

# Cluster of systemic lupus erythematosus (SLE) associated with an oil field waste site: a cross sectional study

James Dahlgren MD<sup>1</sup>, Harpreet Takhar MPH<sup>2</sup>, Pamela Anderson-Mahoney PhD<sup>3</sup>,  
Jenny Kotlerman MS<sup>4</sup>, Jim Tarr<sup>5</sup>, Alexander Lee<sup>2</sup>, ~~Raphael Ray~~ Warshaw<sup>6</sup>

1. UCLA School of Medicine 2. James Dahlgren Medical 3. Epidemiology Resources
4. UCLA School of Public Health 5. Stone Lions
6. Comprehensive Health Screening Services

Please address correspondence to:

James Dahlgren, MD

2811 Wilshire Blvd.

Santa Monica, CA 90403

Voice: 310-449-5525 ext. 226

FAX: 310-449-5526

[dahlgren@envirototoxicology.com](mailto:dahlgren@envirototoxicology.com)

Short Title: SLE cases on an abandoned oil field

**Abstract:**

This is a community comparison study that examines persons living in a subdivision exposed to petroleum products and mercury and compares their health status and questionnaire responses to those living in another community with no known exposures of this type. Pristane house dust among the exposed homes was ~~6.23 times~~ higher than in the comparison community ~~( $p < 0.05$ )~~. ~~Statistical test used~~. The exposed subdivision has higher ambient air mercury levels compared to the control community. The prevalence of rheumatic diseases and lupus was greater in the exposed population compared to the unexposed (OR = 10.78; CI = 4.14, 28.12 and 19.33; 1.96, 190.72, respectively). A higher prevalence of neurological symptoms, respiratory symptom rates and several cardiovascular problems including stroke and angina (OR = 15.41; CI = 0.78, 304.68 and 5.72; 1.68, 19.43, respectively) was seen. There were statistically significant differences in B cells, Natural Killer Cells, gamma glutamyl transferase, globulin and serum calcium levels between control and exposed subjects.

Key words: lupus, SLE, mercury, phytane, pristane, oil field, contamination, environment, autoimmune

**Introduction:**

Systemic lupus erythematosus (SLE or lupus) is an autoimmune disease in which the body produces anti-nuclear antibodies that attack healthy tissues leading to inflammation and damage to various body tissues. Lupus can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. It is a chronic, complex, and potentially fatal multi-system inflammatory disorder that can be difficult to diagnose.<sup>1,2</sup> No single laboratory test confirms a diagnosis of SLE. Many physicians use the American College of Rheumatology's "Eleven Criteria of Lupus" to aid in the diagnosis where the appearance of four of the "Eleven Criteria of Lupus" qualifies as a positive diagnosis of Lupus<sup>2</sup> (Figure 1).

SLE can occur at any age and in either sex. However, women are more likely to have SLE and women of color are more likely to have SLE compared to white women.<sup>3</sup> Migration studies suggest that environmental factors play a role in the development of SLE.<sup>4</sup> Residents living near industrial emissions or environmental contamination have been shown to have an increase prevalence of SLE.<sup>5,6</sup> Research indicates that a combination of genetic and environmental factors can trigger the development of SLE<sup>7,8</sup> however, there is a need for additional research to identify and characterize the specific exposures that contribute to the incidence and aggravation of SLE.

Animal studies suggest that pristane and mercury may be environmental triggers for SLE.<sup>9-15</sup> It has been demonstrated that both pristane and mercury will induce a condition in mice that mimics clinical features and the autoantibody pattern characteristic of SLE in humans. We know of no reports in the medical literature of SLE in humans following exposure to pristane. There have been case reports linking mercury to autoimmune disease in humans<sup>8,9</sup> and a recent epidemiologic study of occupational risk factors for SLE identified mercury as a potential causal agent<sup>7</sup> (OR=3.6; 95% CI=1.3,10.0).

We investigated of an apparent cluster of SLE cases in a community in Hobbs, New Mexico. This investigation was initiated by residents of a six square block area, who noted an excess of SLE cases in their neighborhood. Most of the cases occurred in a new subdivision built on land that was an active oilfield from 1927 until the late 1960s. This subdivision was built on that site in 1976. Some of the homes were built on ground that had previously been used as a pit for oil field waste, which was estimated to be 200 feet long and 30 feet wide.

The residents experienced petroleum and/or rotten egg odors inside their homes on frequent occasions. They also found black oily material oozing out of the

ground either spontaneously or when digging in the soil around their property. The residents sought legal advice because they were concerned that there was a connection between the apparent residual oil field waste and the elevated SLE cluster in their neighborhood.

There was a tank battery and several active oil wells located directly to the west of the subdivision which continued operating until 2000 (Figures 2 & 3). The oil company had installed a vapor recovery system for these oil wells and an accompanying tank battery to reduce vapors escaping from the storage tanks in 1969. When a lawsuit was filed the oil company investigated and based on the results, closed down the tank battery and purchased the three homes closest to that tank battery site. The surface soil from the tank battery and home sites was transferred to a hazardous waste site because of very high Total Petroleum Hydrocarbons (TPH). Soil testing for metals, semi-volatiles and polycyclic aromatic hydrocarbons (PAHs) at other nearby homes did not reveal levels high enough to oblige remediation. Both soil and air testing by the oil company and the experts retained by the plaintiffs' counsel revealed the presence of aromatic hydrocarbons including benzene, toluene, ethylbenzene, xylene, pristane and phytane. People are still living in the remaining adjacent homes.

We compared the health status of 90 residents along with their environmental and biomonitoring test results to a reference population. We also compared their health questionnaire results to NHANES prevalence rates.

**Methods:**

***Study Design.*** This is a community comparison study that examines persons living in a subdivision exposed to petroleum products and mercury and compares their health status and questionnaire responses to those living in another community with no known exposures of this type. A volunteer sample of 90 adults from the exposed neighborhood completed a questionnaire and donated blood for the measurement of pristane, pristanic acid and phytane. We compared the environmental exposures and questionnaire responses and pristane/phytane blood levels to those living in another community with no unusual exposures to these contaminants. We compared the observed prevalence of SLE in this community with values reported in the literature. Exposed study participants were all plaintiffs in a lawsuit.

