequency of ALS in Bexar County is expected to be too low to yield clear patterns that may be indicative of subtle variations in disease mortality, this evaluation will provide a useful general description of the ALS disease burden in the community.

Methods

We searched the 1989-98 Multiple-Cause-of-Death Mortality Files from the National Center for Health Statistics (NCHS) for all death records in the United States with any mention of motor neuron disease (MND) (ICD Code 335.2) on the record axis. The classification system for recording cause of death does not include a code specifically for ALS, but deaths from ALS would be expected to represent most of the deaths reported under ICD Code 335.2 (3, 4, 56). The record axis is an automated classification algorithm which determines the underlying cause of death from the conditions and their positions as listed on the death certificates. Variables obtained for each record included age at death, sex, race, state and county of death, and state and county of residence. Population data stratified by age, sex, and race/ethnicity for the United States, the state of Texas, and Bexar County, Texas in the years 1990-1998 were obtained from the U.S. Census Bureau (95). Intercensal estimates were used for the years 1990 through 1998, and 1990 figures were used for 1989.

Age-specific mortality rates and 95% confidence intervals (CIs) were calculated. To adjust for possible differences in the age distributions, overall rates for Bexar County, the state of Texas, and the United States were age-standardized to the year 2000 U.S. population. To determine whether there was an excess of mortality due to MND in Bexar County, we calculated standardized mortality ratios (SMRs) and 95% CIs. The SMR is the age-standardized ratio of the observed number of MND deaths in Bexar County to an expected number of deaths based on a comparison population. For a brief discussion to assist with understanding and interpreting SMRs and 95% confidence intervals, see Appendix B. SMRs were calculated using both the state of Texas as the comparison population and the United States as the comparison population. SMRs and 95% CIs were calculated separately for females and males.

Results

Table 1 presents the number of deaths with MND indicated on the death certificate for Bexar County, the state of Texas, and the United States. Of the 154 MND deaths in Bexar County

(with an average population of 1,261,799 during the years 1989 to 1998), 52% were among females, as compared to 45% and 46% in the state of Texas and the United States, respectively (data not shown). Table 1 also presents age-specific MND mortality rates for the three areas considered. In all three areas the highest mortality rates occurred among the 65 to 74 and 75 to 84 age groups. The overall crude rate in Bexar County, 1.22 per 100,000, was similar to the overall crude rate for the state of Texas and slightly lower than the overall crude rate for the United States. After age-standardizing to the U.S. year 2000 population, the Bexar County mortality rate remained lower than the state of Texas or the United States. However, due to the relatively few numbers of cases, the 95% confidence interval was wide, and the estimate for Bexar County was not statistically different from either Texas or the United States. The age-standardized rates for females and males in Bexar County were 1.44 (95% CI 0.46, 2.42) and 1.60 (95% CI 0.37, 2.84), respectively.

SMRs for MND in Bexar County using the state of Texas as the comparison population and the United States as the comparison population are presented in Table 2. Using Texas as the comparison population, the overall SMR was 91.3 (95% CI 76.9, 105.7). Females had an SMR above 100, but the estimate was imprecise with wide 95% confidence intervals. When using the United States as the comparison population, the overall SMR was 84.7 (95% CI 71.3, 98.1).

Table 1. Age-specific MND deaths and mortality rates (per 100,000) for Bexar County, Texas, and the United States, 1989-1998.

Age	Bexar County		Texas		United States	
	MND Deaths	Rate (95% CI)	MND Deaths	Rate (95% CI)	MND Deaths	Rate (95% CI)
< 35	3	0.04 (-0.01, 0.09)	33	0.03 (0.02, 0.04)	474	0.04 (0.03, 0.04)
35-44	9	0.46 (0.16, 0.77)	111	0.39 (0.31, 0.46)	1550	0.38 (0.36, 0.40)
45-54	22	1.67 (0.97, 2.37)	234	1.18 (1.03, 1.33)	3880	1.32 (1.28, 1.36)
55-64	33	3.45 (2.31, 4.69)	506	3.68 (3.36, 4.00)	8628	4.05 (3.97, 4.14)
65-74	46	5.96 (4.24, 7.68)	893	8.39 (7.84, 8.94)	15763	8.54 (8.41, 8.67)
75-84	34	8.73 (5.79, 11.66)	555	9.30 (8.52, 10.07)	11505	10.55 (10.36, 10.74)
85+	7	5.39 (1.40, 93.8)	115	5.92 (4.84, 7.01)	2573	7.33 (7.05, 7.62)
Crude	154	1.22 (1.03, 1.41)	2447	1.34 (1.29, 1.40)	44373	1.71 (1.70, 1.73)
Age-adjusted ^a	154	1.50 (0.74, 2.25)	2447	1.62 (1.42, 1.83)	44373	1.76 (1.71, 1.81)

