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: Dr.

**Member, Subject Matter Expert Panel**

Camp Lejeune Contaminated Water Project

Time Dedicated to this review: XXX Minutes

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

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

Contention 1: Bladder cancer

Diagnosis 1:

Nexus: The diagnoses above Choose an item.

**Case Specific Discussion**:

Smoking:

Other risk factors:

Days at CL:

Age:

Gender:

Dates of Military Service:

MOS:

Dates at CL:

Occupational Hx:

Family HX:

DX:

Age at Dx:

Disease status-Active, Treated<5, Remission>5

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

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

**VBMS/Claims file review ( files):**

**VVA/VistA/CPRS review**:

**Other possible 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

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**Disease Specific Discussion, Bladder Cancer:**

**Disease Description:** Bladder cancer is cancer which arises from the cell of the urinary bladder. Urothelial (transitional cell) carcinoma if the most common form of bladder cancer accounting for approximately 90% of all bladder cancers. Other less common types of bladder cancer include small cell carcinoma, squamous cell carcinoma, and adenocarcinoma. These later two types of cancer are frequently due to chronic irritation and inflammation.

Incidence: In 2015, there were a projected 74,000 new cases in the US. The rates of new cancers have been falling over the last 10 years, while death rates have been stable [1].

About 9 out of 10 people with this cancer are over the age of 55. Median age of diagnosis is 73 years of age, with increasing incidence with age. Men have a three to four time greater chance of developing bladder cancer than women. White males have twice the incidence of black males.

**Risk Factors:** The National Cancer Institute reports the following risk factors:

•Using tobacco, especially smoking cigarettes.

•Having a family history of bladder cancer.

•Having certain changes in the genes that are linked to bladder cancer.

•Being exposed to certain chemicals in the workplace.

•Past treatment with certain anticancer drugs, such as cyclophosphamide or ifosfamide, or radiation therapy to the pelvis.

•Drinking well water that has high levels of arsenic.

•Drinking water that has been treated with chlorine.

•Having a history of bladder infections.

•Using urinary catheters for a long time i.e. spinal cord injuries.

Cigarette smoking is the greatest risk factor for development of bladder cancer. The Centers for Disease Control (CDC) reports that tobacco smoke contains a mix of more than 7,000 chemicals; hundreds are toxic and approximately 70 are carcinogenic. Tobacco smoking is classified by The International Agency for Research on Cancer (IARC) as a cause of bladder cancer [2]. The American Cancer Society reported in June2015 that “Approximately half of the deaths from cancers of the oral cavity, esophagus, and urinary bladder were due to smoking” [3]. Burger et al (2013) also noted that smoking is the most important risk factor for bladder cancer and accounts for approximately one-half of all cases [4]. Bladder cancer risk is 3.8 times higher in current smokers compared with never-smokers, a meta-analysis of cohort studies showed (Freedman et al. 2011); while the WHO reports a 2-6 fold increase in smokers [5]. The Freedman study indicated that the proportion of bladder cancer cases attributable to ever-smoking is 66% for all men and 73% for men younger than 60. Stopping smoking will decrease the risk for bladder cancer, but even after 25 years of abstinence the risk does not return to the level of never-smokers. Second hand smoke exposure, for greater than 10 years, doubles the risk of developing bladder cancer in women [6]. To summarize, smoking has consistently been shown to be the greatest overall risk factor for the development of bladder cancer [7, 8].

Smoking of cigars and pipes has also been found to be carcinogenic to the urinary bladder. A European pooled analysis found the odds ratio for cigarette smoking was 3.5, for pipe smoking was 1.9 (95% CI 1.2-3.1), and cigar smoking was 2.3 (95% CI 1.6-3.5) [9]. Cannabis use has been associated with an increased risk of bladder cancer, prostate cancer and nonseminomatous germ cell tumors in case–control studies [10].

A cohort study by Frank et al. reported that bladder cancer risk is 1.8 times higher in people with a first-degree relative (parent, sibling, child) with the disease, compared with the general population [11].

