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

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

Contentions 1: Renal cancer

Diagnosis 1:

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**:

**VistaWeb/CAPRI/VVA review:**

**Other possible risk factors:**

Employment history prior to military service:

Smoking:

Alcohol use:

Obesity:

Genetic:

Employment history after military service:

Hobbies/ recreational leading to possible chemical exposure:

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**DISEASE DISCUSSION:**

Disease Description: Kidney cancer and renal cell cancer are two terms meaning a cancer that forms in tissues of the kidneys. The terms kidney and renal cancers are used interchangeably. Renal cell cancer (also called kidney cancer or renal adenocarcinoma) is a disease in which malignant (cancer) cells are found in the lining of tubules (very small tubes) in the kidney and renal pelvis carcinoma (cancer that forms in the center of the kidney where urine collects). It also includes Wilms tumor, which is a type of kidney cancer that usually develops in children under the age of 5 and will most likely not be relevant for CLCW case discussions.

Incidence of renal cell carcinoma: Malignant tumors of the kidney and renal pelvis account for approximately 3.7% of all new primary cancer cases diagnosed in the United States. Rates for new kidney and renal pelvis cancer cases have been rising on average 1.4% each year over the last 10 years. Renal cell carcinoma (RCC) is approximately 50 percent more common in men compared with women. RCC occurs predominantly in the sixth to eighth decade of life with median age at diagnosis of 64, according to 2008 to 2012 NCI's Surveillance, Epidemiology and End Results (SEER) Cancer Statistics Review [1].

Estimated new cases and deaths in the United States in 2015[1]

New cases:

Deaths: 13,680

The median age at diagnosis is 64; with the majority of new cases being diagnosed between 55-64 years of age.

**Risk Factors**:

•Older age

•Smoking

•Obesity

•High blood pressure

•Prior treatment for kidney failure

•Using certain pain medicines, including over-the-counter pain medicines, for a long time.

•Having certain genetic conditions, such as von Hippel-Lindau disease or hereditary papillary renal cell carcinoma

In RCC the major established etiological risk factors to account for approximately 50% of cases include cigarette smoking, obesity, HTN and diabetes [2]. Tobacco smoking is the single best recognized risk factor for kidney cancer and obesity is the second [3]. Most case-control and cohort studies have reported significant associations with cigarette smoking, with relative risks ranging from 20% to

threefold, and significant dose-response trends. Kidney cancer risk increases with the amount smoked; it is 58-103% higher in those who smoke more than 20 cigarettes per day, compared with never-smokers, a meta-analysis showed [4]. In addition, Theis et al. noted prolonged exposure to second hand smoke has also been identified as a risk factor for RCC. An approximate 40% reduction in risk after 16 or more years of smoking cessation is reported by Cote et al (2012) [5].

The Macleod study identified a significant association of renal cell carcinoma with obesity, smoking, hypertension, and renal disease [6]. The Chow article states these risks are independent and individuals with both conditions (overweight and hypertension) have a much higher risk for renal cancer [7].

Weight and RCC risk appear to follow a dose dependent relationship. The most pronounced increased risk is seen in obese patients (BMI > 30, RR 2.5.). “Compared with healthy BMI (18.5 – 24.9), being obese (BMI 30 – 39) was associated with an 80% increase in RCC risk for both men (OR = 1.8; 95% CI: 0.9 – 3.6) and women (OR = 1.8; 95% CI: 1.0 – 3.3)” [8]. A population-based case control study of Los Angeles county demonstrated a greater than 4-fold risk of RCC in the extremes of BMI (>30). For European and US populations, the percentage of RCC cases attributable to obesity are 31.1% and 42.5%, respectively [9]. The American Cancer Society also reports that obesity results in up to 30% of RCC. The Goodman study noted that the increased risk for kidney cancer from obesity was calculated to be 2.7 (95% confidence interval (CI) = 1.5-5.9) among men with a BMI of 28 or more [10]. In the Stocks et al. pooled study of seven European cohorts, high levels of a metabolic risk score of five components—BMI, blood pressure and plasma levels of glucose, total cholesterol and triglycerides—were related to increased overall risks of cancer incidence and mortality in men and in women. The largest study to date on the joint influence of metabolic factors on risk of separate cancers showed increased risks for several cancers, in particular renal cell and liver cancer in men and endometrial and pancreatic cancer in women [11]. Kidney cancer risk among women is 38% higher in those who are overweight and 95% higher in those who are obese, a meta-analysis showed [12].

