ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases. September 11, 2015. (DRAFT)

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Overview

This review is intended to assist the VA in making policy decision regarding the relationship between drinking water exposures to chemicals at Camp Lejeune and various health effects. The results of this review represent ATSDR's assessment of the state of evidence at this time and we recognize that classifications used and the strength of evidence are subject to differing opinions and interpretations.

The drinking water serving the main portion of the base at Camp Lejeune was contaminated with measured levels of trichloroethylene (TCE) as high as 1,400 ppb as well as contaminants such as tetrachloroethylene (also known as perchloroethylene or PCE), vinyl chloride and benzene. Another drinking water supply serving the Tarawa Terrace housing area at Camp Lejeune was contaminated with measured PCE levels as 215 ppb. ATSDR has been tasked to provide the U.S. Department of Veteran Affairs (VA) with an assessment of the strength of the evidence for causal links between these contaminants and specific diseases. This report summarizes the evidence for 18 diseases for which there is at least some epidemiological evidence for an association with one or more of these contaminants.

ATSDR has developed tables for each disease that list the results from any meta-analyses that have been performed as well as epidemiological studies that were not included in meta-analyses because they appeared after the meta-analyses were conducted. These studies are mostly of workers exposed to these chemicals as well as the few drinking water studies that evaluated exposures to these chemicals. In addition, studies that have information on exposure duration, exposure intensity and/or cumulative exposure are included even if they were evaluated in a meta-analysis. Following each table, ATSDR provides its assessment of the evidence provided in the tables as well as assessments made by other agencies mandated to evaluate the health effects of these chemicals: EPA, NCI, NTP and IARC. Although the evidence from epidemiological studies is emphasized, the findings from animal studies, mechanistic studies, and other toxicological information is mentioned if necessary to support our conclusions.

The report provides a summary table listing each disease and ATSDR's conclusion concerning the evidence in bold type. Our conclusions are heavily influenced by the recent meta-analyses and/or the reviews conducted by IARC (100F, 2012; 106, 2014; Vlaanderen et al 2014), EPA (2011, Scott et al 2011), NCI (Karami et al 2012, 2013,) and NTP (2015).

Our assessment of the evidence for each disease uses the following classifications: "Sufficient evidence for causation", "Modest evidence for causation", "Sufficient evidence of an association", and "Limited/Suggestive evidence of an association".

Our classification of "**sufficient evidence for causation**" is similar to the IARC Group 1 classification: (1) there is sufficient evidence from human studies in which chance and biases (including confounding) can be ruled out with reasonable confidence, **or** (2) there is less than sufficient evidence from human studies but sufficient evidence in animal studies and strong evidence that the agent acts through a

relevant mechanism in humans. Sufficient evidence from human studies can be provided by a meta-analysis or by several well-conducted studies in which biases can be ruled out with reasonable confidence.

Our classification of "**modest evidence for causation**" is when the degree of evidence from human studies is less than sufficient but there is supplementary evidence from animal studies and/or mechanistic studies that support causality. Modest evidence for causation could also occur if a meta-analysis does not provide convincing evidence (e.g., the summary risk estimate is close to the null value of 1.0, or if the meta-analysis finds no exposure-response relationship) but there are additional well-conducted epidemiological studies (for which biases can be reasonably ruled out), possibly occurring after the meta-analysis has been conducted, that provide supporting evidence for causality.

Our classification of "**sufficient evidence of an association**" occurs when a positive association has been observed in several epidemiological studies but biases (including confounding) that could explain all or most of the associations cannot be reasonably ruled out. This is similar to the NTP classification of "reasonably anticipated to be a human carcinogen" in which the evidence from human studies "indicates that causal interpretation is credible but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded."

Our classification of "**Limited/Suggestive evidence of an association**" is when the evidence from epidemiological studies is weak. This could occur if there are conflicting findings among well-conducted studies; or the studies that have positive findings have serious limitations; or the number of studies are too few to support a stronger classification.

Literature Search Methods

Reviews of epidemiological studies involving TCE and PCE exposure have been conducted by EPA (2011), IARC (2014) and NTP (2015). In addition, meta-analyses have recently been conducted by NCI (Karami et al 2012, Karami et al 2013), EPA (Scott 2011), and IARC researchers (Vlaanderen et al 2014) for TCE and kidney cancer, hematopoietic cancers and liver cancer, and PCE and bladder cancer. ATSDR utilized these reviews and meta-analyses to identify relevant epidemiological studies for TCE and PCE. Meta-analyses of benzene and hematopoietic cancers (Khalade et al 2010, Vlaanderen et al 2011, 2012) were used to identify relevant epidemiological studies for benzene. In addition, literature searches using PubMed were conducted to identify epidemiological studies conducted after the meta-analyses and reviews were completed, using the following keywords: trichloroethylene, tetrachloroethylene, perchloroethylene, and benzene. For vinyl chloride, we reviewed the IARC monograph 100F (2012) that evaluated vinyl chloride and conducted a literature search using PubMed with the key word, vinyl chloride.

Assessment of the Evidence

ATSDR reviewed the journal articles (including meta-analyses) identified through the literature search as well as the overall reviews published by EPA (2011), IARC (2012, 2014) and NTP (2015). **Tables**

for each disease were developed listing the results of: (1) any meta-analysis that was conducted, (2) epidemiological studies <u>not</u> included in a meta-analysis, and (3) epidemiological studies that were included in a meta-analysis that had additional information on exposure duration, exposure intensity, and/or cumulative exposure. After each table, any assessments made by EPA, IARC, or NTP were presented along with ATSDR's assessment of the evidence. Although the evidence from epidemiological studies (in particular meta-analyses, pooled analyses, and those studies considered well-conducted) is emphasized, the findings from animal studies, mechanistic studies, and other toxicological information is mentioned if necessary to support our conclusions. If there is evidence concerning the relationship between risk of the disease and duration or level of exposure, this is presented. Also included is the 5-year survival percent and whether a study evaluated mortality or incidence. For diseases with a high 5-year survival percentage, an incidence study would have a greater capability than a mortality study of evaluating the risk from exposure to these chemicals for several reasons: (1) the exposure may cause a less fatal form of the disease; (2) a cancer that is not an underlying or contributing cause of death will be missed in a mortality study, and in general, there will be many more incident cases than mortality cases so precision should be improved (i.e., width of confidence intervals will be narrower) in an incidence study; and (3) there is greater accuracy of the cancer information provided by cancer registries (e.g., histological information and identification of primary and metastatic sites) compared to the information available from the death certificate, so disease misclassification should be reduced in incidence studies.

In the disease-specific tables, 95% confidence intervals are provided for the key findings in a study to indicate the level of precision or uncertainty in the effect estimates. We discourage the use of confidence intervals as tests of statistical significance. For the information on exposure duration, we generally do not provide the confidence intervals unless the findings are from a meta-analysis or pooled analysis because the focus is on the intervals were risks appear elevated and the concern is not about the precision of the estimates. Similarly for cumulative exposure and exposure intensity, we generally do not provide confidence intervals unless this is the key finding in a study.

<u>Bias Evaluation</u>

The vast majority of the relevant studies are occupational studies. The key limitation of all the studies was **exposure misclassification**. Most of the occupational studies utilized job-exposure matrices of varying quality. A few studies had information on urinary TCA levels that improved the exposure assessment. The impact of exposure misclassification bias would likely be to bias dichotomous comparisons (e.g., exposed vs unexposed) towards the null if an effect of the exposure is truly present, and to distort exposure-response trends (e.g., the curve may flatten or attenuate at high exposure levels). **Healthy worker/veteran effect** bias likely occurred in studies that compared incidence or mortality rates in worker or veteran cohorts with rates in the general population. Such a bias would tend to produce underestimates of the effect of exposure, and in many situations, reduce measures of association (e.g., SIR or SMR) below the null value.

Another issue for most of the studies is **confounding** due to co-exposures to other workplace chemicals. For example, dry cleaning workers employed before the early 1960s were likely exposed to other solvents besides PCE. Dry cleaning workers also used solvents for spot removal although these exposures would be considerably lower than exposures to the primary solvent. Workers in aircraft manufacturing or maintenance may have been exposed to TCE, PCE and other solvents. In the Camp Lejeune studies and the NJ studies, both TCE and PCE appeared together as drinking water contaminants.

An additional concern raised by IARC and NTP was confounding by other risk factors such as smoking and alcohol consumption. However, for appreciable confounding by smoking or any other risk factor to occur, at least two requirements must be met: (1) the risk factor must have an association with the outcome of interest at least as strong as the exposure of interest, and (2) the risk factor must also have a strong association with the exposure of interest. For the latter requirement to be met, the prevalence of the risk factor must be very different in the compared groups. This might occur for example when a worker (or veteran) cohort is compared to the general population. However, the prevalence of risk factors (other than the exposure of interest) should be similar when comparisons are made either internal to a cohort or between similar cohorts (e.g., similar workforces or similar military personnel), and therefore confounding would be expected to be minimal for these comparisons.

In general, substantial confounding due to smoking or any other risk factor is rare in occupational and environmental epidemiology. Even for studies of an occupational or environmental exposure and lung cancer, a summary measure (e.g., RR, OR) adjusted for smoking rarely differs by more than 20% from the unadjusted summary measure (Blair et al 2007). In any case, the amount of bias due to confounding will not be greater than the weaker of these two associations: (1) between the exposure of interest and the confounder; (2) between the confounder and the disease of interest (Smith and Kriebel 2010).