Other prominent life-style risk factors for bladder cancer include metabolic syndrome, obesity and diabetes [12-21] A large meta-analysis in 2012 analyzed 166 datasets from 43 articles, including 38,940 cases of cancer, which found the presence of metabolic syndrome was associated with bladder cancer in men (1.10, p=0.013) [14]. In the Metabolic Syndrome and Cancer project (Me-Can), during a mean follow-up of 11.7 years, hypertension and a composite metabolic syndrome score were significantly but modestly associated with an increased risk of bladder cancer among men [15]. The 2015 meta-analysis by Sun et al. indicates that (overweight) has a statistically significant 7% increased risk of bladder cancer, while obesity increases the risk of bladder cancer by approximately 10%. The dose-response meta-analysis suggests a linear association between BMI and bladder cancer, and showed each 5 kg/m2 increment of BMI corresponded to a 4.2% increase in risk of bladder cancer [16]. Diabetes has also been implicated in modestly increasing the risk of bladder cancer in men (especially those with DM of 16 years duration or more) [17]. In addition the diabetes drug pioglitazone has been implicated in slight-to-modest increase in the risk of bladder cancer [22, 23].

Bladder cancer risk is elevated in individuals previously treated for cancer of the larynx, lung, head and neck, prostate, testicular, cervical and kidney, cohort studies have shown. This is likely attributed to the effects of radiotherapy or chemotherapy treatment, and shared risk factors with the first cancer, including smoking. Cyclophosphamide (Cytoxan, Revimmune) used to treat systemic sclerosis, leukemia and lymphomas is classified by IARC as a cause of bladder cancer. The risk of bladder cancer is higher in people with spinal cord injuries which may be due to indwelling catheters, UTI or bladder calculi [24]. A 3.18-fold higher SIR (95% confidence intervals (CI): 1.34-7.53, P=0.008) for bladder cancer in patients following renal transplantation compared with the general population has been reported [25].

Kotros et al reported that carcinogenic compounds have also been identified in hair dyes [26]. They found that a fivefold increase in risk of bladder cancer was observed in individuals who worked for 10 or more years as hairdressers or barbers. This increase in risk does not appear to extend to personal users of such hair dyes.

The International Agency for Research on Cancer (IARC) Working Group concluded that there was sufficient evidence in humans for the carcinogenicity of diesel exhaust (Group 1). In addition, the Working Group found that diesel exhaust has “a positive association (limited evidence) with an increased risk of bladder cancer” [27]. An evaluation specifically of exposure to diesel exhaust was done in a pooled analysis of European case-control studies and four more studies in Canada, Belgium, and Sweden. All five studies identified the highest risk among those with the greatest exposures, although overall the risk was only modest [28].

**Scientific Review:**

The link between oral exposure to trichloroethylene (TCE) and the incidence of cancer in humans remains controversial [29]. The EPA concluded that TCE is carcinogenic to humans by all routes of exposure based on exposure in humans and kidney cancer (EPA 2011e). The IARC has reclassified TCE as “carcinogenic to humans” (IARC 2012). The EPA (2012a) considers tetrachloroethylene (PERC) “likely to be carcinogenic to humans by all routes of exposure” based on suggestive evidence in human studies and clear evidence in animal studies. The IARC considers PERC a “probably carcinogenic to humans” based on limited evidence in humans and sufficient evidence in animals.

The ATSDR Draft Toxicological Profile for Trichloroethylene (TCE) (October 2014) does not list bladder cancer as a complication; while the ATSDR Draft Toxicological Profile for Tetrachloroethylene (PERC/PER) (October 2014) reported that studies in humans suggest that exposure to tetrachloroethylene might lead to a higher risk of getting bladder cancer; but the evidence is not very strong.

The 2009 NRC reported concluded that there was limited/suggestive evidence of an association between trichloroethylene (TCE) or tetrachloroethylene (PERC/PCE) and bladder cancer [30]. 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 more likely than not or equipoised evidence. In the body of this report there is no reported association between vinyl chloride and benzene and bladder cancer.

**Environmental Exposure literature Review**: A PubMed search of literature for TCE/PERC/VC and benzene was conducted, focusing on literature primarily after 2008 and thus after the NRC report. Extensive research of the scientific literature found only limited data regarding environmental exposures to PERC and TCE.