Hypertension has been a well-recognized risk factor for renal cancer since the 1990's. Hypertension has been extensively studied with significant agreement among epidemiologists. One case control study (Colt-2011) showed that Hypertension doubled renal cancer risk (OR=2.0 [CI=1.7–2.5]) overall. The ORs increased with time after hypertension diagnosis reaching up to 4.1. [13]. Studies have also shown a dose-dependent increase in RCC risk with increasing blood pressure. In one European study, hypertensive patients in the highest risk category (systolic blood pressure 160 vs.120) were 2.4-fold more likely to develop RCC[9]. Hypertension predisposes to RCC development, which seems to be independent of anti-hypertensive medications or obesity.

Kidney cancer risk is 40% higher in diabetics compared with non-diabetics; meta-analyses have shown that kidney cancer risk among diabetics may be higher in insulin users than non-users [14, 15].

Other potential risk factors described in the literature include analgesic use (>20 years), long term hemodialysis, hormonal/reproduction factors, diet, family history of RCC, and other genetic conditions.

A September 2014 study (Cheungpasitporn-2014) showed that men with a history of renal stones had an increased risk of developing RCC [16]. Kidney cancer risk among men is 41% higher in those with kidney stones.

 Kidney cancer risk is 3.6 times higher in people with end stage renal disease receiving dialysis, and risk increases with the number of years on dialysis, a cohort study showed [18].

Complex renal cysts (as opposed to simple cysts) are associated with an increased risk of malignancy. Category IIF Bosniak need close follow-up to watch for malignancy. In one study, the malignancy rate in surgically excised Bosniak IIF and Bosniak III cystic renal lesions was 25% and 54%, respectively [19].

Renal cell carcinoma risk is 2.2-2.6 times higher in people with a first-degree relative with kidney cancer, a meta-analysis showed [20]. Renal cell carcinoma risk is higher in people whose parent have a history of lung or prostate cancer, and those whose sibling have a history of bladder or thyroid cancer, melanoma, or non-Hodgkin lymphoma.

**Scientific Review:**

“Occupational exposure to toxic compounds, such as cadmium, asbestos, and petroleum by-products, has been associated with an increased risk of RCC. In one international multicenter study of over 1700 patients with RCCs and 2300 controls, an increased risk of cancer was observed in those exposed to asbestos (RR 1.4, 95% CI 1.1-1.8), cadmium (RR 2.0, 95% CI 1.0-3.9), and gasoline (RR 1.6, 95% CI 1.2-2.0). Cadmium workers who smoke may have a particularly high incidence of RCC. Studies of occupational exposures are often limited by the lack of specific exposure details.” [2].

Exposure to trichloroethylene is classified by IARC and EPA as a cause of kidney cancer. The link between oral exposure to trichloroethylene and the incidence of cancer in humans remains controversial [21]. In the National Academies Press, National Research Council (NRC) document: Contaminated Water Supplies at Camp Lejeune dated 2009, referenced are studies of similarly exposed populations [22]. These are detailed on pages 165-179, and are further delineated in tables 6-1 and 6-2 of the document. Levels of exposure in these study populations are comparable to those modeled at Camp Lejeune. In the context of human occupational and animal toxicological studies, the potential exposure of human populations at Camp Lejeune is considered as being "low" and epidemiologic studies of human populations exposed to solvents in the drinking water have not documented any increased incidence of renal cancers.