^aDirect adjusted to the U.S. year 2000 standard population.

Table 2. SMRs for MND in Bexar County, TX using Texas and the United States as comparison populations.

	SMR	95% CI
Texas as comparison population		
Females	107.5	(84.5, 130.5)
Males	77.9	(59.7, 96.2)
All	91.3	(76.9, 105.7)
U.S. as comparison population		
Females	97.6	(78.7, 118.4)
Males	73.6	(56.4, 90.9)
All	84.7	(71.3, 98.1)

Discussion

Based upon the mortality data, Bexar County does not appear to have an excess burden of MND mortality for the years 1989-1998. The direct age-adjusted mortality rate for Bexar County was similar to that found for the state of Texas. Similarly, when comparing the observed MND deaths in Bexar County with the number of deaths that would be expected if the age distributions were similar to that found in the United States or the state of Texas, there was no evidence of an elevated MND mortality risk. In Bexar County, a higher percentage of MND deaths occurred among females as compared to Texas and the United States. However, after standardizing to the U.S. population, the mortality rates followed the state and national patterns with a higher mortality rate for males compared to females.

The interpretation of this analysis must take into account the acknowledged limitations. Inherent inaccuracies exist when identifying cases based upon death certificate data, particularly when considering neurological disorders with complex case definitions and a high potential for misdiagnosis. Compared with many other neurological diseases, ALS is most often a fatal disease that is relatively unique in its presentation. Follow-up of ALS patients from specialty neurology clinics in the United States revealed that the disease was reported in 72% to 91% of the death certificates (96, 97). A review of former U.S. military personnel found 36 of 37 confirmed ALS cases to have the condition reported on their death certificate (42). Studies from Italy and the United Kingdom reflect a similar pattern with approximately 75% to 95% of known MND cases being accurately reported as such on the death certificates (67, 98, 99). Another study in Japan demonstrated an equal proportion of those with confirmed MND but coded as another condition (false negatives) and those found to be absent of the condition but with MND recorded on the death certificate (false positives) (100). The authors cited this as evidence that death

certificates are relatively accurate indicators of the true mortality burden from the disease (100). The data from each of these studies is from previous decades, but no current information is available on the reporting accuracy of MND in the United States during the 1990s. Moreover, reporting accuracy could vary within the country depending upon factors such as health care coverage and the availability of specialty physicians.

Another important limitation of death certificate data is the lack of information on length of residence and migration. There exists the possibility that some individuals included among the MND deaths for Bexar County moved to the area after the time when an important determinant of the disease may have occurred. In such circumstances, residence in Bexar County may not be a relevant factor in disease onset or progression. By contrast, former residents of Bexar County who died elsewhere would not be captured in this analysis. Further, the data presented are for the years 1989 through 1998. We are unable to comment on whether or not aberrations in MND mortality may have occurred in previous years, and recently diagnosed living cases are not included in this analysis:

Finally, the above data were evaluated at the county level to determine if the pattern of MND mortality differed from what is found at the state and national level. It is expected that the data presented for Bexar County is not precise enough with regard to possible exposures from Kelly Air Force Base. There exists the possibility that the mortality analysis at the county level could dilute any elevations in mortality that may exist in areas closer to the Air Force Base.

CONCLUSIONS

It is expected that this document will provide useful background information on ALS for community members residing near Kelly AFB. This report presents an overview of the environmental factors that have been investigated for an association with the risk of ALS. Several potential environmental risk factors have been proposed, but more epidemiological research is required before strong causal linkages can be established. This report also presents some basic descriptive mortality data for MND/ALS in Bexar County. Given the limitations described above, these data should not be interpreted as evidence for an absence of ALS risk associated with Kelly AFB, nor can these data offer any support for such an association. Rather, these data provide some preliminary background information that should be evaluated in the context of the other ALS investigations of former Kelly AFB workers currently being conducted.