Many of the studies included in the meta-analyses or listed in the tables did have information on smoking and were able to evaluate whether confounding due to smoking was present and affected the results. Most of the studies that did not have information on smoking were able to indirectly assess whether confounding due to smoking affected the results by evaluating whether a smoking-related disease that was not known to be associated with the exposure of interest was elevated in the study. Another indirect approach to evaluate possible confounding due to smoking would be to evaluate all smoking-related diseases in the study for which the risk from smoking is known (or expected to be) much larger than the risk from the exposure of interest. If appreciable confounding due to smoking were present, one would expect that all these diseases would be elevated.

Many of the studies evaluated, or adjusted for, risk factors in addition to smoking such as alcohol consumption and SES factors. The appendix lists the studies included in the tables, whether or not they evaluate smoking as a possible confounder, and any additional potential confounders. The appendix also provides comments on the quality of many of the studies included in the table from reviews conducted by IARC (2014) and NTP (2015).

Duration of Exposure

There is limited information on the minimum duration of exposure necessary to cause diseases related to the drinking water contaminants at Camp Lejeune. Moreover, even when duration information is provided in a study, it is often categorized into wide ranges (e.g., > 0 to 5 years). An additional difficulty is the possible inverse relationship between duration and exposure intensity, e.g., high exposure intensities may require only a short duration of exposure whereas low exposure intensities may require longer exposure durations. Although cumulative exposure is a useful metric, it obscures this interplay between duration and intensity. Specifying a minimum duration of exposure also presupposes that there is a known threshold amount of exposure below which there is no excess risk. However, there is no compelling evidence that such thresholds exist for these contaminants and specific cancers.

The 2012 Honoring America's Veterans and Caring for Camp Lejeune Families Act established a minimum duration at Camp Lejeune of 30 days in order to be eligible for health benefits under the Act. The evidence from the epidemiological studies included in the tables is not sufficient to contradict this minimum duration. Moreover the evidence from the Camp Lejeune mortality studies tends to support a 30 day minimum duration with elevated risks for many of the diseases occurring for an exposure duration of 1-3 months.

For cardiac defects, it is possible that durations of exposure to the mother as short as 1 day may be sufficient if the exposure occurs during the relevant vulnerability period for cardiac defects, i.e., 3-9 months gestation. Very short in-utero exposures (i.e., less than a month) may also be sufficient to cause childhood leukemia.

Given the insufficient evidence for a threshold level of exposure to these contaminants, it may be helpful to explore how other programs have resolved this issue when information on exposure duration or evidence for a threshold level are lacking. For example, although the exposures are very different from those considered in this document, the World Trade Center (WTC) Health Program uses site-specific minimum exposure durations ranging from 4 hours to a maximum of 400 hours.

Given that sufficient evidence for a threshold is lacking, ATSDR recognizes that a decision to establish a specific minimum exposure duration for presumption will primarily be based on social, economic and legal factors. It is ATSDR's position that the minimum exposure duration of one month in the 2012 Honoring America's Veterans and Caring for Camp Lejeune Families Act is an appropriate minimum exposure duration and should be considered by the VA in developing its program for presumption at Camp Lejeune.

Summary of the Evidence*

Disease	Chemicals	Meta-analysis available?	Preliminary Conclusion
Kidney Cancer	TCE	Kelsh 2010, Scott (EPA) 2011, Karami (NCI) 2012	**Sufficient evidence for causation**. IARC (2014), EPA (2011), and NTP (2015) support this classification.
Non-Hodgkin Lymphoma	TCE PCE	Kelsh 2010, Scott (EPA) 2011, Karami (NCI) 2013	**Sufficient evidence for causation**. EPA (2011) supports this classification: "The human evidence of carcinogenicity from epidemiologic studies of TCE exposure is strong…" **Modest evidence for causation** for PCE based on the epidemiologic studies.
Multiple Myeloma	TCE Benzene PCE	Alexander 2006, Karami (NCI) 2013; Vlaanderen 2011, Vlaanderen 2013, Infante 2006	**Modest evidence for causation** for TCE based on epidemiological and mechanistic evidence. **Modest evidence for causation** for Benzene based on IARC's review and meta-analyses. **Sufficient evidence of an association** for PCE
Leukemias	Benzene TCE	Alexander 2006, Karami (NCI) 2012, Vlaanderen 2011, Vlaanderen 2012, Khalade 2010	**Sufficient evidence for causation** for Benzene and all subtypes of leukemias based on IARC review and epidemiological evidence. **Modest evidence for causation** for TCE and all subtypes of leukemias based on epidemiologic and mechanistic studies.
Liver Cancer	Vinyl chloride TCE	Alexander 2007, Scott (EPA) 2011, Boffetta 2003	**Sufficient evidence for causation** for vinyl chloride. IARC (2012) concurs. **Modest evidence for causation** for TCE based on meta-analyses and animal data.
Pancreatic Cancer	PCE TCE	Ojajarvi 2001	**Sufficient evidence of an association** for PCE based on dry cleaning studies
Prostate Cancer	TCE		**Sufficient evidence of an association** based on studies of TCE workers.
Breast Cancer (male & female)	TCE, PCE, Benzene		**Limited/Suggestive evidence of an association** for TCE, PCE, Chlorinated Solvents, and Benzene and breast cancer.
Bladder Cancer	PCE	Vlaanderen (IARC) 2014	**Sufficient evidence for causation** based on dry cleaning worker studies. This is supported by the IARC meta-analysis (Vlaanderen et al 2014
Parkinson's Disease	TCE solvents	Pezzoli and Cereda 2013	**Modest evidence for causation** for TCE based on evidence from epidemiological, animal and mechanistic studies. **Sufficient evidence of an association** for solvents
Kidney Diseases	TCE PCE		**Modest evidence for causation f**or TCE based evidence from human and animal studies. **Sufficient evidence of an association** for PCE.
Esophageal Cancer	TCE, PCE		**Sufficient evidence of an association** for TCE and PCE.
Lung Cancer	PCE	Boffetta 2003 (Vizcaya 2013 pooled analysis)	**Sufficient evidence of an association** for PCE

Disease	Chemicals	Meta-analysis available?	Preliminary Conclusion
Rectal Cancer	PCE		**Sufficient evidence of an association** for PCE
Cervical Cancer	TCE, PCE		**Sufficient evidence of an association** for TCE and PCE
Brain/CNS Cancers	Vinyl chloride	Boffetta 2003	**Sufficient evidence of an association** for vinyl chloride. **Insufficient evidence of an association** for PCE and TCE.
Systemic Sclerosis/ Scleroderma	TCE	Cooper 2009 (pooled analysis)	**Modest evidence for causation** for TCE
Cardiac Defects	TCE		**Sufficient evidence for causation**. This is supported by EPA (Chiu et al 2013): "Strong evidence, based on weakly suggestive epidemiologic studies, limited experimental animal studies, and multiple mechanistic studies, that TCE causes fetal cardiac malformations."

Bolded text are ATSDR's conclusions.

* The evidence for a causal association between each exposure and disease is presented in more detail in the following tables and accompanying text.

Kidney Cancer

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Moore 2010+	TCE	High confidence, any exposure: OR=2.05 (1.13, 3.73)	<1,080 hours, OR=1.22	<1.6 ppm-years: OR=1.77 <0.076 ppm intensity: OR=1.73
Hansen 2013	TCE	Any: RR <1.0 "high" U-TCA: RR=2.04 (0.81, 5.17)	Low duration of exposure	Low exposure intensity
Vlaanderen 2013	TCE	"high exposure": RR=1.10 (95% CI: 0.97, 1.25)	Low duration of exposure	Low exposure intensity
Christensen 2013#	TCE PCE	"substantial": OR=0.6 (0.1, 2.8) "substantial": OR=1.6 (0.3, 8.1)	–	–
Lipworth 2011++	Aircraft Manufacturing TCE PCE	 SMR=0.66 (0.38, 1.07) SMR=0.80 (0.43, 1.37)	–	–
Silver 2014	Microelectronics firm TCE PCE	Cumulative exposure to TCE (5 exposure-yrs): RR=1.24 (0.87, 1.77) RR < 1.0	–	–
Karami 2012, NCI **meta-analysis**	TCE	Summary RR=1.32 (1.17, 1.50)	–	–
Scott 2011, EPA **meta-analysis**	TCE	Summary RR=1.27 (1.13, 1.43); High cumulative exposure, summary RR=1.64 (1.31, 2.04)	–	–
Kelsh 2010 **meta-analysis**	TCE	Summary RR=1.42 (1.13, 1.77); "More likely exposed": summary RR=1.34 (1.07, 1.67)	"Shortest" duration: RR=1.50 "Longest" duration: RR=1.24	"Low" cumulative exposure: RR=1.29 "High" cumulative exposure: RR=1.39
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=1.16 (0.84, 1.57) RR=1.35 (0.84, 2.16)	Exposure duration (months) 1-3: RR=1.27 4-6: RR=1.21 7-12: RR=1.90 >12: RR=1.74	Elevated risks observed in the low, medium and high cumulative exposure levels
Bove 2014 (Camp Lejeune Civilian workers)	VOC contaminated drinking water U.S. population vs. Camp Pendleton	 SMR=1.30 (0.52, 2.67) RR=1.92 (0.58, 6.34)	5 of 7 deaths had exposure duration >12 months	All 7 deaths had cumulative exposures above the median for PCE, TCE and VC

* Exposures are occupational unless otherwise noted.
+ Included in the EPA and NCI meta-analyses
++ Included in the NCI meta-analysis
# ORs are based on 2 exposed cases

Summary

The Moore et al. 2010 study was a hospital-based case-control study conducted in heavy industrialized regions of four countries in Central/Eastern Europe that assessed the risk of kidney cancer from TCE exposure as well as the interaction between TCE exposure and genotypes for the GSTT1 and renal-CCBL1enzymes which are highly active in the kidney and involved in the bioactivation of TCE (via GSH-conjugation pathway). This study was included in both the EPA and NCI meta-analyses and was considered of "high utility" by the NTP (2015) review of TCE. In addition to finding exposure-response trends for TCE exposure and kidney cancer, perhaps the most important finding was that those exposed to TCE with at least one intact GSTT1 allele had elevated risks for kidney cancer, but those with a functionally inactive GSTT1 enzyme (i.e., with two deleted alleles, the null genotype) had **no elevated risk**. Findings for the interaction between TCE exposure and minor alleles for the renal-CCBL1 enzyme supported the findings for the GSTT1 enzyme. The findings of this study are in agreement with the hypothesized mechanism for TCE-induced kidney cancer and therefore provide strong evidence for causality.