Raaschou-Nielsen et al. (2003) reported an SIR of 1.6 (95% CI, 1.1-2.3) for occupational TCE exposure in men employed for 5 years or more. The studies of PCE showed no increased risk [23]. A retrospective cohort study conducted by Zhao, et al., 2005 found an increased risk of kidney cancers with TCE exposure, however, the increased risk was only at the highest exposure levels for a duration of at least 2 years and exposure assessments were based on a job exposure matrix which has yet to be validated. The lack of validation raises doubts about the validity and accuracy of the findings.

Other studies have been performed regarding trichloroethylene (TCE), PCE and mixed solvents. One large, long-term cohort study with comprehensive exposure assessment found no consistent evidence of increased cancer risk overall or by site among aircraft workers, including those with long-term exposure to TCE, PCE, and mixed solvents . The Lipworth study had a cohort of 77,943 workers. They utilized a comprehensive exposure assessment method, lacking in most other studies. There were over 5400 aircraft manufacturing workers with known exposure to TCE allowing for a robust and reliable assessment of the associations of TCE. The workers were followed for mortality for almost a half century [24].

A meta-analysis of occupational risk for TCE exposure and the development of renal cancer showed a significant association only among workers with the longest duration of exposure (5+ years and 10+ years) but not among workers with a shorter exposure duration (<1 year and <10 years).” [25]. . Chow et al (2010) reported that the difficulties in determining the mode of action and pharmokinetic complexities of TCE, solvent co-exposures and study limitations preclude establishment of a causal conclusion.

A recent case control study (Christensen 2013) looked at the risk of several cancers upon exposure to solvents. To be classified as exposed to solvent at the "substantial" level, a subject had to have been exposed at a frequency of medium or high, and duration greater than 5 years. All other exposed subjects were then classified in the "nonsubstantial category.” The odds ratio for renal cancer after exposure to TCE or several other chlorinated solvents all include 1 in the confidence interval. Thus, there was no significant increased risk from exposure, even at a substantial level, which would have been working around the solvents daily for at least 5 years [26].

A recent analysis of 3 cohort studies (Hansen 2013) showed no increase in risk for developing renal cell cancer for those working directly with TCE. The median duration of employment in the company with TCE exposure was 6 years [27].

Industries which have been associated with an elevated renal cancer risk include employment in dry cleaning, agricultural and food, petroleum and gasoline, paper and printing/publishing, and the automotive industries. Considerable interest has been focused on the solvent trichloroethylene (TCE), largely as a result of findings in animals and of several studies conducted in Germany, which were initiated in response to clusters of renal cell cancer cases. These reported a strong correlation for renal cell cancer associated with TCE exposure. In addition, the mode of action for TCE in the kidney has been an area of ongoing investigation. This research has indicated that TCE exposure is associated with an increased renal cancer risk limited to individuals with a particular genotype (GST) required for the reductive metabolism of TCE. “Extensive epidemiologic cohort studies of TCE-exposed workers do not indicate significant increases in cancer incidence, but case-control studies suggest that prolonged exposure to high concentrations of TCE (hundreds to thousands of ppm) can increase the incidence of renal cancer” [28]. TCE was classified as carcinogenic to humans by the IARC Working Group in October 2012. The 2013 Hansen et al. analysis of workers in three Nordic cohort studies exposed to TCE, found no association between TCE and kidney cancer. It was determined that if TCE is a risk factor for kidney cancer, it was only at extremely high levels of exposure. This same year, Vlaandern et al performed an analysis of occupational exposures in four Nordic countries for TCE and PCE found no association between these exposures and kidney cancer [29].

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 [30].

The Bove et al study evaluated a cohort of CL civilians with an average employment on base of 2.5 years [31]. They found slightly elevated rates (which did not reach statistical significance) of renal cancer in the exposed CL cohort compared to the control Camp Pendleton(CP) cohort [Hazard ratio (HR) was 1.92 and the 95% confidence interval (CI) was .58-6.34]. In addition, a Bove et al study of CL marines with an average exposure of 18 months found a similar slight increase in renal cancer rates (which also did not meet statistical significance ) compared to a CP control cohort (HR was 1.35 with 95% CI of .84-2.16) [32]. The interpretations were not definitive as the confidence intervals were wide and thus there remained a significant possibility that these findings could be due to chance alone. In addition, renal cancer risk factors such as obesity, hypertension, and smoking were not available in these studies. While these studies do not rule out a causal effect of CLCW exposure on renal cancer, no definitive diagnostic conclusions can be drawn.