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APPENDIX A

Studies Evaluating Environmental Risk Factors for ALS

Table A. Studies Evaluating Environmental Risk Factors for MND/ALS.

Reference	Location	Time Period	Case Source	Study Design	Health Outcome(s)	Results
Armon et al. (1991)	Minnesota	1991	Clinic-based	Case-control	ALS	Lead ++ Welders + Rural residence NS
Bharucha et al. (1982)	US	1968-1978	Population-based	Ecological	MND	Rural residence + Proximity to metal industry -
Buckley et al. (1982)	England and Wales	1959-1979	National	Mortality	MND	Painters NS Textile workers NS Electrical workers NS Rural residence/farming NS Leather workers +
Buckley et al. (1983)	Englans/Wales	1959-1979	National	Mortality, Occupational	MND	Farmers NS
Burns et al. (2001)	US	1945-1994	Cohort	Mortality	ALS	2-4-D (herbicide) ++
Campbell et al. (1970)	UK	1960-1970	Clinic-based	Case-control	MND	Lead contact ++
Chanceflor et al. (1993)	Scotland	1990-1991	Population-based	Case-control	MND	Occupational exposure to lead + Occupational exposure to solvents/chemicals + Pesticides NS
Chio et al. (1991)	Italy	1960-1992	Clinic-based	Case-control	MND	Tanners ++ Rubber industry + House painters ++ Textile industry NS Farmers ++ Hairdressers ++
Cruz et al. (1999)	Western Washington	1990-1994	Clinic-based	Case-control	ALS	Electrical shock + Rural residence NS
Davanipour et al. (1997)	California	1997	Clinic-based	Case-control	ALS	Electromagnetic fields ++

NS = no association; +, positive but not statistically significant association; ++, statistically significant positive association

Table A (continued). Studies Evaluating Environmental Risk Factors for ALS.

Reference	Location	Time Period	Case Source	Study Design	Health Outcome(s)	Results
Deapen et al. (1986)	US	1977-1979	National	Case-control	ALS	Plastic manufacturing ++ Electrical shock + Electrical occupation ++ Pesticides + Metals NS
Felhus et al. (1976)	Texas	1976	Clinic-based	Case-control	ALS	Lead ++ Mercury ++
Gallagher et al. (1987)	Florida	1987	Clinic and registry	Case-control	ALS	Electric shock +
Gawel et al. (1983)	UK	1983	Clinic-based	Case-control	MND	Electric shock ++
Graham et al. (1997)	UK	1979-1989	Death registry	Twin study	MND	Paints used in job ++ Metal manufacturing/fitting NS Petrochemical length/time NS
Graziari et al. (1988)	Italy	1964-1982	Population-based	Case-control	MND	Rural residence ++ Agriculture ++ Organic solvents + Agricultural chemical NS Heavy metals NS
Gresham et al. (1980)	San Diego, CA	January 1985 - May 1985	Clinic-based	Case-control	ALS	Heavy metal exposure NS
Guidetti et al. (1996)	Emilia, Italy	1980-1992	Clinic-based	Mortality	ALS	Lead (plasma, cerebrospinal fluid and spinal cord) + Lead NS
Gunnarsson et al. (1989)	Sweden	1970-1983	Population-based	Case-control	ALS	Tanners/shoemakers NS Rubber manufacturing industry NS Gas station assistant/petroleum industry +
Gunnarsson et al. (1996)	Sweden	1961-1990	Population-based	Ecological	MND	Agricultural work +

NS = no association; +, positive but not statistically significant association; ++, statistically significant positive association

Table A (continued). Studies Evaluating Environmental Risk Factors for ALS.