***Setting and study populations.***

Exposed Population - Hobbs, New Mexico is a predominantly Caucasian (63.5%) town of 28,657<sup>16</sup> residents located in Lea County on the southeast corner of New

Mexico, 5 miles from the Texas border. Hobbs was founded in 1907 as an agricultural and ranching community and became prominent after the discovery of oil in 1928. Hobbs is known as the oil capital of New Mexico.<sup>17</sup> Numerous oil and gas wells are scattered throughout the area and this industry is the principal source of employment in Hobbs. We estimated a total population of 1490 residents in the study neighborhood by counting 532 homes and estimating 2.8 individuals in each household. The bulk of the SLE cases are on two streets that roughly correspond to the location of the oil field waste pit until it was covered with fill dirt in the late 1960's. The study population of 90 adults had lived in the area for at least two years, and voluntarily enrolled in the study. We assumed that the rest of community did not have SLE.

Comparison Population – One hundred and twenty nine volunteers from a similar [southwestern](#) town without unusual chemical exposures were recruited through a church. We invited the members to participate in the study by filling out a questionnaire and volunteering to have blood drawn for biomonitoring. As with the exposed population, trained and experienced proctors administered a nearly identical questionnaire to all volunteers in small groups. The questionnaire differed only with respect to questions regarding exposure experiences unique to the Hobbs neighborhood. The control subjects were paid a small fee for their

participation. The control town was matched for size, altitude, and demographics. The control population was not free of unusual petroleum hydrocarbon exposure. Fifteen of the controls had been raised in Bakersfield a town similar to Hobbs with many nearby oil fields. Furthermore, the town is the site of a large railroad-switching yard. Given that Hobbs has a large Hispanic population we note some possible dietary issues specific to Hispanic populations (herbal teas, etc.).

The Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS), Division of Health Examination Statistics (DHES) has conducted health and nutrition surveys since the early 1960's and is publicly available data. These surveys known as National Health and Nutrition Examination Surveys (NHANES), are designed to obtain a nationally representative sample of the health and nutritional status of the U.S. population. Details for each survey as well as the public use data files are available online (CDC).

The most recent NHANES began in 2001. Every year, approximately 7,000 civilian, non-institutionalized U.S. citizens, of all ages, are interviewed. From this group, approximately 5,000 complete the health examination component of the

survey. NHANES 2001-2002 over-samples low-income persons, adolescents 12-19 years, persons over 59 years of age, African Americans and Mexican Americans (NHANES).

NHANES data were available and used to estimate expected rates of disease in the exposed population for all cancers, angina, asthma, chronic bronchitis, emphysema and stroke.

***Data Collection.***

The questionnaire obtains data on demographics including age, gender, occupational and residential history as well as medical, social and behavioral history. Other topics covered in the questionnaire are health symptoms, diseases, surgeries, medications, family history, income, chemical exposures, and life style measures including smoking and alcohol drinking. One unlikely symptom question is designed to test for the veracity of the responses provided.

Questionnaire responses are machine-readable, scanned on-site and verified before subjects leave. This basic questionnaire has been used in prior studies of exposed and unexposed groups.<sup>18</sup>

***Case Definition.***

We defined a case of SLE as an individual who had received a physician's diagnosis. We confirmed the diagnosis with medical records to confirm that the diagnosis had been reached in accordance with American Rheumatology Association's "Eleven Criteria of Lupus."<sup>2</sup> We excluded cases that were diagnosed within 6 months of moving to the neighborhood or cases that were diagnosed more than 5 years after moving away. This criteria for diagnosis is consistent with previously published studies.<sup>5,19</sup>

### ***Exposure Assessment***

#### ***House Dust***

We collected house dust samples from residents who permitted access to their homes. House dust samples were collected in the exposed and control community from 2/27/03 to 3/1/03 by Stone Lions Environmental Corporation (Rolling Hills Estates, CA). A total of 19 house dust samples were collected in the exposed subdivision and three additional samples were taken about 2 miles northeast of the subdivision. Nine house dust samples were collected from the control community.

Stone Lions Environmental Corporation collected house dust samples using current state-of-the-art method for household dust sampling which involves using the HVS-3 forensic vacuum or a Sears Kenmore canister vacuum model 22085

sampling system. Dust was drawn into a new vacuum bag, which was removed after each house. The vacuum bags were immediately placed into a double Ziploc bag and labeled accordingly. Samples were collected in various places in each house depending on the availability of dust. The primary locations were attic, heater vents, windowsills, tops of furniture and appliances, tops of doorways and doorway frames, exposed shelves, and carpet (only for houses with minimal dust elsewhere). The vacuum and attachments were cleaned with reagent-grade methanol between each sample. All cleaning and bag removal activities were performed while wearing powder free surgical gloves. The samples were analyzed for analytes, polycyclic aromatic hydrocarbons (PAHs), total petroleum hydrocarbons (TPH), radiochemistry, pristane and phytane. Metals, PAHs, and TPH were analyzed by West Coast Analytical Services (Santa Fe Springs, CA). Metals were analyzed using Inductively Coupled Plasma – Mass Spectrometry. PAHs were analyzed using EPA method 625/8270C/SIM. TPH were analyzed using EPA method 418.1. Radiochemistry was analyzed at Fruit Growers Laboratory (Santa Paula, CA) using 901.0 (Gamma isotopic and 9310 (Radiochemistry). Pristane and phytane exposures were analyzed at Humble Geochemical Services (Humble, Texas) using high-resolution gas chromatography. This method to measure and quantify pristane and phytane in

crude oil is standard in the petroleum industry. The petroleum industry uses pytane/pristane fingerprints to determine the source of crude oil.

### *Air Monitoring*

An ambient air monitoring station for volatiles and reduced sulfur compounds was established at a site located directly on the old waste pit in the exposed subdivision. The site was located on a front lawn within a 10 by 10 foot chain link fence. Silica-lined Summa canisters were used to collect 24 ambient air samples on a schedule of approximately once every six days. The first sample was collected on October 18<sup>th</sup>, 2002 and the final sample was collected on February 11<sup>th</sup>, 2003. Over that period of five months, nineteen 24-hour samples were collected including one field blank. Canister preparation and sample analyses were performed by Zymax Envirotechnology (San Luis Obispo, California). Each sample was analyzed for volatile organic compounds (VOCs) and reduced sulfur compounds. VOCs were analyzed using EPA method TO-14 GC/FPD.

A meteorological station (Davis Instruments) was installed at the same location as the ambient air-monitoring site. Instruments measuring wind speed, wind direction, ambient temperature, pressure, relative humidity and rainfall were

mounted on a two-meter tower. Those parameters were recorded at half-hour intervals for the duration of the ambient air-monitoring period.