After trichloroethylene and tetrachloroethylene were identified in the drinking water supply of two towns in Finland (1991-1992), the incidence rates of total cancer were compared with the rest of the country [31]. No significant difference was found. In response to concerns about cancer stemming from drinking water contaminated with ammonium perchlorate and trichloroethylene, Morgan et al. assessed observed and expected numbers of new cancer cases for all sites combined and 16 cancer types in a California community from 1988 to 1998, to include bladder cancer. These findings did not identify a generalized cancer excess [32]. Studies regarding health effects of contaminated drinking water in Massachusetts evaluated for cases of cancer and found no elevated risk of bladder cancer [33, 34]. 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 [29]. The Bove et al study of Marines with an average exposure duration of 18 months in CL did not find elevated rates of bladder cancer in exposed CL marines compared to a cohort of unexposed Camp Pendleton controls; the Hazard Ratio of bladder cancer in the exposed CL cohort compared to the unexposed cohort of Camp Pendleton marines was less than one [35]. The Bove et al study of CL civilians exposed for an average of 25 months found similar findings [36]. These findings do not support a causal association between exposure to CLCW and bladder cancer.

**Occupational Exposure Literature Review:** Occupations that have been linked to an increased risk of bladder cancer include metal workers, machinists, painters, rubber industry workers, leather workers/shoe makers, textile industry workers, transport workers, printers, hairdressers and dry cleaners. Exposures associated with an increased risk in these occupations/industries include polycyclic aromatic hydrocarbons (PAHs), diesel exhausts, paints, dyes, chlorinated hydrocarbons and other solvents, metal and industrial oils/cutting fluids.

A meta-analysis of dry cleaning worker studies evaluating PERC exposure and bladder cancer risk by Vlaanderen et al. (2014) demonstrated an increased risk of bladder cancer in dry cleaners (smoking-adjusted studies, the mRR was 1.50 (95% CI: 0.80, 2.84; 4 case-control studies), reported in both cohort and case-control studies, and some evidence for an exposure-response relationship [37]. Dry cleaners were noted to be exposed to a mix of solvents. The higher risk of bladder cancer in dry cleaners may have been due to tetrachloroethylene (PERC) exposure, the primary solvent used in dry cleaning. However, with limited evidence from studies that specifically assessed exposure to tetrachloroethylene, this hypothesis could not be corroborated.

In the Montreal case control studies (Christensen et al. 2013) the authors found there was little evidence that exposure to chlorinated solvent (including TCE and PERC) exposures was associated with an increased risk of bladder cancer [38].

In a large, long-term cohort follow-up study of aircraft workers exposed to TCE, PERC, chromates and mixed solvents, Lipworth et al (2011) reported no consistent evidence of increased cancer risk overall or by site, including those with long-term exposure to TCE, PERC and mixed solvents [39].

Colt et al (2011) found an increased risk of bladder cancer in “men reporting use of metal working fluids (MWF).” These fluids could contain chemicals similar to those found in CLCW, however, changes over time in the composition and prevalence of use of the different MWF make it difficult to identify the components potentially associated with bladder cancer. The OR was =1.7 (95% CI: 1.1, 2.5). The occupations showing statistically significant association were with exposures greater than 10 and/or 15 years. The rates for metalworkers showed significance at 5-10 years, but not after 10 years, which argues against a dose response relationship. The exposure was based on “lifetime” occupational exposure which would most likely significantly exceed the environmental exposure due to service at Camp Lejeune [40].

The 2011 historically prospective cohort study of cancer morbidity in Swedish dry-cleaners and laundry workers noted that there was no significant excess of cancer of the urinary bladder. The authors concluded that no clear association between PERC exposure and subsequent cancer morbidity in the workers was evident [41].

The Clavert et al. (2010) mortality study of dry cleaning workers reported an increased risk of bladder cancer among those with both 5 or more years of employment in PERC-using shops and 20 or more years of latency [42]. However, limitations included that some members were exposed to “other” dry cleaning solvents in addition to PERC. There was no available information on confounders such as smoking and alcohol consumption. In addition diagnoses on death certificates may be erroneous or incomplete, leading to disease misclassification.

**SUMMARY**

Transitional (urothelial) carcinoma of the bladder is the most frequent bladder cancer. Cigarette smoking is the strongest known risk factor for developing bladder cancer. The environmental studies cited have not found an association between environmental exposures to chemicals found in CLCW and bladder cancer. Some occupational studies have suggested that there is an increased risk of bladder cancer with exposure to PERC. The levels of exposures higher than exposures found at Camp Lejeune

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