Reference	Location	Time Period	Case Source	Study Design	Health Outcome(s)	Results
Gunnarsson et al. (1992)	Sweden	1990	Population-based	Case-control	MND	Welding ++ Electrical work ++ Solvents (comb w/ inherit) ++ Heavy metals + Aromatic hydrocarbons NS Electric shock NS Agricultural chemicals NS Halogenated hydrocarbons NS Mixed volatile hydrocarbon NS Painters NS
Gunnarsson et al. (1991)	Sweden	1970-1983	Population-based	Case-control	ALS	Farm workers ++ Electrical workers + Metal-related industry NS Chemical manufacturing industry NS Printers + Textile industry NS
Hanisch et al. (1976)	Los Angeles, CA		ALS Registry	Case-control	ALS	Birthplace (rural vs urban) NS
Hawkes et al. (1981)	UK	1959-1963; 1970-1972	Death registry	Mortality, Occupational	MND	Leather workers ++
Hawkes et al. (1989)	England and Wales	1952-1963; 1970-1972; 1973; 1979; 1980; 1982, and 1983.	National	Mortality	MND	Leather workers +
Holloway et al. (1982)	Scotland	1968-1977	Population-based	Mortality	MND	Agricultural work +
Holloway et al. (1986)	Scotland	1961-1986	Population-based	Case-control	MND	Electrical workers + Rubber workers NS Farmers NS Leather workers NS Painters NS Textile industry NS

NS = no association; +, positive but not statistically significant association; ++, statistically significant positive association

Table A (continued). Studies Evaluating Environmental Risk Factors for ALS.

Reference	Location	Time Period	Case Source	Study Design	Health Outcome(s)	Results
Johansen (2000)	Denmark	1900-1993	National	Mortality	MND/ALS	Electromagnetic fields +
Johansen et al. (1998)	Denmark	1900-1993	National	Mortality	ALS	Magnetic fields +
Kalfakis et al. (1991)	Greece	1964-1988	Clinic-based	Case-control	ALS	Farming ++
Kilness et al. (1977)	South Dakota	1965-1974	Population-based	Ecological; Case reports	ALS	Selenium +
Kondo et al. (1981)	Japan	1973	Clinic-based	Case-control	MND	Rural residence NS Electrical occupation ++ Electrical shock NS Chemicals NS Rubber manufacturing NS Printing NS Textile NS Radiation NS
Kurtzke et al. (1980)		1963-1967	National	Mortality	ALS	Welding NS Farming NS
Li et al. (1990)	London	1965-1982	Clinic-based	Retrospective	MND	Printing NS Leather work NS
Longnecker et al. (2000)	Massachusetts	1993-1996	Clinic-based	Case-control	ALS	Dietary magnesium (protective) NS
Maryn et al. (1989)	UK	1951-1988	Occupation	Cohort	MND	Boot/shoe industry (solvents/leather) NS
McGuire et al. (1997)	Western Washington	1990-1994	Population-based	Case-control	ALS	Agricultural chemicals ++ Metals NS
Mitchell et al. (1995)	Lancashire and South Cumbria (UK)	1989-1993	Clinic-based	Case-control	MND	Exposed to fumes and dust +
Neilsen et al. (1995)	Japan	1953-1990	National	Geologic	MND	Radiation +
Nelson et al. (2000)	Western Washington	1990-1994	Population-based	Case-control	ALS	Copper and zinc (dietary) NS Calcium and iron (dietary) NS

NS = no association; +, positive but not statistically significant association; ++, statistically significant positive association

Table A (continued). Studies Evaluating Environmental Risk Factors for ALS.

Reference	Location	Time Period	Case Source	Study Design	Health Outcome(s)	Results
Nicholas et al. (2001)	US and Canada	1998	Occupational	Cohort	MND	Pilots +
Nicholas et al. (1993)	US	1984-1991	Population-based	Mortality, Occupational	MND	Pilots/navigation ++
Norris et al. (1989)	California	1989	Clinic-based	Case-control	ALS	Metals NS
Palo et al. (1977)	Finland	1969-71	Population-based	Mortality/prev	ALS	Farming NS Rural residence NS
Pierce-Ruhland et al. (1981)	Texas	1981	Clinic-based	Case-control	MND	Lead ++ Mercury ++
Provinciali et al. (1990)	Italy	1979-1987	Clinic-based	Case-control	ALS	Rural residence NS Exposure to heavy metals NS
Roozefs-Iverson et al. (1984)	Rochester, Minnesota	April 1977-September 1978	Clinic-based	Case-control	ALS	Heavy metals ++
Savettieri et al. (1991)	Palermo, Italy		Population-based	Case-control	ALS	Agricultural chemicals + Organic solvents + Electric shocks +
Savitz et al. (1998)	US	1950-1986	National	Mortality	ALS	Electrical workers ++
Savitz et al. (1993)	US	1985-1991	National	Case-control	ALS	Electrical workers ++
Scarpa et al. (1988)	Modena, Italy	1976-1986	Clinic-based	Ecological	ALS	Exposure to lead +
Schulte et al. (1996)	US	1982-1991	National	Mortality, Occupation	MND	Metal-related industry NS Painters/sculptor/craft artists + Chemical engineers + Hairdressers +