#### *Mercury Ambient Air Testing*

The Lumex Zeeman Mercury Analyzer RA-915+ was used to measure the ambient air concentration of mercury from various locations inside and outside the homes in both the exposed and control communities. 30-second ambient air samples were taken in the center of each room and on the front porch.

#### ***Biomonitoring.***

##### *General Health Screening Panel*

A trained phlebotomist collected blood and urine from volunteers from both the exposed and control communities. One tiger top, two lavender tops and one grey top (for urine) was shipped overnight on ice to Pacific Toxicology Laboratories (Woodland Hills, California) for analyses. A complete blood count, chemistry panel and a urinalysis were performed using standard laboratory techniques.

##### *Lymphocyte Subpopulation Analysis*

The Lymphocyte Subpopulation Analysis (Enumeration Panel) was done to estimate the distribution of the common lymphocytes. A trained phlebotomist

collected one yellow top of blood from both exposed and control participants and shipped overnight on ice to Immunoscience Laboratories (Beverly Hills, California)

#### *Pristane and Phytane*

Pristane is a straight chain seventeen carbon alkane; phytane is an eighteen-carbon alkane. Pristanic acid is a metabolite of pristane. All three were measured in blood of exposed and comparison subjects by Southwest Research Institute (San Antonio, Texas). An aliquot of 1 ml of serum was removed and 20  $\mu$ l of phosphoric acid was added to the serum sample. Pristanic acid-d<sub>3</sub> was then added to the serum to monitor the extraction efficiency of pristanic acid. The serum was extracted twice using 5 ml hexane saturated with acetonitrile. The organic layer was decanted and was concentrated to 1 ml. The organic extract was then derivatized using diazomethane to convert pristanic acid to its ester form. After derivatization, the organic extract was further concentrated to 0.2 ml and serum samples were ready for GC/MS analysis. The GC/MS instrument was calibrated using a 5-pt calibration curve. The range was from 0.8 - 0.25 ug/ml. The instrument was operated under selected ion monitoring (SIM) mode to enhance sensitivity.

***Data Analysis.***

Frequencies and percents for demographic, social, behavioral and physical characteristics are presented for exposed and unexposed populations. P-values for the difference between the two groups were estimated using the Pearson chi square test.

NHANES. Standardized Prevalence Ratios (SPRs) for certain diseases were calculated using the NHANES 2001 - 2002 data files for comparison rates. NHANES data were restricted to 18 and older. Rates were calculated for each medical condition using the sampling weights developed specifically for the NHANES data controlling for age. The sampling weights account for the sampling methods as well as the non-response rates and render the data representative of the total U.S. population. The weights also provide for accurate assessment of the sampling error of statistics based on these survey data (National Center for Health Statistics, 1992).

Odds ratios and 95% confidence intervals are estimated for binary health outcomes using logistic regression to compare exposed and unexposed populations while controlling for age, gender, education and race/ethnicity. Odds ratio and confidence intervals are estimated for those health outcomes where the

response possibilities include a scale from 1 to 11 using multinomial logistic regression models. The odds ratio is interpreted as the odds of the exposed being in a higher response category compared to the unexposed.

All statistical analyses were performed using SAS 8.0.

### **Results:**

Ninety adult volunteers from the exposed community and 129 adults from the comparison community participated in the study (Table 1). The age, gender and smoking history (ever/never) were similar between the two groups. The exposed population was more diverse in terms of race/ethnicity; the comparison group was Caucasian. Level of education was higher in the comparison group.

#### *Environmental measures*

House dust samples for pristane and phytane were higher in the exposed homes (Table 2). Pristane and phytane were found in every sample tested from both the exposed and unexposed communities, however, significantly higher values were found in the exposed community. Pristane house dust among the exposed homes was ~~6.23 times~~ higher than in the comparison communities ( $p < 0.05$ ). House dust samples for mercury were not elevated in exposed homes (data not shown).

Air sampling by the oil company for pristane and phytane in the exposed neighborhood during both at baseline and soil removal operations consistently showed positive values (Table 3). The baseline air sampling was conducted in July of 2001. The air samples were taken during the remediation that lasted approximately 6 months starting in March of 2002. The SVOC samples were obtained in the exposed subdivision at 6 sites.

Results of ambient mercury air measurements are displayed in Table 4. Outdoor air blanks (front porch readings) were consistently much lower than indoor values. Data is not shown. Summary of the ambient mercury air measurements are displayed in Table 5. The exposed subdivision has nearly 6.2 times higher mercury levels compared to other locations in Hobbs located two miles away and nearly 2.5 times higher mercury levels compared to the control community.

#### *Biomonitoring*

One of twenty-five (4.0%) from the comparison subjects and five of twenty (25%) from the exposed who were tested had detectable positive blood levels for pristane, phytane and/or pristanic acid. Each subject who had a detectable level of pristane, phytane and/or pristanic acid also had either a frank diagnosis of lupus or

common symptoms associated with immune system disorders. The students' t-test produces a p-value of  $<0.05$  for this difference.

Blood samples were obtained from 97% (87/90) of the exposed subjects. Forty-three of 90 (47%) exposed subjects and 37/129 (28%) unexposed subjects agreed to provide additional vials of blood for natural killer cell and CD 19 (B cell) analysis. Ten additional control subjects participated only in the natural killer cell and CD 19 (B cell) analysis (Table 6). There were biologically and statistically significant differences in B cells, Natural Killer Cells, gamma glutamyl transferase, globulin and serum calcium levels. Creatinine Phosphokinase (CPK) was not significantly different for the overall group; however, an examination of blood results for men only reveals the mean value in the exposed population is 220 versus 139 in the comparison group. Five of the nineteen exposed males (26.3%) had CPK above the laboratory normal of 269 IU/L and none of the comparison men were above that value. There was no influence by alcohol or other factors.

#### *Disease prevalence and symptoms*

Lupus cases were confirmed by both phone call follow up and review of medical records (Table 7). The prevalence of rheumatic diseases and lupus was greater in

the exposed population compared to the unexposed (OR = 10.78; CI = 4.14, 28.12 and 19.33; 1.96, 190.72, respectively) (Table 8). The long tailed confidence interval for lupus reflects the single case found in the unexposed community. Increased rates of symptoms thought to be predictive of autoimmune disorder were found in the exposed community including: numb fingers, mouth sores, and persistent rash on the cheeks and pain on deep breath.

The presence of neurological symptoms was elevated in the exposed community including: dizziness, lightheadedness, loss of balance, extreme fatigue, sleep disorders, lack of concentration and memory loss (Table 9).