The EPA meta-analysis concluded that confounding by smoking and other risk factors would have a minimal impact on the meta-analysis results.

The NTP Monograph on trichloroethylene (2015) concluded: "Epidemiological studies have demonstrated a causal relationship between trichloroethylene exposure and kidney cancer based on consistent evidence of increased risk across studies with different study designs, in different geographical areas, and in different settings; evidence of increasing cancer risk with increasing level or duration of exposure; and meta-analyses showing statistically significantly increased cancer risk across studies." The IARC review (2014) states unequivocally: "Trichloroethylene causes cancer of the kidney." All 3 meta-analyses and the EPA Toxicological Review of Trichloroethylene (2011) support the NTP and IARC conclusion that TCE causes kidney cancer.

Mechanistic Information: "The mode of action for trichloroethylene-induced kidney cancer is not completely understood but the available data provide support for a mutagenic and cytotoxic mode of action mediated by GSH-conjugation-derived metabolites. There is experimental evidence that GSH metabolites (particularly DCVC) are genotoxic and nephrotoxic and are both formed in and delivered to the kidney following exposure to trichloroethylene." (NTP Monograph on Trichloroethylene, 2015, p. 106.)

ATSDR Assessment: Based on the findings from the meta-analyses and the supporting evidence from mechanistic studies, there is sufficient evidence for causation for TCE and kidney cancer.

Duration of exposure: The Moore et al. 2010 study found increased risks among those exposed for **≤6 months**. The Camp Lejeune mortality study of Marines/Navy personnel found an elevated risk among those with exposure **≤3 months** to the drinking water contaminants including TCE. Radican et al 2008 observed the highest RR for >0-5 unit years (RR=1.87, 95% CI: 0.59, 5.97) and for low-intermittent exposure (RR=1.58, 95% CI: 0.52, 4.76) and low-continuous exposure (RR=1.79, 95% CI: 0.57, 5.62).

Mortality Studies: Lipworth 2011, Silver 2014, Bove 2014

Incidence Studies: Moore 2010, Christensen 2013, Vlaanderen 2013, Hansen 2013

5-year survival % (SEER): 73%

Non-Hodgkin Lymphoma

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Mandel 2006 **Meta-analysis**	TCE (All workers) "more likely exposed"	SumRR =1.29 (1.00, 1.66) SumRR =1.59 (1.21, 2.08)	< 5 yrs exposed: SumRR=1.47 (1.08, 2.0) ≥ 5 yrs exposed: SumRR=1.60 (1.20, 2.10)	low intensity: sumRR=2.33 (1.29, 3.91) high intensity: sumRR=2.11 (0.76, 5.84)
Scott 2011 **Meta-analysis (EPA)**	TCE	Summary RRs/ORs: All studies: 1.23 (1.07, 1.42) Cohort: 1.33 (1.13, 1.58) Case-control: 1.11 (0.89, 1.38)	--	higher TCE exposure, summary RRs/ORs: All studies: 1.43 (1.13, 1.82) Cohort: 1.60 (1.24, 2.08) Case-control: 1.29 (0.76, 2.20)
Karami 2013 **Meta-analysis (NCI)**	TCE TCE exposure confirmed by U-TCA	Summary RRs/ORs: All studies: 1.32 (1.14, 1.54) Cohort: 1.52 (1.29, 1.79) Case-control: 1.14 (0.93, 1.40) SIR=2.15 (1.34, 3.45)	Cohort studies: "low": RR=1.30 (0.92, 1.84) "high": RR=1.56 (1.02, 2.40) Case-control studies: "low": OR=1.46 (0.78, 2.73) "high": OR=1.18 (0.60, 2.34)	Cohort studies: "low intensity": RR=1.68 (1.14, 2.46) "high intensity": RR=1.27 (0.83, 1.96) Case-control studies: "low intensity": RR=1.06 (0.79, 1.42) "high intensity": RR=1.42 (0.86, 2.33)
Vlaanderen 2013	Unexposed as ref. grp. TCE exposure tertiles PCE exposure tertiles	 RRs ≤1.01 RRs ≤1.06	--	RRs < 1.0 for TCE PCE median intensity, males: RR=1.74 (1.15, 2.64)
Christensen 2013	TCE PCE	"any"exposure: OR=1.2 (0.5, 2.9) "substantial": OR= 1.0 (0.3, 3.5) "any"exposure: OR=1.7 (0.5, 6.2) "substantial": OR=1.7 (0.3, 8.5)	–	–
Hansen 2013	TCE	All: RR=1.26 (0.89, 1.73) Men: RR= 1.55 (1.06, 2.20) Women: RR=0.63 (0.23, 1.37)	Similar RRs were obtained for zero, 10 year, and 20 year latency periods.(RRs between 1.11 and 1.26)	U-TCA (mg/L) 5 - 25: RR=1.16 >25- 50: RR=1.56 >50: RR=0.66
Silver 2014	Microelectronics plant TCE PCE	 RR < 1.0 for cumulative exposure RR=1.25 (0.90, 1.73), cumulative exposure (5 exposure-years)	–	–
Cocco 2013¥	High probability of TCE exposure	All NHL: OR=1.4 (0.9, 2.1) Follicular: OR=1.5 (0.7, 3.2) CLL: OR=2.0 (1.0, 4.0)	1-14 years: OR=0.7 15-29 years: OR=1.9 30-39 years: OR=2.8 40+ years: OR=3.3	Intensity level (ppm) ≤5: OR=1.1 5-75: OR=1.3 >75: OR=2.2
Raaschou-Nielsen 2003 £	TCE TCE (20 year exposure lag)	Men: SIR=1.2 (1.0, 1.5) Women: SIR=1.4 (0.7, 2.3) Men: SIR=1.3 (0.9, 1.9) Women: SIR=1.9 (0.8, 3.9)	High exposure group, Duration of employment (years): 1 – 4.9: SIR=1.5 ≥5: SIR=1.6	High exposure group, Lag time (years): 0-9: SIR=1.8 10-19: SIR=1.3 ≥20: SIR=1.7

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Anttila 1995Ψ	PCE	SIR=3.76 (0.77, 11.0)		
Seidler 2007	TCE cumulative exposure >90% PCE cumulative exposure >90% Benzene cumulative exposure >90%	B-NHL: OR=2.3 (1.0, 5.3) T-NHL: OR=4.7 (0.8, 26.1) B-NHL: OR=3.2 (0.6, 16.7) Could not evaluate T-NHL B-NHL: OR=1.0 (0.4, 2.3) One case of T-NHL		
Miligi 2006®	PCE, medium/high	OR=1.2 (0.6, 2.5)		
Lipworth 2011	Aircraft manufacturing TCE PCE	 SMR=1.31 (0.97, 1.73) SMR=1.43 (1.00, 1.98)	Years exposed: <1: TCE RR=0.84; PCE RR=1.26 1-4: TCE RR=1.10; PCE RR=1.00 >4: TCE RR=1.02; PCE RR=1.02	–
Radican 2008€	Aircraft maintenance TCE	RR=1.36 (0.77, 2.39) Men: RR=1.56 (0.72, 3.35) Women: RR=1.18 (0.49, 2.85)	Cumulative exposure score (unit-yrs): 0-5: Men, RR=1.83; Women, RR=1.48 5-25:Men, RR=1.17; Women, RR=0 >25: Men, RR=1.50; Women, RR=1.30	Low, intermittent RR=1.50 Low, continuous RR=1.74 Peak, infrequent RR=1.90 Peak, frequent RR=1.57
Calvert 2011	Dry Cleaning (All) PCE only PCE plus	SMR=1.57 (0.78, 2.81) SMR=2.46 (0.90, 5.36) SMR=1.10 (0.36, 2.56)		
Lynge 2006	Dry Cleaning	RR=0.95 (0.65, 1.41)	0-1 year, RR=1.35 > 1 year, RRs < 1.0	
Blair 2003	Dry Cleaning	SMR=0.9 (0.5, 1.6)		
Selden 2011	Dry Cleaning: PCE subcohort	 Men: SIR=2.02 (1.13, 3.34) Women: SIR=1.14 (0.68, 1.81)	<1 year 1-4 years >4 years 6.0 1.0 1.6 2.0 1.0 1.0	
't Mannetje 2015	Dry cleaning Ever employed >10 years employment	 OR=0.92 (0.70, 1.20) OR=1.29 (0.74, 2.23)		
Carreón 2014	Vinyl chloride	SMR=2.03 (0.88, 4.0)	SRRs < 1.0 for exposure durations > 0	
Linet 2015	Benzene	RR=3.9 (1.5, 13.2)		
Stenehjem 2015	Benzene	RR=1.49 (0.90, 2.48) (B-NHL)	Duration exposed (years) >0 – 5.49: RR=1.44 5.5 – 12.9: RR=1.52 ≥13: RR=1.54	Cumulative exposure (tertiles): 1st: RR=1.44 2nd: RR=1.44 3rd: RR=1.62
Bassig 2015	Benzene	RR=1.87 (1.19, 2.96)	Exposure Duration (years) 1-11: OR=1.44 12-21: OR=2.10 >21: OR=2.07	Cumulative Exposure (tertiles) 1st OR=0.93 2nd OR=2.22 3rd OR=2.16

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Cohn 1994	TCE-contaminated drinking water (>5 µg/L	NHL, high grade, non-Burkitt: Men: RR=1.92 (0.54, 6.81) Women: RR=3.17 (1.23, 8.18)	–	–
Bove 2014	Camp Lejeune	No association	–	–

* Exposures are occupational unless otherwise noted.