Literature review:

1. National Cancer Institute: PDQ® Renal Cell Cancer Treatment. Bethesda, MD: National Cancer Institute. Date last modified 05/12/2015. Available at: [http://www.cancer.gov/types/kidney/patient/kidney-treatment-pdq. Accessed 05/26/2015](http://www.cancer.gov/types/kidney/patient/kidney-treatment-pdq.%20Accessed%2005/26/2015).
2. Occupational Cancers, S. Anttila, P. Boffetta. Springer 2014
3. A Quick Guide to Cancer Epidemiology, P. Boffetta et all, Springer 2014
4. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. Hunt JD, van der Hel OL, McMillan GP, et al. Int J Cancer 2005; 114:101-8
5. Cigarette smoking and renal cell carcinoma risk among black and white Americans: effect modification by hypertension and obesity, Michele L. Cote et al., Cancer Epidemiol Biomarkers Prev. 2012 May ; 21(5): 770–779
6. Risk factors for renal cell carcinoma in the VITAL study. Macleod LC, Hotaling JM, Wright JL, Davenport MT, Gore JL, Harper J, White E. J Urol. 2013 Nov; 190(5):1657-61.
7. Epidemiology and risk factors for kidney cancer. Wong-Ho Chow, Senior Investigator,\* Linda M. Dong, postdoctoral fellow, and Susan S. Devesa, contractor and former Senior Investigator. Nat Rev Urol. 2010 May; 7(5): 245–257.
8. Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population-based case-control study, Theis RP, Dolwick Grieb SM, Burr D, Siddiqui T, Asal NR, BMC Cancer. 2008; 8:387
9. Environmental and modifiable risk factors in renal cell carcinoma. Nevai N and Wood CG. Urologic Oncology: Seminars and Original Investigations 30 (2012) 220–224
10. A case control study of factors affecting the development of renal cell cancer. Goodman, M.T., Morgenstern, H., and Wynder, E, .L., Amer. J. Epidemiol., 124,926-941 (1986).
11. Metabolic risk score and cancer risk: pooled analysis of seven cohorts, Tanja Stocks et al., International Journal of Epidemiology, 2015, 1–11.
12. Body mass index and risk of renal cell cancer: A dose-response meta-analysis of published cohort studies. Wang F, Xu Y., Int J Cancer 2014
13. HYPERTENSION AND RISK OF RENAL CELL CARCINOMA AMONG WHITE AND BLACK AMERICANS. Colt, J., Epidemiology. 2011 November ; 22(6): 797–804
14. CARING (Cancer Risk and Insulin analogues): The Association of Diabetes Mellitus and Cancer Risk with Focus on Possible Determinants- a Systematic Review and a Meta-Analysis. Starup-Linde J, Karlstad O, Eriksen SA, et al. Curr Drug Saf 2013.
15. Diabetes mellitus and incidence and mortality of kidney cancer: a meta-analysis. Bao C, Yang X, Xu W, et al. J Diabetes Complications 2013;27(4):357-64.]
16. The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis. Cheungpasitporn W1, Thongprayoon C2, O'Corragain OA2, Edmonds PJ2, Ungprasert P2, Kittanamongkolchai W2, Erickson SB2QJM. 2014 Sep 9.
17. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. Stewart JH, Buccianti G, Agodoa L, et al. J Am Soc Nephrol 2003;14:197-207
18. Bosniak Category IIF and III Cystic Renal Lesions: Outcomes and Associations Smith, A. RSNA Radiology.. January 2012. 262 (1).
19. Family history and risk of renal cell carcinoma: results from a case-control study and systematic meta-analysis. Clague J, Lin J, Cassidy A, et al. Cancer Epidemiol Biomarkers Prev 2009;18:801-7.
20. TOXICOLOGICAL PROFILE FORTRICHLOROETHYLENE-DRAFT, Agency for Toxic Substances and Disease Registry, October 2014].
21. Epidemiologic Studies of Solvent-Contaminated Water Supplies," Contaminated Water Supplies at Camp LeJeune: assessing Potential Health Effects, National Research Council of the National Academies. The National Academies Press, Washington, D.C. 2009.
22. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. Raaschou-Nielsen O, Hansen J, McLaughlin JK, Kolstad H, Christensen JM, Tarone RE, Olsen JH. Am J Epidemiol. 2003 Dec 15;158(12):1182-92.
23. Cancer mortality among aircraft manufacturing workers: an extended follow-up. Lipworth L., J Occup Environ Med. 2011 Sep; 53(9):992-1007
24. Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis. Karami S, Lan Q, Rothman N, et al. Occup Environ Med. 2012; 69(12):858-67.
25. Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal. Christensen KY, Vizcaya D, Richardson H, Lavoué J, Aronson K, Siemiatycki J., J Occup Environ Med. 2013 Feb;55(2):198-208.
26. Risk of cancer among workers exposed to trichloroethylene: analysis of three Nordic cohort studies. Hansen J1, Sallmén M, Seldén AI, Anttila A, Pukkala E, Andersson K, Bryngelsson IL, Raaschou-Nielsen O, Olsen JH, McLaughlin JK. , J Natl Cancer Inst. 2013 Jun 19; 105(12):869-77.
27. Cancer Epidemiology and Prevention, 3rd Ed. Schottenfeld D, Fraumeni JF (eds). New York: Oxford University Press, 2006
28. Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries. Vlaanderen J, Straif K, Pukkala E, Kauppinen T, Kyyrönen P, Martinsen JI, Kjaerheim K, Tryggvadottir L, Hansen J, Sparén P, Weiderpass E., Occup Environ Med. 2013 Jun;70(6):393-401.
29. Agency for Toxic Substances and Disease Registry 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005
30. Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study, Bove et. al. Environmental Health 2014, 13:10
31. Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study. Bove FJ, Ruckart PZ, Maslia M, Larson TC. Environ Health. 2014 Feb 19; 13(1):10.