A higher prevalence of several cardiovascular problems occurred in the exposed population including stroke and angina (OR = 15.41; CI = 0.78, 304.68 and 5.72; 1.68, 19.43, respectively) chest tightness and pain in the chest (Table 10). Again, the long tailed CI for stroke reflects the paucity of stroke sufferers in the comparison community. No difference was found for the overall measure of heart disease or myocardial infarction.

Respiratory symptom rates were significantly elevated in the exposed population including shortness of breath and wheezing, cough with blood or mucus, dry cough and chronic bronchitis (Table 11).

Other elevated symptom rates include gastrointestinal problems like diarrhea, constipation, nausea, stomach swelling and loss of appetite (Table 12). Diabetes was also more prevalent in the exposed population; the difference nearly reached the level of statistical significance at the 0.05 level (OR = 3.26, CI = 0.96, 11.10; p-value = 0.06).

Standardized prevalence ratios were estimated using NHANES data (Table 13). Prevalence rates for angina, stroke and chronic bronchitis were statistically significantly higher than expected. Asthma and all cancer rates were not higher than expected.

### **Discussion:**

We not only observed a significantly increased prevalence of SLE but also an increase of cardiovascular, neurological and respiratory problems in this subdivision of Hobbs, New Mexico. The literature reports a prevalence rate for SLE that varies from 14.6 to 50.8 cases/100,000. The highest rate is seen in

African Americans.<sup>4,20,21,22</sup> If all the cases reported here in this one neighborhood were the only cases in the entire town of Hobbs, we would have a SLE prevalence rate of 45 cases/100,000 (13 cases/28,657). However, that method of calculation would most likely be inaccurate because there are no doubt other SLE cases in Hobbs. Thirteen SLE cases are found on two blocks alone. This two-block area was on or near the site of the oil field waste pit and presumably would reflect a higher exposure than other areas. Taking the exposed neighborhood only we obtain a lupus rate of 872/100,000 (13 cases/1490 [532 homes x 2.8 individuals in each household]). In addition to the diagnosed SLE, there is an increased rate of reported immunologic symptoms/problems in the exposed population compared to controls and general population rates. Rheumatic disease is 10 times as likely; SLE is 10 times as likely in the exposed compared to their unexposed counterparts. Other symptoms common among those with immune problems are also reported with increased frequency in the exposed population including mouth sores, numbness, and rash.

The magnitude of the prevalence rate of SLE may be understated for three reasons. First there were other possible SLE cases however we could not confirm a physician diagnosis in their medical records. Second we compared the prevalence rate using the highest-available expected estimates for prevalence to

be conservative. Third, we did not collect data on the entire subdivision or town; therefore we may not have identified all the cases of SLE, even in the exposed subdivision.

In addition to the finding of a significant increase in the prevalence of SLE in the exposed neighborhood the lymphocyte testing of the exposed population's immune system shows significant abnormality compared with the controls. The lymphocyte population of the exposed residents is not normal. Natural Killer Cells (NKC) are significantly lower in the exposed population. Analysis of B-lymphocytes shows that the exposed population has significantly higher B-lymphocytes compared to controls. This finding is consistent with the known compensatory effects of B cells when other lymphocytes are inhibited. The natural killer cells are reduced causing compensatory changes in B-cells. Such a decrease of an essential component of the body's immune cells indicates a potentially significant impairment with implications for increased susceptibility to infection and cancer. The data presented here reports for the first time an adverse effect on lymphocytes numbers associated with environmental exposures to oil field waste. The spectrum of long-term health effects arising from this exposure will require long-term follow-up. At the very least this data demonstrates a perturbation of the immune system, which in concert with the finding of a

significant cluster of SLE indicates that the exposure in this neighborhood is likely have additional effects on the residents, even those who have not been diagnosed with SLE. We are attempting to further characterize the immunological defect that is present in these residents.

Calcium is tightly regulated in the body because it is an essential mineral in many body functions. Even slight changes in serum calcium reflect alterations in hormone balance. In this case, there is a significantly higher serum calcium level in the exposed population. This finding reflects differences in hormone balance and is consistent with the endocrine disrupting effects of environmental pollutants. In this case the chemical agent or agents that may explain this phenomenon are unknown.

Creatinine Phosphokinase (CPK) is an enzyme, which appears in the blood. Elevations of this enzyme indicates damage to either heart, brain or muscle tissue. The cause of the elevated CPK in the exposed males is another objective indication of adverse effects in the residents most logically as a result of their environmental exposure to oil field waste. As with the disruption of calcium metabolism the chemical agents responsible are unknown. In our experience CPK is often elevated in patients with exposure to neurotoxic agents. It is likely that the

source of the elevated serum CPK in this case is from damage to the nervous tissue.

The residents in the exposed community were exposed to higher than usual background levels of various hydrocarbons including benzene, xylene, toluene, pristane, phytane and polycyclic aromatic hydrocarbons (PAHs). We found higher levels of air mercury and house dust pristane/phytane in the affected neighborhood compared to other areas of Hobbs and the control town. Mercury is very volatile and so the major route of exposure would be through vapor inhalation. Pristane/phytane on the other hand is not volatile and it would be expected to be higher in the house dust.

Mercury is one of the *few* chemicals that are conclusively known to cause adverse immune system disruption in animals and humans. Exposure to mercury can depress or stimulate the immune system.<sup>23</sup> Inorganic mercury salt poisoning which was once a common cause of renal failure is now less common.<sup>24</sup> Recent research has been done on the adverse effects of mercury on various components of the immune system.<sup>25-31</sup> Some strains of rodents develop autoimmunity upon very low exposure to mercury while other strains are not affected.<sup>9,23,32,33</sup> This finding reveals a key element to understanding mercury toxicity and the immune

system. Only those persons with the susceptibility will develop the disease. The occurrence of autoimmunity in animal studies depends on the dose, chemical form or strain of animal. Animal studies show that low doses of mercury damages T cells,<sup>34,35</sup> leads to immune system dysfunction<sup>36-41</sup> and induces autoimmunity.<sup>9,42-47</sup> The immune reaction in humans to mercury exposure is varied. Humans have increased activity of the immune system leading to autoimmunity<sup>48</sup> or sensitivities to the environment.<sup>49,50</sup> On the other hand there can be immune suppression with decreases in immune defenses such as macrophage function.<sup>51</sup> Low-level chronic exposure to mercury has been associated with Crohn's disease, endometriosis, lupus,<sup>8</sup> and other autoimmune processes.<sup>28,52</sup> There have been case reports linking mercury to autoimmune disease in humans<sup>8,9</sup> and a recent epidemiologic study of occupational risk factors for SLE identified mercury as a potential causal agent<sup>7</sup> (OR=3.6; 95% CI=1.3,10).