NS = no association; +, positive but not statistically significant association; ++, statistically significant positive association

Table A (continued). Studies Evaluating Environmental Risk Factors for ALS.

Reference	Location	Time Period	Case Source	Study Design	Health Outcome(s)	Results
Strickland et al. (1996)	Minnesota	1996	Clinic-based	Case-control	ALS	Welding ++ Electric plating + Petroleum industry + Paint/pigment manufacture NS Organic solvents NS Farming NS
Vinceti et al. (1996)	Reggio Emilia, Italy	1986-1994	Population-based	Cohort	ALS	Selenium + (via drinking water)

NS = no association; +, positive but not statistically significant association; ++, statistically significant positive association

APPENDIX B

Standardized Mortality Ratios and 95% Confidence Intervals

To determine whether there is an excess of a particular disease or health condition, the observed number of cases in the population living in the area of concern is compared to an "expected" number of cases from a standard population. The ratio of observed-to-expected number of deaths (mortality) can be standardized to eliminate possible effects due to race, sex, and age. This ratio is referred to as the standardized mortality ratio (SMR).

An O:E ratio of 100 indicates that the number of cases observed in the population being evaluated is equal to the number of cases expected based on the rate of disease in the comparison population. A ratio greater than 100 indicates that more cases occurred than expected; and a ratio less than 100 indicates that fewer cases occurred than expected. Accordingly, a ratio of 150 is interpreted as 50% more cases than expected; and a ratio of 90 indicates 10% fewer cases than would be expected.

Caution should be exercised, however, when interpreting these ratios. The interpretation of a ratio depends on both the value of the ratio and the numbers used to compute the ratio. Two ratios can have the same size but be interpreted differently. For example, a ratio of 150 based on 2 expected cases and 3 observed cases indicates a 50% excess in disease, but the excess is actually only 1 case. However, a ratio of 150 based on 200 expected cases and 300 observed cases represents the same 50% excess in disease, but because the ratio is based upon a greater number of cases, the estimate is less likely to be attributable to chance. It is very unlikely that 100 excess cases of disease would occur by chance alone. However, a single excess case very easily could be due to chance occurrence.

A certain amount of chance variation can be expected when looking at the occurrence of different health conditions in communities, and statisticians have developed methods to take this into account. One method is to calculate a 95% confidence interval (CI) for the O:E ratio. The 95% CI is the range of estimated ratio values that has a 95% probability of including the true ratio for the population. The confidence interval is a statistical measure of the precision of the risk estimate.

"Statistically significant" means there is less than 5% chance that the observed difference is merely the result of random fluctuation in the number of observed cases. For example, if the confidence interval does not include 100 and the interval is below 100, then the number of cases is significantly lower than expected. Similarly, if a confidence interval does not include 100 and the interval is above 100, then there is a significant excess in the number of cases. If the confidence interval includes 100, then the true ratio may be 100, and it cannot be concluded with sufficient confidence that the observed number of cases reflects a real excess or deficit. As long as the 95% confidence interval contains 100, that indicates that the ratio is still within the range one might expect based on the disease experience of the comparison population. However, if either the upper or lower bound of the confidence interval is 100, it is considered of borderline statistical significance. This means that the ratio is close to being statistically significant and that the number of cases was either higher or lower than expected.

In addition to the number of cases, the width of the confidence interval also reflects the precision of the ratio estimate. For example, a narrow confidence interval (e.g., 103–115) indicates that the population's size was sufficiently large to generate a fairly precise estimate of the ratio. A wide interval (e.g., 85–450) indicates far less precision, and more uncertainty, in the calculated ratio.