¥ Short frequency of exposure during work time (i.e., ≤5%) had similar OR as higher frequencies of exposure during work time.

£ Included in the NCI, EPA and Mandel et al meta-analyses. Included in the table because of information on employment duration and exposure lag time.

Ψ Included in the NCI, EPA and Mandel et al meta-analyses for TCE exposure. Included in the table for PCE exposure information.

® Included in the NCI and EPA meta-analyses for TCE exposure. Included in the table for PCE exposure information.

€ Included in the NCI and EPA meta-analyses. Included in the table because of information on exposure intensity (men only; there were small number of cases among women) and cumulative exposures.

SumRR: Summary RR from the meta-analysis.

Summary For TCE and NHL

EPA Toxicological Review of TCE (2011): "The human evidence of carcinogenicity from epidemiologic studies of TCE exposure is strong for NHL but less convincing than for kidney cancer…." "Associations observed in epidemiologic studies of lymphoma and TCE exposure suggest a causal relation between TCE exposure and NHL."

IARC (Vol 106, 2014) concluded that there was a positive association between TCE and NHL. In particular, the cohort studies of biologically monitored workers in the Nordic countries found an increased risk for NHL. The meta-analyses were consistent in finding that TCE exposure increased the risk of NHL. Higher risks were observed in the cohort studies compared to the case-control studies. This may be due to better exposure assessment in the cohort studies.

NTP Monograph on TCE (2015): "Overall, there is some evidence of an association between exposure to trichloroethylene and NHL based on findings of a modest increase in risk of NHL in several studies with different study designs and in different populations, although the strength of the evidence varied." (p. 132-33)"

Mechanistic information: "Severe immune dysregulation, whether from immunosuppression, inflammation, or autoimmune disease, is associated with an increased risk of NHL. Thus, it is biologically plausible that the mode of action of trichloroethylene-induced NHL could involve altered immunity. … Although few applicable studies were conducted in humans, the available data provide evidence that trichloroethylene can alter the immune system based on some studies finding an association between markers of immune modulation and other studies showing an association with autoimmune disease (e.g., systemic sclerosis). … However, the available data are insufficient to demonstrate that immunomodulation is operant as a mode of action for trichloroethylene-induced NHL." (NTP Monograph on

Trichloroethylene 2015, p. 148). Evidence from animal studies indicates that TCE exposure causes immunomodulation including autoimmune disease and immunosuppression. Both autoimmune disease and immunosuppression are associated with NHL.

ATSDR Assessment: NTP (2015) found that TCE exposure increased the risks for NHL among all studies they considered of high or moderate utility (N=3), and all but one of the studies considered to be of low to low/moderate utility (i.e., 5 out of 6). (The one study that did not find an increased risk for TCE was a mortality study whose workforce was relatively young.) NTP considered the pooled InterLlymph analysis study by Cocco et al 2013 to be the most informative study because it evaluated NHL subtypes. This study found an increased risk of NHL as well as increased risk for the NHL subtypes, follicular lymphoma and CLL. ATSDR concurs with EPA that the epidemiological studies provide strong evidence of causation for TCE and NHL. These findings are supported by the mechanistic information that TCE alters immune function. Therefore ATSDR concludes that there is sufficient evidence for causation for TCE and NHL.

Summary for PCE and NHL

From **EPA's 2012 Toxicological Review of PCE**: "*The results from the collection of studies pertaining to non-Hodgkin lymphoma indicate an elevated risk associated with tetrachloroethylene exposure. The results from five cohort studies that used a relatively high quality exposure-assessment methodology generally reported relative risks between 1.7 and 3.8 (Calvert et al., 2011; Seldén and Ahlborg, 2011; Radican et al., 2008; Boice et al., 1999; Anttila et al., 1995) and support an association with tetrachloroethylene. The studies with tetrachloroethylene-specific exposure measures and exposure-response analysis (based on intensity, duration, or cumulative exposure) (Seidler et al., 2007; Miligi et al., 2006; Boice et al., 1999) provide further support for an association, reporting higher non-Hodgkin lymphoma risks in the highest exposure category, with the strongest evidence from the large case-control study in Germany, in which a relative risk of 3.4 (95% CI: 0.7, 17.3) was observed in the highest cumulative exposure category (trend p-value = 0.12) (Seidler et al., 2007). Lynge et al. (2006) distinguished dry cleaners from other workers but used an approach with greater potential for misclassification because exposure was assigned only for jobs held in 1970. This study did not report an association between dry cleaners and non-Hodgkin lymphoma, nor did risk estimates increase with exposure duration. Effect estimates in studies with broader exposure assessments showed a more variable pattern (Seldén and Ahlborg, 2011; Pukkala et al., 2009; Ji and Hemminki, 2006b; Blair et al., 2003; Travier et al., 2002; Cano and Pollán, 2001; Lynge and Thygesen, 1990). Confounding by lifestyle factors are unlikely explanations for the observed non-Hodgkin lymphoma results because common behaviors, such as smoking and alcohol use, are not strong risk factors for non-Hodgkin lymphoma (Besson et al., 2006; Morton et al., 2005).*"

ATSDR Assessment: ATSDR agrees with EPA's assessment that the epidemiological evidence supports an association between PCE and NHL that is likely not affected by confounding biases. Although there are conflicting findings among the dry cleaning studies, other studies of PCE exposed workers, and the study of PCE-contaminated drinking water in NJ, support an association. Therefore, based on the human evidence and lack of supporting animal and mechanistic evidence, the overall evidence falls somewhere between sufficient evidence for causation and sufficient evidence of an association. Therefore ATSDR concludes that there is modest evidence for causation for PCE and NHL.

5-year survival % (SEER): 70%

Mortality Studies: Blair 2003 Radican 2008, Lipworth 2011, Calvert 2011, Silver 2014, Carreón 2014, Bove 2014

Incidence Studies: Anttila 1995, Miligi 2006, Seidler 2007, Raaschou-Nielsen 2003, Lynge 2006, Selden 2011, Hansen 2013, Vlaanderen 2013, Christensen 2013, Cocco 2013, Linet 2015, Stenehjem 2015, Cohn 1994

Multiple Myeloma

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Alexander 2006 **Meta-analysis**	TCE	summary RR = 1.05 (0.80, 1.38)	–	–
Karami 2013 **NCI Meta-analysis**	TCE	summary RR = 1.07 (0.86, 1.34)	–	–
Costantini 2008	TCE Benzene		Years of exposure (ORs) TCE Benzene ≤15 0.5 0.8 >15 1.3 4.1	Exposure Intensity (ORs) TCE Benzene Low 1.5 (0.7, 3.5) 0.6 (0.3, 1.5) Med/hi 0.9 (0.3, 2.4) 1.9 (0.9, 3.9)
Gold 2011£	TCE PCE	"likely exposure": OR = 1.7 (1.0, 2.7) "likely exposure": OR = 1.5 (0.8, 2.9)	1-4 years: OR=0.9 5-7 years: OR=1.3 8-24 years: OR=2.5 >24 years: OR=1.9 1-4 years: OR=0.9 5-7 years: OR=2.0 8-24 years: OR=1.3 >24 years: OR=2.1	ORs increased with increasing cumulative exposure but not strictly monotonically. Similar findings for no lag and 10-year lag. ORs increased with increasing cumulative exposure but not monotonically. Slightly stronger findings for 10-year lag in the higher cumulative exposure categories.
Vlaanderen 2013	TCE Men Women PCE Men Women	RRs < 1.0 RR= 1.10 (0.87, 1.39), 3rd tertile RRs < 1.0 except 1st tertile, RR=1.13 (0.92, 1.38). RR=1.06 (0.85, 1.32), 3rd tertile	Median intensity x prevalence: RR=1.0 for men RR=1.11 for women RR=0.85 for men RR=1.28 for women	Median cumulative exposure: RR=0.95 for men RR=1.09 for women RR=1.22 for men RR=1.14 for women
Hansen 2013	TCE	RR < 1.0	–	–
Silver 2014	Microelectronics plant TCE PCE	–	5 exposure-yrs cumulative exposure: RR=1.18 (0.70, 1.99) RR < 1.0	–
Lipworth 2011	Aircraft manufacturing TCE PCE	 SMR=1.21 (0.76, 1.81) SMR=1.07 (0.58, 1.79)	Years exposed (RRs): TCE PCE <1: 0.7 0.9 1-4: 1.5 1.1 >4: 0.7 0.3	–
Radican 2008€	Aircraft maintenance TCE	RR=1.08 (0.43, 2.71), men RR=2.37 (0.67, 8.44), women	Cumulative exposure (unit-yrs), RRs: Men Women >0-5: 0.7 2.2 >5-25: 1.6 2.8 >25: 1.2 2.4	(RRs) Men Women Low, intermittent: 1.0 4.3 Low, continuous: 1.2 1.7 Peak, infrequent: 1.8 3.2 Peak, frequent: 1.3 1.9
Blair 2003	Dry Cleaning	SMR=0.8 (0.3, 1.6)		