Cooper's epidemiologic study of human exposure to mercury reveals increased rates of immunologic disease. Associations were seen with self-reported occupational exposure to mercury (OR=3.6; 95% CI=1.3, 10.0) and reported a significantly increased prevalence of SLE among dental workers (OR=7.1; 95% CI=2.2, 23.4).<sup>7</sup> None of our subjects had been dental workers. Mercury's presence can be explained in this community by mercury presence in crude oil and its use

in instruments found in oil fields.<sup>53-55</sup> Studies have implicated residents living near industrial emissions or environmental contamination to increased prevalence of SLE.<sup>5,6</sup>

In 1976, Cancro and Potter injected mineral oil or the pure alkane pristane into mice.<sup>56</sup> Cancro and Potter reported that in as little as three days plasmacytosis was evident.<sup>56</sup> Pristane injected into a rat also induces arthritis.<sup>57-61</sup> In certain strains of mice, pristane exposure is known to induce autoimmunity<sup>12,62-65</sup> and systemic lupus erythematosus.<sup>13,66-73</sup> Satoh in 2000 reported that pristane was able to induce lupus in virtually any strain of mouse regardless of its genetic background (Satoh 2000). Phytane is also likely to have a similar effect because of its similar structure and toxicity.<sup>72</sup> Pristane is a likely candidate to be an environmental trigger for SLE in susceptible sub-populations. The authors wrote in their paper “Finally, it may be worth noting that pristane is found in mineral oil, shark oil, and many foods, raising the possibility that environmental exposure to pristane could be involved in the pathogenesis of some cases of human SLE.”<sup>12</sup>

It has been demonstrated that both pristane and mercury will alter immune system function.<sup>57,58,74,75</sup> We are not aware of any human cases of pristane induced SLE,

this study should encourage further research on autoimmune diseases and environmental exposures.

The fact that all of the subjects with pristane or phytane in their blood have significant autoimmune diseases or symptoms of autoimmune disease is consistent with the animal models implicating pristane as a causal factor in the development of SLE. Interestingly, the one control subject with pristane and phytane in her blood reported a rash after being in the sun and also a diagnosis of pleurisy. These two symptoms are often antecedent to developing lupus.

The combination of two or more immune system disrupting chemicals may be interacting to cause clinical disease at the levels we encountered in this oil field waste contaminated site. The presence of other chemicals in the exposed community further confounds the issue of targeting the cause. Whether or not the increased SLE prevalence is triggered by the chemicals we have identified pristane/phytane and /or mercury versus other oil field waste chemicals needs further research. For example, the presence of a third chemical of concern such as benzene could be playing a role. Benzene is known to adversely affect the immune system<sup>76,77</sup> in rats and mice. Previous in vivo studies have shown that chronic low exposure to benzene in mice<sup>78</sup> and humans<sup>79-81</sup> can induce sister

chromatid exchange (SCE) in peripheral blood lymphocytes. Other studies have associated benzene to adversely affect the immune system in humans as well.<sup>82-87</sup> Benzene is a component of crude oil and was found to be present in the air of the exposed neighborhood. Jet fuel, another complex mixture of mostly long chain hydrocarbons also containing pristane, has been shown to disrupt and decrease immune system function in rats.<sup>88-89</sup> Most research on chemically induced SLE or other autoimmune disease has studied only a single agent. Our findings, the findings of Harris and colleagues regarding jet fuel,<sup>88-89</sup> the findings from Kardestuncer<sup>5</sup> and the findings from Balluz<sup>6</sup> suggest that studying populations with exposures to mixtures may provide more information on the etiology of these very debilitating diseases.

The effect of exposures in the real world to a mixture of chemicals causes effects that would not be seen if the exposure was to only one compound. Determining health risks from mixtures are complicated because much of our understandings of health risks arise from a single dose response that can be altered to observe for disease conditions.<sup>90</sup> Guidelines are then set in place from establishing no observable adverse effect levels (NOAEL). Mechanisms for multiple chemical interactions are more complicated. Chemicals can interfere with the metabolism of one another. Others may act at the cell receptor site to either produce synergistic,

additive or antagonistic effects. Studies support the notion that solvents show association with connective tissue diseases and sclerosis<sup>91,92</sup> and have an additive immunotoxic effect.<sup>93</sup>

The limitations of this study include small sample sizes for rare outcomes, lack of a true unexposed comparison group and potential self-selection bias of study participants. We reduce the limitation of the small sample size by analyzing symptom responses as well as the occurrence of frank disease. National statistics estimated using NHANES data address the need for a robust comparison group if only for a few symptoms. Selection bias is unlikely in this study. The symptom and disease pattern in this exposed cohort is consistent with other studies, either in animal models or humans, suggesting increased rates of immune disease from pristane and mercury exposure. Even if there were a selection bias with a disproportionate number of sick study subjects in the exposed group, it is unlikely that only sick subjects with illnesses consistent with their particular exposures would be more likely to volunteer for the study.

Some researchers question whether reliable data can be obtained from participants involved in litigation. While it is claimed that litigants exaggerate their symptoms we know of no evidence that this is true, particularly when examining averaged

group responses. A study by the Agency for Toxic Substance and Disease Registry (ATSDR) revealed no evidence of “litigation bias” among subjects being followed for health effects from trichloroethylene in their drinking water with no statistically significant difference in the validity of the survey responses from litigant versus non-litigant populations.<sup>94</sup> These authors write, “Litigants are no more likely than non-litigant(s) to provide inaccurate or exaggerated responses.”

Observational bias is unlikely to influence these results because the techniques used to collect the data do not require interpretation. In addition, there is no indication that there would have been differential bias in this regard. The questionnaires were filled out in a neutral environment supervised by trained proctors. All subjects were given the same instructions. Recall bias is also unlikely to affect the results, particularly when it comes to lupus. Most people who were ever diagnosed with this disease would never forget it.

### **Conclusions:**

Despite some possible limitations, the findings in this study are compelling. The hypothesis that environmental toxins may induce lupus is consistent with the known ability of certain medications to cause SLE.<sup>95-97</sup> There exists a plausible biological basis for such an association.<sup>98</sup> Examples include the association of

prolonged silica-dust exposure with scleroderma,<sup>99</sup> the occurrence of Raynaud's phenomenon, sclerodermatous skin changes, and acroosteolysis among vinyl chloride workers.<sup>100,101</sup>

This study adds to the evidence implicating pristane and mercury in the development of lupus and generates questions as to the possible synergistic effects of organic solvents including pristane and phytane, mercury and other exposures. Further research is needed to determine the mechanism of effect for each of the suspected causal exposures and to assess possible synergy between exposures.

