Name:

SSN:

Date:

Date of Birth:

Sex: male

Dates of military service: DD214

Dates of service at Camp Lejeune:

The following report was based on record review.

Reviewer:

**Member, Subject Matter Expert Panel**

Camp Lejeune Contaminated Water Project

Time Dedicated to this review: XX Minutes

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Contention, the veteran claims the following condition as secondary to exposure to CLCW:

Contention 1: Lung Cancer

Diagnosis:

Nexus: The diagnosis above Choose an item.

**Case Specific Discussion:**

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Claims file and other available evidence of record was review, applicable evidence is summarized below:

**VBMS/Claims file review**:

 **VVA/VistaWeb/CARPI review**:

**Other possible veteran risk factors**:

 Employment history prior to military service:

Smoking:

Alcohol use:

Obesity: BMI—

Genetic:

Employment history after military service:

Hobbies/recreational leading to possible chemical exposure: UNK

**Disease Specific Discussion, Lung Cancer:**

**Disease Description:** The National Cancer Institute defines lung cancer as: cancer that forms in tissues of the lung, usually in the cells that are lining air passages. The two main types are small cell lung cancer and non-small cell lung cancer. These types are diagnosed based on how the cells look under a microscope.

Incidence:Lung cancer is the most common cancer worldwide. Lung cancer (both small cell and non-small cell) is the second most common cancer in both men and women (not counting skin cancer). Lung cancer accounts for about 13% of all new cancers. Overall, lung cancer is more common in men than women [1]. Lung cancer accounts for about 27% of all cancer deaths in the US each year, and more people die of lung cancer than of colon, breast, and prostate cancers combined. Approximately 10-15% of all lung cancers arise in individuals that have never smoked, thus resulting in one of the leading causes of cancer-related mortality [2].

Estimated new cases and deaths from lung cancer (non-small cell and small cell combined) in the United States in 2015:

* New cases: 221,200
* Deaths: 158,040

**Risk Factors:** Lung cancer has several known risk factors with the most important being smoking, second hand smoke, radon exposure, asbestos exposure (home and work), personal history of radiation treatment (chest or breast), and genetic factors (positive family history) [3]. Additional risk factors with consistent evidence of increased lung cancer risk include: older age, acquired lung diseases (COPD -2.8 times increased risk 95% CI, 1.8-4.4), TB, pneumoconiosis, idiopathic pulmonary fibrosis (7 times increased risk) and systemic sclerosis [1]. HIV infection increases lung cancer risk independent of smoking by at least 2.5 fold.

 IARC has classified numerous occupational exposures as carcinogens for the lung: aluminum production, arsenic, asbestos, beryllium, bis(chloromethyl)ether, chloromethylmethyl ether, cadmium, chromium(VI), coal, coal-tar pitch, coke production, diesel engine exhaust, hematite mining, iron and steel founding, nickel , painting, plutonium, radon-222 and its decay products, rubber production industry, crystalline silica dust, soot, sulfur mustard, secondhand tobacco smoke, X-radiation, and gamma-radiation. There is limited evidence for strong inorganic acid mists, manufacture of glass, exposure to oxidized and hard bitumens, carbon electrode manufacture, alpha-chlorinated toluenes and benzoyl chloride, cobalt metal with tungsten carbide, creosotes, occupational exposures in spraying and application of insecticides, printing processes, 2,3,7,8-tetrachlorodibenzopara-dioxin, welding fumes, or living where there is air pollution [4].

The CDC reports that tobacco smoke contains a mix of more than 7,000 chemicals. Hundreds are toxic and approximately 70 are carcinogenic. The most important, based on their carcinogenic potency and established levels in cigarette smoke, were polycyclic aromatic hydrocarbons, N-nitrosamines, aromatic amines, 1,3-butadiene, benzene, and various aldehydes [5]. The ATSDR Tox Guide for Benzene states: “About 50% of the entire nationwide exposure to benzene results from smoking tobacco or from exposure to tobacco smoke.” The ATSDR Public Health Statement reports: “The average smoker (32 cigarettes per day) takes in about 1.8 milligrams (mg) of benzene per day. This amount is about 10 times the average daily intake of benzene by nonsmokers.”