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR = 1.05 (0.61-1.69) RR = 1.68 (0.76, 3.72)	1 – 3 months: RR=3.0 4 – 12 months: RR=2.5 >12 months: RR=0.8	TCE Cumulative exposure: Very low: RR=1.3 Low to high: RR=1.6
Bove 2014 (Camp Lejeune Civilian workers)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=1.50 (0.55, 3.28) RR =1.84 (0.45, 7.58)	–	No association with cumulative exposure to TCE or PCE 4 of the 6 cases had above median average exposure for TCE
Infante 2006 **Meta-analysis**	Benzene	summary RR = 2.13 (1.31, 3.46)	–	–
Vlaanderen 2011 **Meta-analysis**	Benzene Semi-quantitative exposure assessment: Higher quality studies:	 summary RR = 1.48 (0.96, 2.27) summary RR = 1.49 (1.13, 1.95)	–	–
Stenehjem 2015	Benzene (offshore oil industry workers)	RR = 1.64 (0.55, 4.89)	Years exposed >0 – 5.49: RR = 1.31 5.5 - <13: RR = 2.05 ≥ 13: RR = 1.65	Cumulative exposure (tertiles) 1st: RR=0.99 2nd: RR=1.14 3rd: RR=3.25
Cocco 2010	Benzene	OR=0.9 (0.5, 1.6)	–	Low: OR=0.7 Medium: OR=0.4 High: OR=1.4

* Exposures are occupational unless otherwise noted.

£ Included in the NCI meta-analysis. Included in the table because of information on exposure duration and cumulative exposure.

€ Included in the NCI meta-analysis. Included in the table because of information on exposure intensity and cumulative exposures. For PCE, RR=1.7 (0.4, 6.9) for men and RR=7.8 (1.4, 43.1) for women.

Summary of TCE/PCE and Multiple Myeloma

EPA Toxicological Review of PCE (2012): "For non-Hodgkin lymphoma and multiple myeloma, the presence of higher relative risk estimates in studies with better exposure-assessment methodologies and evidence of an exposure-response trend in one or more studies provide the basis for considering the collection of studies as supportive of a role of tetrachloroethylene as a likely carcinogen."

Mechanistic Information: Evidence from animal data indicates that TCE causes autoimmune disorders. In humans, TCE has been associated with systemic sclerosis. In a recent meta-analysis (McShane CM et al 2014), any autoimmune condition was associated with subsequent risk of multiple myeloma (pooled RR=1.13, 95% CI: 1.04, 1.22). Systemic sclerosis had a pooled RR of 1.28 (0.66, 2.48) for multiple myeloma

based on 3 studies. A much stronger association was observed between systemic sclerosis and subsequent risk of Monoclonal Gammopathy of Undetermined Significance (MGUS), a precursor to multiple myeloma, with a pooled RR of 4.87 (2.49, 9.54) based on two studies. In one of these two studies, based on patients identified in the VA PTF from 1969 to 1996, the RRs for systemic sclerosis and multiple myeloma and MGUS were 2.41 (1.08, 5.36) and 4.21 (1.89, 9.38), respectively (Brown LM et al 2008). In general, systemic sclerosis is associated with hematopoietic cancers including NHL and leukemia (Onishi A et al 2013; Zhang J-Q et al 2013). One hypothesis is that chronic stimulation of the immune system may lead to multiple myeloma. Another hypothesis is that the dysfunctional immune system found in autoimmune diseases may allow malignant clones to exist, escape and persist (McShane CM et al 2014). Premature aging of the immune system associated with autoimmune diseases could reduce the ability to distinguish "self" and "foreign" antigens.

ATSDR Assessment: The meta-analyses indicate that TCE exposures are associated with a slight elevation in risk. Elevated risks for multiple myeloma were also observed in a large case-control study (Gold et al. 2011). The Camp Lejeune mortality studies found elevated risks for multiple myeloma, which is noteworthy given that multiple myeloma is a disease of older populations (median age=69 for diagnosis, and 75% are diagnosed after age 55) and the Camp Lejeune cohorts were relatively young at the end of the studies: marines/navy personnel, median age=49, years, <3% aged 55 or older; and civilian workers, median age=58, over 70% under the age of 65. ATSDR concludes that the evidence from the epidemiological studies for PCE and TCE is less than sufficient for causation. However, for TCE there is mechanistic information in support of a causality since TCE causes autoimmune disorders and autoimmune disorders are associated with multiple myeloma. Combining the epidemiological and mechanistic evidence, ATSDR concludes that there is modest evidence for causation for TCE. For PCE, ATSDR concludes that there is sufficient evidence of an association.

ATSDR Assessment of Benzene: IARC (2012, Monograph 100F) concluded that a positive association was observed for benzene exposure and multiple myeloma. The review was completed before the Vlaanderen et al 2011 meta-analysis and the recent study of Norwegian offshore oil industry workers which provided additional strong evidence for an association between benzene exposure and multiple myeloma. Given the epidemiological evidence, ATSDR concludes that there is modest evidence for causation for benzene.

Duration of Exposure: The literature suggest that higher cumulative exposures and longer duration of exposures (e.g., >4 years) to TCE and/or PCE are associated with increased risk of multiple myeloma. However the Camp Lejeune study observed elevated RRs for very short duration of exposure, 1-3 months. There was agreement between the benzene studies that elevated RRs are observed only at higher cumulative exposures. However, the recent Norway study suggests that elevated RRs may be observed with short exposure duration and low average exposure intensity.

5-year survival % (SEER): 46.6%

Mortality Studies: Radican 2008, Lipworth 2011, Silver 2014, Bove 2014

Incidence Studies: Gold 2011, Cocco 2010, Hansen 2013, Vlaanderen 2013, Christensen 2013, Stenehjem 2015

Leukemias*

Reference	Exposure**	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Alexander 2007 **Meta-analysis**	TCE	RR = 1.11 (0.93, 1.32)	–	–
Karami 2013 NCI **Meta-analysis**	TCE	summary RR = 1.10 (0.94, 1.28)	–	–
Costantini 2008	TCE Benzene		Years of exposure (ORs) for **CLL** TCE Benzene ≤15 0.7 1.8 >15 1.2 4.7	Exposure Intensity (ORs) for **CLL** TCE Benzene Low 1.2 0.7 Med/hi 0.9 1.8
Hansen 2013	TCE	RR of 1.19 (0.72, 1.86) for males RR <1.0 for females (4 cases)	–	–
Silver 2014	Microelectronics plant TCE PCE	Non-CLL leukemia evaluated	5 exposure-yrs cumulative exposure: RR=1.31 (0.98, 1.75) RR=1.05 (0.66, 1.66)	–
Cocco 2013	High probability of TCE exposure	CLL: OR=2.0 (1.0, 4.0)	1-14 years: OR=0.9 15-29 years: OR=2.3 30-39 years: OR=3.8 40+ years: OR=4.3	Intensity level (ppm) ≤5: OR=1.4 5-75: OR=1.7 >75: OR=3.2
Saberi Hosnijeh 2013	TCE Benzene (high exposure)	RRs ≤1.0 for AML, CML, & CLL RR=1.52 (0.78, 2.98) for AML RR=1.97 (0.75, 5.19) for CML RR=0.56 (0.27, 1.14) for CLL	–	–
Blair 2003	Dry cleaning	SMR=0.8 (0.4, 1.4)	–	–
Morton 2014	Dry cleaning	CLL/SLL: OR=1.20 (0.66, 2.18) ALL: OR=1.10 (0.15, 8.12)	–	–
Mannetje 2015	Dry cleaning	OR=1.21 (0.67, 2.21) for **CLL/SLL**	–	–
Cohn 1994	Drinking water: TCE > 5µg/L PCE > 5µg/L	 RR=3.26 (1.29, 8.28), ALL among females less than 20 years of age RR = 1.5 (1.1, 2.1), CLL RR = 1.79 (0.90, 3.55), CML among females RR=1.08 (0.63, 1.86), AML among males OR =1.58 (0.74, 3.36), ALL among females	–	–