**Competing Interests:**

The author was first hired by a law firm to investigate, however the law case has been dropped for several years, therefore the authors declare that they have no competing interests.

**Authors' contributions:**

JD conceived of the study and supervised all aspects of its implementation and reviewed drafts of the manuscript; HT and PAM assisted in writing the manuscript; JK completed the analysis; ~~Format: JTAB~~ carried out the

environmental testing and participated in drafting the manuscript; AL designed questionnaire and assisted in collection and management of data; and RW assisted in the design of the study. ~~molecular genetics studies, participated in the sequence alignment and drafted the manuscript.~~

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**FF**igure 1. American College of Rheumatology - The “Eleven Criteria” for diagnosis of SLE.

1. Malar rash: butterfly-shaped rash across cheeks and nose
2. Discoid (skin) rash: raised red patches
3. Photosensitivity: skin rash as a result of unusual reaction to sunlight
4. Mouth or nose ulcers: usually painless
5. Non-erosive Arthritis (bones around joints do not get destroyed): in 2 or more joints with tenderness, swelling, or effusion

6. Cardio-pulmonary involvement: inflammation of the lining around the heart (pericarditis) and/or lungs (pleuritis)
7. Neurologic disorder: seizures and/or psychosis/cognitive dysfunction
8. Renal (kidney) disorder: excessive protein in the urine, or cellular casts in the urine
9. Hematologic (blood) disorder: hemolytic anemia, low white blood cell count, or low platelet count
10. Immunologic disorder: antibodies to double stranded DNA, antibodies to Sm (smooth Muscle), or antibodies to cardiolipin
11. Antinuclear antibodies (ANA): positive test in absence of drugs known to induce it

Figure 2. Photograph of Oil Field in Relation to Residents Homes.



Figure 3. Close up Photograph of Tank Battery in Relation to one of the two main exposed Streets.



Table 1. Demographic frequencies in Hobbs\* and in a control community\*\*

	<b>Exposed</b>	<b>Unexposed</b>	
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	No.	%	No.	%	P-value
<b>Age Category</b>					
18-34	35	37.63	37	28.68	0.85
35-49	35	37.63	62	48.06	
50-64	19	20.43	28	21.71	
65+	4	4.30	2	1.55	
Total	93		129		
<b>Race/Ethnicity</b>					
Hispanic	44	48.89	5	3.88	<0.0001
White	29	32.22	121	93.80	
African American	12	13.33	0	0	
Others	5	5.55	3	2.33	
<b>Gender</b>					
Male	34	37.36	61	47.29	0.21
Female	57	62.64	68	52.71	
<b>Ever Smoked</b>					
Yes	35	38.89	52	40.31	0.83
No	55	61.11	77	59.69	
<b>Education Level</b>					
Less than 9 <sup>th</sup> grade	6	6.45	0	0	<0.0001
9 – 11 <sup>th</sup> grade	22	23.66	13	10.08	
12 <sup>th</sup> /Vocational/Some College	57	61.29	86	66.67	
College Graduate	8	8.60	30	23.26	

\*a residential population exposed to petroleum products and other environmental contaminants

\*\*no known exposures.

Table 2. Summary Results for pristane and phytane house-dust sampling for Hobbs, Hobbs-Control, and Control Community.

Sample Group / Chemical	Pristane*				Phytane*			
	Avg	SD	Max	Min	Avg	SD	Max	Min
Hobbs (n=19)	480.831	784.216	2441.230	13.770	262.522	542.694	2464.530	18.750
Hobbs-Control** (n=3)	42.437	25.868	66.290	14.940	155.277	153.763	324.320	23.730
Tehachapi (n=9)	99.029	116.491	349.310	17.940	223.969	138.587	557.440	85.220

\* results in ppm

\*\* Samples collected 2 miles outside of the Westgate Subdivision

AVG – Average

SD – Standard Deviation

Max – Maximum

Min - Minimum

Table 3. Air monitoring data for pristane, phytane and PAHs (Semi Volatile Organic Compounds (SVOC)) taken at baseline and during trenching operations\*

	<b>Summary Statistics for SVOC Air Monitoring - Baseline</b>			<b>Summary Statistics for SVOC Analysis of Air - Trenching Operations</b>		
	<b>Concentration (ng/m<sup>3</sup>)</b>			<b>Concentration (ng/m<sup>3</sup>)</b>		
<b>Compound</b>	<b>Minimum</b>	<b>Maximum</b>	<b>Mean</b>	<b>Minimum</b>	<b>Maximum</b>	<b>Mean</b>
Phytane	6.10	145	37.7	7.85	83.9	43.1
Pristane	4.43	182	50.5	8.21	110	41.9
Total PAH	57.0	655	178	89.4	769	224

\*Sampling conducted by Oil Company

Table 4. Complete Results for ambient air mercury sampling for Hobbs, Hobbs-Control, and Control Community.

Sampling Group	Address	MULTIPLE SAMPLES AT EACH RESIDENCE*															Average
		Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8	Sample 9	Sample 10	Sample 11	Sample 12	Sample 13	Sample 14	Sample 15	
Hobbs	Location Point 1	19	18	21	19	21											19.60
	Location Point 2	17	18	18	18	20	19	19	18								18.38
	Location Point 3	7	8	8	10	17	17	15	16	16							12.67
	Location Point 4	46	73	79	82	68	94	97	157.25	171	67	103	96	72.333	90	19	87.64
	Location Point 5	11	15	32	17	34	23	24	28	27	28	20					23.55
	Location Point 6	11	9	10	9	12	12	11	14	10							10.89
	Location Point 7	13	14	13	13	15	13	14									13.57
	Location Point 8	32	24	33	27	30	35	30	32	35							30.89
	Location Point 9	19	15	14	12	9	15	14	2								12.50
	Location Point 10	14	13	13	14	10	12	11									12.43
Hobbs Control**	Location Point 11	7	5	7	6	9	9	7									7.14
	Location Point 12	4	0	0	0	0	0										0.67
Control	Location Point 13	15	17.5	15	19	19	21										17.75
	Location Point 14	2	5	6	6	7											5.20
	Location Point 15	16	15	16	8	13	28	31	30	29	29	32					22.45
	Location Point 16	7	9	9	12												9.25
	Location Point 17	6	7	7	8												7.00
	Location Point 18	18	18	18	12												16.50
	Location Point 19	9	7	6	1	7	5										5.83
	Location Point 20	4	5	6	3	2	4	9									4.71
	Location Point 21	10	11	8	16	12	6										10.50
	Location Point 22	5	6														5.50

\* 30-second averages, results in nanograms per cubic meter

\*\*Samples collected 2 miles outside of the Westgate Subdivision

Table 5. Summary Results for ambient air mercury sampling for Hobbs, Hobbs-Control, and Control Community.