The American Cancer Society states that at least 80% of lung cancer deaths are thought to result from smoking, and this number is probably even higher for small cell lung cancer. The risk of lung cancer in smokers relative to non-smokers is in the order of over 20 fold [6]. The greater the length and quantity of smoking, the greater the cancer risk. Former smokers continue to have an elevated risk for lung cancer years after quitting. There is not a decrease in risk until 5 years of smoking cessation. During the first 5 years following stopping smoking, the risk of former cigarette smokers was high (RR = 16.1), but as cessation continued, it declined steeply. In a cohort of Veterans followed from 1954-1980, the relative risk (RR) for lung cancer for former cigarette smokers was 3.6. However, after 40 years of smoking cessation, the risk of lung cancer among former smokers has decreased, but remains elevated compared with never smokers [1]. The cumulative lung cancer risk among heavy smokers may be as high as 30 percent, compared with a lifetime risk of lung cancer of 1 percent or less in never smokers.

Second hand smoke can increase the risk for developing lung cancer [7]. A 2014 pooled analysis of 18 case-control studies found that among never smokers, the odds ratios (OR) comparing those ever exposed to secondhand smoke with those never exposed was 1.31 (95% CI: 1.17-1.45) for all cell types combined, 1.26 (95% CI: 1.10-1.44) for adenocarcinoma, 1.41(95% CI: 0.99-1.99) for squamous cell carcinoma, 1.48 (95% CI: 0.89-2.45) for large cell lung cancer, and 3.09 (95% CI: 1.62-5.89) for small cell lung cancer [8]. The estimated excess risk of lung cancer for never smokers married to smokers has been reported as 23-27% [2]. A more recent study reported that passive smoking during childhood increased lung cancer risk in adulthood by 3.6 fold [9].

Smoking cigars or a pipe is also associated with an increased risk of lung cancer. In a cohort study that followed pipe-only and cigar-only smokers, findings confirmed a carcinogenic effect to the lungs for both. The hazard ratio for incident cases was 3.9 for cigar smokers and 13.3 for pipe smokers [10]. The risk of lung cancer correlated with the intensity and duration of smoking. Other studies have shown similar results.

Marijuana smoke contains tar and many of same cancer-causing substances that are in tobacco smoke. Marijuana cigarettes are typically smoked all the way to the end, where tar content is the highest, are non-filtered, and inhaled very deeply [11]. The smoke is traditionally held in the lungs for a longer time than with cigarettes, which gives any cancer causing substances more opportunity to deposit in the lung. Nitrous oxides, hydrogen cyanide, and aromatic amines were present in marijuana smoke at levels 3-5 times higher than in mainstream tobacco smoke, while ammonia was present at levels 20 times higher than tobacco [12].

Radon is an inert gas that is produced naturally from radium in the decay series of uranium. Two of the decay products of radon emit particles that by virtue of their high energy and mass can cause damage to the DNA of cells of the respiratory epithelium. Radon enters buildings in the form of a gas derived from the soil. There is significant evidence that exposure to radon in indoor air is associated with an increased risk for lung cancer [1].

Genetic factors can affect both the risk for and prognosis of lung cancer. Individuals with a first-degree relative with lung cancer had a 2-3-fold increase in the risk of developing lung cancer, after adjustment for smoking and other potential confounders [13]. There is a similar magnitude of effect of family history on lung cancer risk in nonsmokers, suggesting familial risk for lung cancer is independent of those risks associated with cigarette smoking” [14].

**Scientific Review:**

NCR 2009 report: This reported concluded that there was limited/suggestive evidence of an association between exposures to CLCW and lung cancer. Limited and suggestive evidence of an association is defined as “evidence from available studies suggests an association between exposure to a specific agent and specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence.” Therefore, this level of proof does not rise to the level of at least as likely as not.

 In the body of this report there is no reported association between vinyl chloride and benzene and lung cancer. A recent cohort mortality study showed that there was no increased risk of lung cancer in workers exposed to vinyl chloride [15]. There is a paucity of literature on benzene and lung cancer. Benzene is a component of smoking and air pollution and thus it is difficult to isolate benzene exposure.

**Environmental Exposure Literature Review:** Extensive research of the scientific literature, found only limited data regarding environmental exposures to PERC and TCE. The study regarding health effects of contaminated drinking water in Massachusetts evaluated cancer effects. In this study, high cumulative exposure to PERC contaminated drinking water was associated with an increased risk of lung cancer. However, the authors noted that precision of association was low and dose/exposure misclassification was “almost certain” requiring follow-up with a larger study [16]. More recent PERC occupational case control studies (Vizcaya et al) continue to demonstrate inconclusive results. In response to concerns about cancer stemming from drinking water contaminated with PERC and TCE, Morgan et al. in 2002 reviewed new cases for 16 cancer types in a California community with a population of 3.3 million people (1988 to 1998) [17]. Significantly fewer cases were observed than expected for cancer of the lung and bronchus (SIR, 0.71; 99% CI, 0.61 to 0.81). In the ATSDR Trichloroethylene Subregistry health survey of people exposed to trichloroethylene and other contaminants through drinking water in up to 15 locations across five states (Illinois, Indiana, and Michigan, Pennsylvania, and Arizona), no convincing evidence of a significant association between trichloroethylene and cancer was found at baseline assessment or at several follow-up time points.