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Aschengrau 1993	PCE in drinking water	OR=5.84 (1.37, 24.91), >90th percentile exposure, 5-year latency	—	—
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=0.78 (0.60, 0.99) RR = 1.11 (0.75, 1.62)	1-3 months: RR=1.78 4-6 months: RR=1.70 7-12 months: RR=0.89 >12 months: RR=0.90	Elevated RRs were observed for cumulative exposure to both TCE and PCE, but the trend was not monotonic
Bove 2014 (Camp Lejeune Civilian workers)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR = 1.55 (0.80, 2.71) RR = 1.59 (0.66, 3.84)	—	Cumulative exposures to PCE and TCE were associated with an increasing risk, with the trend for PCE being monotonic
Reference	**Exposure***	**RR (SIR, SMR, OR) & 95% CI**	**Exposure Duration information**	**Exposure intensity/cumulative exposure information**
Ruckart 2013	VOC contaminated drinking water	OR=1.6 (0.5, 4.8) PCE exposed (similar finding for vinyl chloride), childhood hematopoietic cancers		
Costas 2002	TCE-contaminated drinking water, Woburn, MA	OR=8.33 (0.73, 94.67), childhood ALL	—	Highest cumulative exposure: OR=14.3 (0.92, 224.5)
Khalade 2010 **Meta-analysis**	Benzene	summary RR = 1.40 (1.23, 1.57) AML: RR = 1.38 (1.15, 1.64) CML: RR = 1.05 (0.83, 1.34) CLL: RR = 1.31 (1.09, 1.57)	—	—
Vlaanderen 2011, 2012 **Meta-analysis**	Benzene Quantitative/semi-quantitative exposure assessments	summary RRs: AML: 1.82 (1.25, 2.66) ALL: 1.26 (0.5, 3.16) CML: 1.44 (0.82, 2.53) CLL: 1.54 (0.72, 3.31)	—	—
Schnatter 2012	Benzene		Duration of employment (yrs), ORs: AML CLL CML >15.6: 1.0 2.1 3.1 >28: 1.7 1.2 1.4	Cumulative exposure (tertiles), ORs: AML CLL CML 1.0 1.5 5.0 1.4 1.1 2.2
Linet 2015	Benzene	RR = 2.8 (1.6, 5.5) ALL: RR = 4.5 (0.8, 83.9) CML: RR = 2.5 (0.8, 10.7) AML: RR = 2.1 (0.9, 5.2)	—	—
Hsieh 2011	Polyvinyl chloride workers	SMR=3.93 (1.40, 8.54) during high exposure period		
Reference	**Exposure***	**RR (SIR, SMR, OR) & 95% CI**	**Exposure Duration information**	**Exposure intensity/cumulative exposure**

				information
Stenehjem 2015	Benzene (offshore oil industry workers)	AML: RR = 2.18 (0.47, 10) CLL: RR = 5.40 (0.70, 41)	Years exposed (RR) AML CLL >0-5.49: 2.0 7.6 5.5-<13: 3.4 4.8 ≥ 13: 1.0 4.0	Non-monotonic increase in risks with increased cumulative exposures

* The results are for all leukemias combined unless otherwise noted.

** Exposures are occupational unless otherwise noted.

Chronic lymphocytic leukemia/small lymphocytic leukemia **(CLL/SLL)**

Summary for TCE and Benzene

The meta-analyses are in agreement with a summary RR for leukemias from TCE exposure of about 1.10. Positive associations were observed in the three studies conducted subsequent to the meta-analyses. Both CLL and non-CLL leukemias had positive associations with TCE in the two studies that evaluated leukemia subtypes. The drinking water studies at Cape Cod and northern NJ found associations with leukemia, with the northern NJ study finding elevations in ALL, CLL and CML associated with TCE. The Camp Lejeune mortality studies observed elevated risks for leukemias for the marine/navy and civilian worker cohorts compared to the Camp Pendleton cohorts as well as an elevated SMR for the civilian workers compared to the U.S. population.

AML is known to be caused by benzene exposure. IARC (monograph 100F, 2012) has concluded that positive associations exist for ALL and CLL. The epidemiological evidence from the meta-analyses indicates that benzene causes all types of leukemia.

Mechanistic Information: Evidence from animal data indicates that TCE causes autoimmune disorders. In humans, TCE has been associated with systemic sclerosis. In a pooled analysis, systemic sclerosis was associated with leukemia based on 2 studies: SIR=2.75 (1.32, 5.73) (Onishi A et al 2013). In general, there is human and animal evidence that TCE is associated with immunomodulation, autoimmunity and immune suppression, and that these immune disorders are associated with hematopoietic cancers such as leukemias.

ATSDR Assessment: Benzene is known to cause AML. The epidemiological evidence also supports causation for benzene and the other leukemia types. ATSDR concludes that there is sufficient evidence for causation for benzene and all leukemia types. The evidence is less strong for TCE, but based on less than sufficient evidence of causation from the epidemiological studies and the supporting mechanistic information on TCE exposure effects on the immune system, ATSDR concludes that there is modest evidence for causation for TCE and all types of leukemia.

5-year survival % (SEER):

AML: 25.2
CML: 62.0
ALL: 67.6
CLL: 81.8

Mortality Studies: Blair 2003, Hsieh 2011, Silver 2014, Bove 2014, Linet 2015

Incidence Studies: Aschengrau 1993, Cohn 1994, Costas 2002, Schnatter 2012, Hansen 2013, Vlaanderen 2013, Christensen 2013, Cocco 2013, Ruckart 2013, Linet 2015, Stenehjem 2015

Liver Cancer

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Alexander 2007 **Meta-analysis**	TCE-exposed sub-cohorts	Summary RR = 1.41 (1.06, 1.87)	–	–
Scott 2011 **EPA Meta-analysis**	TCE: All studies High exposure group	Summary RR = 1.29 (1.07, 1.56) Summary RR = 1.28 (0.93, 1.77)	–	–
Hansen 2013	TCE	pooled RR = 1.93 (1.19, 2.95)	No association with U-TCA (small numbers of cases)	Lagging exposure by zero, 10, and 20 years: RRs = 1.77, 1.83, and 2.09, respectively
Lipworth 2011	Aircraft manufacturing TCE PCE	 SMR=0.89 (0.57, 1.33) SMR=0.93 (0.56, 1.45)		–
Vlaanderen 2013	TCE tertiles PCE tertiles	RRs ≤1.03 1st tertile: RR=0.91 (0.73, 1.14) 2nd tertile: RR=1.18 (0.97, 1.44) 3rd tertile: RR=1.13 (0.92, 1.38)		
Raaschou-Nielsen 2003£	TCE	Men, SIR=1.1 (0.7, 1.6) Women, SIR=2.8 (1.13, 5.80)	Duration of employment (years): <1: men, RR=1.3; women, RR=2.8 1-4.9: men, RR=1.0; women, RR=4.1 ≥5: men, RR=1.1; women, RR=1.3	Similar SIRs for lag time of zero and 20 years.
Radican 2008€	TCE (men only) Aircraft maintenance	RR=2.72 (0.34, 21.88)	Cumulative exposure score (unit-yrs): 0-5: RR=3.28 5-25: RR=0 >25: RR=4.05	Low, intermittent: RR=3.75 Low, continuous: RR=1.29 Peak, infrequent: RR=6.42 Peak, frequent: RR=2.13
Lynge 2006	Dry Cleaning	RR=0.76 ((0.38, 1.52)		
Blair 2003	Dry Cleaning	SMR=0.8 (0.4, 1.5)		
Selden 2011	Dry Cleaning: PCE sub-cohort	 Men: SIR=2.14 (0.92, 4.21) Women: SIR=0.90 (0.43, 1.65)	<1 year 1-4 years >4 years 0.0 3.2 2.1 1.7 1.5 0.5	
Boffetta 2003 **Meta-analysis**	Vinyl chloride	SMR=2.96 (2.00, 4.39) SMR=1.35 (1.04, 1.77) for liver cancers **except angiosarcoma**		
Hsieh 2011	Polyvinyl chloride workers	SMR=1.93 (1.37, 2.79) during high exposure period		
Carreón 2014	Vinyl chloride	SMR=3.80 (1.89, 6.80)	7.4 - <16 years: SRR=1.45 ≥16 years: SRR=3.92	
Bove 2014 (Camp Lejeune Marines/Navy)	VOC-contaminated drinking water vs. U.S. population vs. Camp Pendleton	 SMR=0.74 (0.55, 0.97) RR = 1.42 (0.92, 2.20)Ψ	1-3 months, RR=1.51 4-6 months, RR=1.73 7-12 months, RR=1.36 >12 months, RR=1.12	RR=1.30 in the very low exposure group RR=1.34 in the low/high exposure group
Reference	**Exposure***	**RR (SIR, SMR, OR) & 95% CI**	**Exposure Duration information**	**Exposure intensity/cumulative exposure information**
Bove 2014 (Camp	vs. Camp Pendleton	RR < 1.0		

Lejeune Civilian Workers)				

* Exposures are occupational unless otherwise noted.

£ Included in the EPA and Alexander et al meta-analyses. Included in the table because of information on employment duration and exposure lag time.

€ Included in the EPA meta-analyses. Included in the table because of information on exposure intensity and cumulative exposures for men only. (There were no exposed cases among women.)

Ψ Liver/biliary/gall bladder cancers.

Note: Christensen et al 2013 had one exposed liver cancer.

Summary for TCE and Liver Cancer

NTP Monograph on TCE (2015): "The epidemiological data suggest that trichloroethylene may be associated with a modest increase in the risk of liver cancer, based primarily on the two meta-analyses. However, the findings are inconsistent across studies, and there was little evidence for exposure-response relationships in the individual studies or the meta-analyses. In addition, the role of chance or confounding by one or more common occupational co-exposures or lifestyle factors cannot be completely ruled out."