Sample Group / Chemical	Mercury*			
	Avg	SD	Max	Min
Hobbs	24.21	31.34	171.00	2.00
Hobbs-Control**	3.90	3.67	9.00	0.00
Tehachapi	10.47	8.08	32.00	1.00

\* 30-second averages, results in nanograms per cubic meter

\*\*Samples collected 2 miles outside of the Westgate Subdivision

AVG – Average

SD – Standard Deviation

Table 6. Ordinary least squares regression analysis comparing blood chemistry test results between exposed and unexposed adults while controlling for age.

Adults	Exposed		Unexposed		Comparison Estimates	
	Number	Mean (SD)	Number	Mean (SD)	Parameter Estimate	P-value
% CD 19 (B-cell)	43	18.07(6.11)	47	14.02(4.68)	3.98	0.0006
% Natural Killer Cells <sup>1</sup>	43	10.77(5.65)	47	14.26(7.33)	-3.41	0.01
Total bilirubin	87	0.61(0.23)	37	0.54(0.16)	0.07	0.12
gamma-Glutamyl transferase (IU/L)	87	40.07(50.25)	37	19.30(11.53)	21.60	0.01
Globulin (mg%)	87	3.02(0.50)	37	2.86(0.34)	0.15	0.09
Serum CALCIUM (mg%)	87	9.71(0.38)	37	9.23(0.36)	0.48	<0.0001
Creatinine Phosphokinase (IU/L)	87	127.44(90.63)	37	110.43(54.02)	16.02	0.32

1. Natural Killer Cells = CD16 + 56+ / CD45+  
SD = Standard Deviation

Table 7. Exposure information for Lupus cases in Westgate Subdivision

<b>Patient</b>	<b>From Age</b>	<b>To Age</b>	<b>Total years</b>	<b>Gender</b>	<b>Date of Birth (age)</b>
1	43	Present	14	Female	8/21/45 (57)
2	26	Present	22	Female	11/6/54 (48)
3	11	22	11	Female	1/4/76 (27)
4	30	Present	19	Female	1/23/54 (49)
5	37	Present	12	Female	7/30/53 (49)
6	31	45	14	Male	6/7/56 (46)
7	33	35	2	Female	8/7/45 (57)
8	38	43	5	Female	12/4/39 (63)
9	28	30	2	Female	1/21/63 (40)
10	62	72	10	Female	12/20/26 (76)
11	18	40	22	Female	4/20/59 (43)
12	35	49	14	Female	9/23/51 (51)
13	3	29	26	Female	12/12/1972 (29)

Table 8. Estimated risk ratios and confidence intervals for autoimmune disorders comparing nearby residents of a Westgate Neighborhood to controls with no known exposure regression controlling for age, gender, race/ethnicity, education and smoking history.

	Exposed N(%) or mean±s.d.	Unexposed N(%) or mean±s.d.	Risk Ratio	95% Confidence Interval	P-value
Rheumatic Diseases	33 (39.29)	16 (12.40)	10.78	4.14, 28.12	<0.0001
Systemic lupus erythematosus	13(14.29)	1 (0.78)	19.33	1.96,190.72	0.01
Immune	9 (11.11)	1 (0.78)	26.44	2.67,261.50	0.005
Anemia	22 (26.19)	29 (22.48)	1.14	0.49, 2.65	0.76
Numbness in Fingers	49 (58.33)	34 (26.36)	3.96	1.93, 8.15	<0.0002
Mouth Sores	18 (21.43)	6 (4.65)	5.66	1.78, 18.03	0.03
Rash on the Cheeks	17 (20.24)	4 (3.10)	8.27	2.20, 31.13	0.002
Rash from Sunlight	17 (20.24)	11 (8.53)	1.44	0.50, 4.13	0.50
Pain on Deep Breath	19 (22.62)	7 (5.43)	11.04	3.68, 33.13	<0.0001

\*Risk ratio and confidence intervals are estimated using logistic regression

\*\* Risk ratio and confidence intervals are estimated using multinomial logistic regression models with generalized estimating equations (GEE); odds ratio interpreted as the odds of exposed being in a higher category compared to unexposed

Table 9. Estimated risk ratios and confidence intervals for neurologic and behavioral disorders comparing exposed residents to community residents with no known exposure controlling for age, gender, race/ethnicity, education and smoking history.

	Exposed N(%) or mean±s.d.	Unexposed N(%) or mean±s.d.	Risk Ratio	95% Confidence Interval	P-value
Dizziness**	4.40±3.10	2.25±1.96	4.42	2.37, 8.24	<0.0001
Lightheadedness**	4.85±3.12	2.65±1.81	5.02	2.69, 9.34	<0.0001
Loss of balance**	3.68±3.07	2.24±1.73	2.83	1.53, 5.22	0.0009
Extreme fatigue**	6.97±3.69	3.12±2.40	11.50	5.94, 22.28	<0.0001
Somnolence**	5.08±3.76	2.11±1.86	4.99	2.66, 9.36	<0.0001
Can't fall asleep**	4.79±3.79	2.89±2.50	1.94	1.06, 3.54	0.03
Wake up frequently**	5.12±3.79	2.91±2.55	3.98	2.16, 7.36	>0.0001
Sleep soundly for only a few hours**	4.83±3.59	2.81±2.51	4.00	2.16, 7.40	>0.0001
Lack of concentration**	5.70±3.73	3.76±2.66	2.67	1.47, 4.84	0.001
Recent memory loss**	5.22±3.82	3.76±2.66	2.87	1.58, 5.23	0.0006
Decreased libido**	4.36±4.00	2.92±2.35	3.00	1.60, 5.59	0.0006

When driving in familiar areas, do you ever get lost or go the wrong way **	2.67±2.73	1.55±1.33	3.05	1.54, 6.08	0.002
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\*Risk ratio and confidence intervals are estimated using logistic regression

\*\* Risk ratio and confidence intervals are estimated using multinomial logistic regression models with generalized estimating equations (GEE); odds ratio interpreted as the odds of exposed being in a higher category compared to unexposed

Table 10. Estimated risk ratios and confidence intervals for cardiovascular disorders comparing exposed residents to community residents with no known exposure controlling for age, gender, race/ethnicity, education and smoking history.