A Bove et al. study evaluated CL civilians with an average employment on base of 2.5 years [18].  They found non-statistically significant elevated rates of lung cancer in the exposed CL cohort compared to a Camp Pendleton cohort (Hazard ratio was 1.25 and the 95% confidence interval was 0.89-1.75).  Another Bove et al. study of CL marines with an average exposure of 18 months found  a slight and non-statistically significant increase in lung cancer (hazard ratio 1.16 with 95% CI of 0.96-1.40) [19].    The interpretations were not definitive as there were a low number of lung cancer deaths, the confidence intervals were wide and thus there remained a significant possibility that these findings could be due to chance alone.  In addition, lung cancer risk factors such as asbestos exposure, family history, smoking and passive smoking were not available in these studies and no definitive dose-response relationships were identified for lung cancer.  Therefore no definitive diagnostic conclusions can be drawn from this data.

**Occupational Exposure Review:** Two case-control studies of occupation and lung cancer were conducted in Montreal, and included 2016 cases and 2001 population controls [20]. When the two studies were pooled, there were indications of an increased risk of lung cancer associated with occupational exposure to perchloroethylene (OR (any exposure) 2.5, 95% CI 1.2 to 5.6; OR (substantial exposure) 2.4, 95% CI 0.8 to 7.7) and to carbon tetrachloride (OR (any exposure) 1.2, 95% CI 0.8 to 2.1; OR (substantial exposure) 2.5, 95% CI 1.1 to 5.7). No other chlorinated solvents showed both statistically significant associations and dose-response relationships. ORs appeared to be higher among non-smokers. TCE results were ambiguous. There was a non-significant indication of excess risk among those exposed at any level, especially for adenocarcinomas, but there was no evidence of excess risk among those with relatively high or long exposure. There were suggestive, albeit inconsistent, indications that occupational exposure to perchloroethylene and carbon tetrachloride may increase the risk of lung cancer. The evidence remains inconclusive on the role of these agents on lung cancer risk.

A cohort of over 6800 workers was studied over a 50 year period at the Paducah Gaseous Diffusion Plant (PGDP) in Kentucky. Trichloroethylene (TCE) used in cleaning process equipment was a concern. Analysis of the data found a low SMR (0.75, 95% CI: 0.72-0.79) for trachea, bronchus, and lung cancer. Lung cancer results reflected regional mortality patterns [21].

A Swedish study sought to determine carcinogenic risks associated with occupational exposure to perchloroethylene (PERC). A national cohort of dry-cleaning and laundry workers comprised of over 10,000 members identified in 1984 were monitored for new cancer diagnoses for 21 years. Over 90% follow-up was completed for the cohort. The authors concluded that “no clear associated between PERC exposure and subsequent cancer morbidity in workers was evident from this historical prospective cohort” [22].

A recent 2014 analysis conducted using data from one of the largest population-based, case–control studies investigating occupational risk factors in respiratory cancer, the ICARE study, did not suggest any association between TCE and lung cancer [23]. Results suggest that exposure to PCE may constitute a risk factor for lung cancer, especially among females, who seemed to have a higher prevalence of exposure than males. The authors preferred to focus on the consistency of the results rather than their statistical significance. These results suggest that the exposure to PCE may be a risk factor for lung cancer; however the results are not statistically significant and further investigations are necessary to replicate these results in a larger exposed population.

Summary:

Exposure to cigarette smoke is by far the greatest risk factor for the development of lung cancer. Several environmental studies have documented no increase lung cancer risk from environmental exposure to the solvents found in CLCW. Literature also suggests that there is no conclusive evidence for an association between lung cancer and occupational exposure to solvents. Occupational exposure is typically more extensive than environmental exposure, suggesting no increased risk for lung cancer from exposure to the solvents found in CLCW.

Literature review:

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ADDITIONAL REFERENCES (FOR USE ON CASE SPECIFIC BASIS-REMOVE UNWANTED PRIOR TO SUBMISSION):

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