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

* Epidemiology, Pathology, and Pathogenesis of Renal Cell Carcinoma. Nov 2014. Up To Date
* Mandel JS, McLaughlin JK, Schlehofer B, et al. International renal-cell cancer study. IV. Occupation. Int J Cancer 1995; 61:601.
* Maclure M. Asbestos and renal adenocarcinoma: a case-control study. Environ Res 1987; 42:353.
* McLaughlin JK, Blot WJ, Mehl ES, et al. Petroleum-related employment and renal cell cancer. J Occup Med 1985; 27:672.
* Sørensen HT, Nørgård B, Friis S, et al. [Non-steroidal anti-inflammatory agents and prevention of colorectal cancer and other types of cancer]. Ugeskr Laeger 2003; 165:1260.
* Cho E, Curhan G, Hankinson SE, et al. Prospective evaluation of analgesic use and risk of renal cell cancer. Arch Intern Med 2011; 171:1487.
* Gulf War and Health: Volume 2. Insecticides and Solvents (2003). Committee on Gulf War and Health: Literature Review. Board on Health Promotion and Disease Prevention (HPDP). Institute of Medicine (IOM)
* Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. Arch Physiol Biochem. 2008 Feb;114(1):71-83.
* Eggers H, Kuczyk MA, Schrader AJ, Steffens S. Influence of obesity on urological malignancies. Urologe A. 2013 Sep;52(9):1270-5.
* Stewart SB, Freedland SJ. Influence of obesity on the incidence and treatment of genitourinary malignancies. Urol Oncol. 2011 Sep-Oct;29(5):476-86.
* Muscat JE, Hoffmann D, Wynder EL. The epidemiology of renal cell carcinoma. A second look.ancer. 1995 May 15;75(10):2552-7.
* Lipworth L, Tarone RE, McLaughlin JK. The epidemiology of renal cell carcinoma. J Urol. 2006 Dec;176(6 Pt 1):2353-8.