EPA Toxicological Review of TCE (2011): "The evidence is more limited for liver cancer mainly because only cohort studies are available and most of these studies have small numbers of cases." IARC (2014) had essentially the same conclusion as the EPA assessment.

Mechanistic Information: "Although species differences in sensitivity to the proposed modes of action are likely, no data suggest that trichloroethylene causes liver tumors in mice by mechanisms that are irrelevant to humans. Most of the hypothesized modes of action for liver tumors have some experimental support and are biologically plausible in humans and rodents." (NTP Monograph on Trichloroethylene, 2015, page 176). "It is likely that multiple mechanisms, potentially including immune dysregulation, epigenetic alterations, cytotoxicity and secondary oxidative stress, alteration of proliferation and/or apoptosis, may contribute to hepatocarcinogenesis." (Rusyn I et al. 2014).

ATSDR Assessment: Both meta-analyses achieved similar positive summary RRs for TCE exposure. The exposure-response evaluation was limited by small numbers of highly exposed cases. Conflicting findings for TCE and liver cancer occurred among studies considered by NTP (2015) to be of low or low/moderate utility (i.e., studies with serious limitations), e.g., Lipworth et al 2011, Vlaanderen et al 2013, and Raaschou-Nielsen et al 2003. The Camp Lejeune mortality studies found an increased risk of liver cancer among marines/navy personnel but not among civilian workers when compared to the Camp Pendleton cohorts. The three cohort studies considered of moderate utility by NTP (2015), i.e., Morgan et al 1998 (not shown in the table because it was included in the meta-analyses and did not have information on duration or cumulative exposure), Radican et al 2008, and Hansen et al 2013 found elevated risks for liver cancer among TCE exposed workers. In particular, the Hansen et al 2013 pooled analysis of studies conducted in three Nordic countries obtained a pooled RR for primary liver cancer of 1.93 (1.19, 2.95) that was similar for males and females. The RRs increased with lagtime when liver cancer was combined with cancer of the biliary passages. The study attempted to evaluate U-TCA levels but had too few cases with U-TCA levels above the reference level. Given the consistent findings in the meta-analyses that TCE is associated with increased risk of liver cancer, in particular, the consistent

findings among well-conducted cohort studies, the evidence from the epidemiological studies is compelling. However, because studies were unable to adequately evaluate exposure-response trends due to small numbers, this is a limitation. Therefore ATSDR concludes that the epidemiological studies provide less than sufficient evidence for causation. Combining the epidemiological evidence with the supporting evidence from animal studies and plausible mechanistic information, ATSDR concludes that there is modest evidence for causation for TCE and liver cancer.

Summary for Vinyl Chloride and Liver Cancer

IARC monograph 100F (2012) concluded: "There is compelling evidence that exposure to vinyl chloride is associated with angiosarcoma of the liver, and strong evidence that it is associated with hepatocellular carcinoma. Together with the observation that vinyl chloride increases the risk of liver cirrhosis, which is a known risk factor for hepatocellular carcinoma, the findings from two large multicentre cohort studies provide convincing evidence that vinyl chloride causes hepatocellular carcinoma as well as angiosarcoma of the liver."

ATSDR Assessment: Since the IARC review, two recent studies, Hsieh et al 2011 and Carreón et al 2014, also found associations between occupational exposures to vinyl chloride and liver cancer. ATSDR concurs with the IARC (2012) assessment and concludes that there is sufficient evidence for causation for vinyl chloride and hepatocellular carcinoma as well as angiosarcoma of the liver.

5-year survival % (SEER): 17.2 %

Mortality Studies: Boffetta 2003, Radican 2008, Lipworth 2011, Hsieh 2011, Carreón 2014, Bove 2014

Incidence Studies: Raaschou-Nielsen 2003, Hansen 2013, Vlaanderen 2013, Christensen 2013

Pancreatic Cancer

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information

Ojajarvi 2001, 2007 **meta-analysis**	Metal degreasing Dry-cleaning TCE Vinyl chloride PCE (1 study) chlorinated hydrocarbon solvents	Summary RR=2.0 (1.2, 3.6) Summary RR=1.4 (1.1, 2.4) Summary RR=1.24 (0.79, 1.97) Summary RR=1.17 (0.71, 1.91) Summary RR=3.08 (0.63, 8.99) Summary RR$^{\Psi}$=2.2 (1.31, 3.68)	–	–
Morgan 1998	TCE (aerospace plant)	SMR=0.76 (0.56, 1.01)	–	–
Anttila 1995$^{\epsilon}$	TCE	SIR=1.61 (0.81, 2.88)		U-TCA (µmol/L): <100 SIR=1.61 (0.59, 3.50) 100 + SIR=1.31 (0.27, 3.82)
Raaschou-Nielsen 2003	TCE	Men: SIR=1.1 (0.9, 1.4) Women: SIR=1.0 (0.5, 2.0)		
Radican 2008	TCE (Aircraft maintenance)	Males: RR=0.91 (0.49, 1.68) Females: RR=1.71 (0.57, 5.12)		
Lipworth 2011	Aircraft manufacturing TCE PCE	 SMR=0.93(0.70, 1.22) SMR=1.05 (0.75, 1.44)	–	–
Hansen 2013	TCE	RR=1.31 (0.93, 1.80); females: 2.18 (1.35, 3.34); males: <1.0	–	–
Zhao 2005	TCE	RR<1.0, except medium exposure score, mortality: RR=1.13(0.58, 2.21)	–	–
Silver 2014	TCE/PCE (microelectronic plant)	SMRs<1.0	–	–
Santibañez 2010	Chlorinated hydrocarbon solvents			All pancreatic cancer: "low" (≤0.83 ppm): OR=0.9 (0.1, 7.8) "high" (>0.83 ppm): OR=2.0 (0.6, 6.4) Ductal adenocarcinoma: "low" (≤0.83 ppm): OR=1.2 (0.1, 12.3) "high" (>0.83 ppm): OR=4.1 (1.1, 15.2)
Lynge 2006	PCE (dry cleaning)	RR=1.27 (0.90, 1.80) 4 countries; RR=1.38 (0.9, 2.2) 2 countries	≤1 year employment: RR=2.14	–
Calvert 2011	PCE (dry cleaning)	SMR = 1.51 (0.95, 2.29) all workers SMR = 1.86 (1.10, 2.94) "PCE +" SMR = 0.82 (0.22, 2.10) "PCE only" (based on 4 deaths)		
Reference	**Exposure**[*]	**RR (SIR, SMR, OR) & 95% CI**	**Exposure Duration information**	**Exposure intensity/cumulative exposure information**
Blair 2003	PCE (dry cleaning)	SMR = 1.1 (0.7, 1.5)		Little/no exposure: SMR=1.2 (0.7, 2.0)
Linet 2015	Benzene	RR=1.7 (1.0, 3.1)		
Paulu 1999	PCE-contaminated drinking water	OR=0.6 (0.1,1.7) based on 3 cases		

Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=0.98 (0.74, 1.27) RR=1.36 (0.91, 2.02)	Duration (months) 1-3 RR=1.01 4-6 RR=1.09 7-12 RR=0.95 <12 RR=1.09	Elevated risk among those with low cumulative exposure
Bove 2014 (Camp Lejeune Civilian workers)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=1.02 (0.53, 1.78) RR = 0.54 (0.24, 1.20)	–	–

[*] Exposures are occupational unless otherwise noted.

[Ψ] Hierarchical Bayesian model combining information from studies that evaluated job titles only and information from a JEM .

[€] This study was included in the Ojajarvi 2001meta-analysis but is listed here because of additional information on U-TCA.

Note: Christensen et al 2013 had no cases of pancreatic cancer with "substantial" exposure to PCE or TCE.

Summary

A review of the evidence for occupational exposures and pancreatic cancer by NCI (Andreotti G and Silverman DT 2012) concluded: "Chlorinated hydrocarbon exposure is one of the most researched and established occupational risk factors for pancreatic cancer." The review stated that, based on the meta-analyses of studies published between 1969 and 1998 of 20 populations in Europe, North America, and Asia (Ojajarvi et al. 2001, 2007) and a recent study (Santibañez et al 2010), the authors concluded that: "…The strongest and most consistent findings linking occupational expsures with pancreatic cancer risk to date are for chlorinated hydrocarbons and PAHs." The authors specifically mentioned that pancreatic cancer was linked to TCE and PCE exposures as well as to dry cleaning and metal-related work including metal degreasing. In the Camp Lejeune mortality studies, pancreatic cancer risk was elevated in the marine/navy cohort but not in the civilian worker cohort when compared to the Camp Pendleton cohorts.

ATSDR Assessment: For TCE, the strongest evidence comes from the meta-analysis, the Radican et al 2008 study, and the pooled Nordic study (Hansen et al 2013). Based on the meta-analysis, there appears to be sufficient evidence of an association for TCE and pancreatic cancer. However, the findings from the Radican et al 2008 and Hansen 2013 studies indicate that the risk from TCE exposure is elevated only among females. Therefore ATSDR concludes that there is less than sufficient evidence of an association for TCE and pancreatic cancer. The epidemiological evidence for PCE is somewhat stronger than for TCE, although dry cleaning workers could have been exposed to other solvents besides PCE. ATSDR concludes that there is sufficient evidence of an association for PCE and pancreatic cancer.