	Exposed N(%) or mean±s.d.	Unexposed N(%) or mean±s.d.	Risk Ratio	95% Confidence Interval	P-value
Heart Disease*	5 (6.17)	4 (3.10)	1.80	0.33, 9.66	0.50
Acute Myocardial Infarction *	3 (3.57)	3 (2.33)	2.11	0.17, 25.93	0.56
Stroke*	5 (5.95)	1 (0.78)	15.41	0.78, 304.68	0.07
Angina*	15 (17.86)	5 (3.88)	5.72	1.68, 19.43	0.005
Rhythm	10 (12.35)	18 (13.95)	0.61	0.22, 1.68	0.34
Chest tightness**	3.74±2.82	1.92±1.54	5.97	3.13, 11.40	>0.0001
Palpitations**	3.03±2.69	2.35±1.98	1.64	0.87, 3.07	0.12
Pain in Chest**	3.42±2.88	1.73±1.65	4.24	2.21, 8.14	<0.0001

\*Risk ratio and confidence intervals are estimated using logistic regression

\*\* Risk ratio and confidence intervals are estimated using multinomial logistic regression models with generalized estimating equations (GEE); odds ratio interpreted as the odds of exposed being in a higher category compared to unexposed

Table 11. Estimated risk ratios and confidence intervals for respiratory disorders comparing exposed residents to community residents with no known exposure and controlling for age, gender, race/ethnicity, education and smoking history.

	Exposed N(%) or mean±s.d.	Unexposed N(%) or mean±s.d.	Risk Ratio	95% Confidence Interval	P-value
Pneumonia*	11(13.58)	18(13.95)	1.19	0.45, 3.15	0.72
Pleurisy*	5 (6.33)	4 (3.10)	1.48	0.29, 7.61	0.64
Chronic bronchitis*	16 (19.75)	3 (2.33)	17.37	4.06, 74.35	0.0001
Dry cough**	4.64±3.21	2.36±1.74	5.06	2.67, 9.60	<0.0001
Cough with mucous**	4.73±3.51	2.79±1.75	2.60	1.43, 4.73	0.002
Cough with Blood**	2.30±2.55	1.11±0.45	11.77	4.33, 32.03	<0.0001
Asthma Diagnosed by MD*	11 (13.41)	17 (13.18)	2.13	0.78, 5.82	0.14
Rhinitis*	24 (29.63)	21 (16.28)	3.45	1.49, 8.01	0.004
Sinusitis range**	4.57±3.71	2.50±1.91	2.62	1.43, 4.79	0.002
Short of Breath at Rest*	23 (27.38)	4 (3.10)	11.28	3.11, 40.98	0.0002
Short of Breath on Walking*	40 (48.19)	6 (4.65)	34.34	10.52, 112.09	<0.0001
Short of Breath Climbing Stairs*	52 (62.65)	34 (26.36)	6.17	2.81, 13.56	<0.0001
Wheezing*	24 (28.57)	7 (5.43)	19.20	5.59, 65.98	<0.0001
Short of Breath and Wheezing*	16 (19.51)	13 (10.08)	4.31	1.55, 12.00	0.005

\*Risk ratio and confidence intervals are estimated using logistic regression

\*\* Risk ratio and confidence intervals are estimated using multinomial logistic regression models with generalized estimating equations (GEE); odds ratio interpreted as the odds of exposed being in a higher category compared to unexposed

Table 12. Estimated risk ratios and confidence intervals for other disorders comparing exposed residents to community residents with no known exposure controlling for age, gender, race/ethnicity and smoking history.

	Exposed N(%) or mean±s.d.	Unexposed N(%) or mean±s.d.	Risk Ratio	Confidence Interval	P-value
Diabetes*	10 (12.35)	6 (4.65)	3.26	0.96, 11.10	0.06
Reduced sense of smell**	3.80±3.53	2.12±2.23	3.77	1.96, 7.25	<0.0001
Nausea**	4.54±3.20	2.23±1.51	4.82	2.58, 8.99	<0.0001
Loss of appetite**	3.80±2.70	2.13±1.49	3.44	1.86, 6.37	<0.0001
Stomach swells or is bloating**	5.07±3.78	2.13±1.80	6.76	3.46, 13.19	<0.0001
Constipation**	4.16±3.36	2.68±2.14	2.90	1.58, 5.35	0.0006
Diarrhea**	3.78±2.89	2.55±1.75	2.75	1.49, 5.06	0.001
Poor bladder control**	3.40±3.59	2.34±2.13	2.50	1.30, 4.82	0.006
Hair Loss*	33 (39.76)	6 (4.65)	14.12	4.57, 43.65	<0.0001
Seizures*	4 (4.76)	5(3.88)	0.85	0.18, 4.02	0.84

\*Risk ratio and confidence intervals are estimated using logistic regression

\*\* Risk ratio and confidence intervals are estimated using multinomial logistic regression models with generalized estimating equations (GEE); odds ratio interpreted as the odds of exposed being in a higher category compared to unexposed

Table 13. Standardized Prevalence Ratio (SPR) comparing observed disease rate per 100,000 among the exposed population to the expected disease rate of the general U.S. population controlling for age and gender.

<b>Disease</b>	<b>Number diseased in exposed</b>	<b>Observed Rates<sup>a</sup> (per 100,000)</b>	<b>Expected Rates<sup>b</sup> (per 100,000)</b>	<b>PR</b>	<b>CI<sup>c</sup></b>
Angina	15	17,857	1,802	9.91	5.36,18.31*
Stroke	5	5,292	1,376	4.33	1.71,10.96*
Emphysema	2	2,469	838	2.95	0.70, 12.37
Chronic bronchitis	16	19,753	5,504	2.59	2.07,6.21*
All Cancer	8	9,324	5,710	1.67	0.78, 3.57
Asthma	11	13,415	11,890	1.13	0.60,2.13

<sup>a</sup>Observed rates are the number of cases reported by questionnaire from the exposed population per 100,000.

<sup>b</sup>Expected rates are from NHANES 2001 – 2002 using sampling weights to calculate an unbiased estimate of national rates while adjusting for non-response, survey design and sampling technique while giving an accurate estimate of sampling error.

<sup>c</sup>95% Confidence Interval

\* Confidence interval excludes the null value