5-year survival % (SEER): 7.2%

Mortality Studies: Morgan 1998, Radican 2008, Lipworth 2011, Zhao 2005, Silver 2014, Calvert 2011, Blair 2003, Linet 2015, Bove 2014

Incidence Studies: Paulu 1999, Raaschou-Nielsen 2003, Zhao 2005, Lynge 2006, Santibañez 2010, Hansen 2013

Prostate cancer

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information

Krishnadasan 2007	Aerospace/radiation TCE			Low/moderate: OR=1.3 (0.8, 2.1) High: OR=2.4 (1.3, 4.4)
Radican 2008	Aircraft maintenance TCE	RR=1.20 (0.82, 1.76)	Cumulative exposure score (unit-yrs): 0-5: RR=1.03 5-25: RR=1.33 >25: RR=1.31	Low, intermittent RR=1.22 Low, continuous RR=1.30 Peak, infrequent RR=1.02 Peak, frequent RR=1.24
Lipworth 2011	Aircraft manufacturing TCE PCE	 SMR = 1.11 (0.93, 1.31) SMR = 0.92 (0.72, 1.16)	Years exposed (RRs): TCE PCE <1: 0.8 0.9 1-4: 1.2 1.1 >4: 1.2 0.7	
Morgan 1998	Aerospace, TCE-exposed subcohort: **Meta-analysis:**	 SMR = 1.18 (0.73, 1.80) summary SMR = 1.09 (0.87, 1.36)		Cumulative exposure: Low: RR= 1.72 High: RR=1.53
Anttila 1995	TCE	SIR=1.38 (0.73, 2.35)		U-TCA (µmol/L): <100 SIR=1.43 (0.62, 2.82) 100 + SIR=0.68 (0.08, 2.44)
Axelson 1994	TCE	SIR=1.25 (0.84, 1.84)	Years exposed: <2: SIR=1.19 ≥2: SIR=1.27	U-TCA (mg/L): Most had levels <49, SIR=1.3
Boice 2006	Any TCE	SMR=0.82 (0.36, 1.62)		
Raaschou-Nielsen 2003	TCE	SIR=0.9 (0.79, 1.08)		
Ritz 1999	TCE "light" TCE "moderate"	RR=1.04 (0.40, 2.70) RR=1.96 (0.25, 15.6)		
Hansen 2013	TCE	SIR < 0.96 (0.80, 1.14)		
Christensen 2013	TCE any TCE "substantial" PCE any PCE "substantial"	OR = 1.3 (0.7, 2.6) OR = 1.2 (0.5, 3.1) OR = 2.2 (0.8, 5.7) OR = 4.3 (1.4, 13.0)		
Blair 2003	PCE (dry cleaning)	SMR = 1.0 (0.6, 1.6)		
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR = 1.73 (1.02, 2.73) RR = 1.23 (0.60, 2.49)	Duration (months) 1-3 RR=0.78 4-6 RR=2.25 7-12 RR=1.17 >12 RR=0.97	For TCE, an elevated RR was observed only for low cumulative exposures
Reference	**Exposure***	**RR (SIR, SMR, OR) & 95% CI**	**Exposure Duration information**	**Exposure intensity/cumulative exposure information**
Bove 2014 (Camp Lejeune Civilian workers)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR = 1.09 (0.52, 2.01) RR = 1.17 (0.49, 2.82)	6/10 deaths had exposure durations of 4 years or more.	Both medium and high cumulative exposures to TCE and PCE had RRs > 2.0 compared to very low cumulative exposure. 8/10 deaths had cumulative

				exposures above the median for TCE, PCE and benzene

* Exposures are occupational unless otherwise noted.

Summary

Prostate cancer was elevated for most of the studies that evaluated TCE exposed workers. Prostate cancer mortality was also elevated among Camp Lejeune marines/navy personnel and civilian workers.

ATSDR Assessment: ATSDR concludes that there is sufficient evidence of an association for TCE and prostate cancer based on the epidemiological evidence.

5-year survival % (SEER): 98.9%

Mortality Studies: Morgan 1998, Ritz 1999, Blair 2003, Boice 2006, Radican 2008, Lipworth 2011, Bove 2014

Incidence Studies: Axelson 1994, Anttila 1995, Krishnadasan 2007, Hansen 2013, Christensen 2013

Breast cancer

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Male breast cancer				
Hansen 2013	TCE	SIR = 2.11 (0.26, 7.60) (2 cases)		
Ruckart 2015 Camp Lejeune drinking water	Stationed at Camp Lejeune PCE (upper tertile) Vinyl chloride	OR=1.14 (0.65, 1.97) OR=1.20 (0.16, 5.89) OR=1.19 (0.16, 5.89)		RRs ranged 1.4-2.7 for age at onset proportional hazards models for TCE, PCE and vinyl chloride
Female breast cancer				
Hansen 2013	TCE	SIR= 1.00 (0.80, 1.24)		
Lipworth 2011	Aircraft manufacturing TCE PCE	SMR = 1.03 (0.53, 1.80) for TCE SMR = 1.52 (0.78, 2.65) for PCE	Years exposed (RRs): TCE PCE <1: 0.8 1.4 1-4: 0.3 0.3 >4: 1.5 1.7	
Radican 2008	Aircraft maintenance TCE	RR = 1.23 (0.73, 2.06)	Cumulative exposure score (unit-yrs): 0-5: RR=1.57 5-25: RR=1.01 >25: RR=1.05	Low, intermittent RR=1.92 Low, continuous RR=1.71 Peak, infrequent RR=1.18 Peak, frequent RR=1.08
Morgan 1998	TCE (aerospace)	SMR=0.75 (0.43, 1.22)		
Raaschou-Nielsen 2003	TCE	SIR=1.1 (0.9, 1.2)		
Blair 2003	Dry cleaning	SMR = 1.0 (0.8, 1.3)		Exposure level: Little/no: SMR=0.8 Medium/high: SMR=1.2
Calvert 2011	Dry cleaning (All) PCE only PCE plus	SMR=1.05 (0.70, 1.52) SMR=1.06 (0.51, 1.94) SMR=1.05 (0.62, 1.66)		
Selden 2011	Dry Cleaning (PCE)	SIR=0.85 (0.72, 1.00)		
Chang 2005	Electronics factory Chlorinated organic solvents	SIR = 1.19 (1.03, 1.36)	Duration of employment (years) ≤1: SIR=1.20 1-5: SIR=1.19 >5-10: SIR=1.69 >10: SIR=0.37	
Reference	**Exposure***	**RR (SIR, SMR, OR) & 95% CI**	**Exposure Duration information**	**Exposure intensity/cumulative**

				exposure information
Oddone 2014	Chlorinated solvents	OR=1.65 (1.04, 2.62)	Duration ≥10 years, OR=2.1	
Glass 2015	Benzene Chlorinated Solvents	OR = 1.08 (0.80, 1.47) OR = 1.53 (0.84, 2.80) for premenopausal women OR = 0.96 (0.67, 1.38) for post-menopausal women OR = 1.05 (0.69, 1.61) OR = 1.47 (0.62, 3.45) for premenopausal women OR = 0.94 (0.57, 1.54) for post-menopausal women		
Costantini 2009	Shoe factory Benzene	latency (years) <30: SMR=58.5 (18.9, 181.2) ≥30: SMR=151.1 (78.6, 290.3)		Cumulative exposure (ppm-yr) ≤40: SIR=116.0 >40: SIR=130.1
Peplonska 2010	Benzene	OR=1.0 (0.8, 1.3)		
Linet 2015	Benzene	RR=1.2 (0.6, 2.5)		
Gallagher 2011	PCE in drinking water	OR=1.5 (0.9, 2.5) for exposures >90th percentile and 13-year latency OR = 2.0 (0.8, 4.8) using LOESS smoothing	Elevated OR was seen only among those with ≥10 years of exposure	
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR < 1.0 RR < 1.0		
Bove 2014 (Camp Lejeune Civilian workers)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR < 1.0 RR = 1.21 (0.58, 2.51)	Most of the cases had more than one year exposure duration	

* Exposures are occupational unless otherwise noted.

Summary

Combining the epidemiological evidence across studies, there is some support for an association between female breast cancer and TCE, PCE, chlorinated solvents and benzene. However, the findings are not consistent across studies. The finding of an association between PCE-contaminated drinking water and breast cancer in the Cape Cod study provides additional support for an association for PCE. In the Camp Lejeune mortality studies, breast cancer was elevated among civilian workers but not marines/navy personnel in comparison with cohorts

from Camp Pendleton. The two studies listed in the tables that evaluated male breast cancer were limited due to small numbers of exposed cases. However there is strong evidence that female and male breast cancers share similar risk factors. For example, age-specific incidence patterns indicate that the biology of male breast cancer resembles that of late-onset female breast cancer, and similar breast cancer incidence trends among men and women suggest common breast cancer risk factors, especially estrogen receptor–positive breast cancer (Anderson et al 2010). In general, anthropometric and hormonal factors are important risk factors for both male and female breast cancer (Brinton LA et al. 2014).

ATSDR Assessment: ATSDR concludes that the epidemiological evidence provides limited/suggestive evidence for associations between female breast cancer and TCE, PCE, chlorinated solvents, and benzene. ATSDR recognizes that the two studies that evaluated male breast cancer provide insufficient information (because of small numbers of cases) to assess the relationship between any of the chemicals found in the drinking water at Camp Lejeune and male breast cancer. However, there is evidence that male and female breast cancer share similar risk factors. Therefore, given the current state of knowledge, ATSDR concludes that the findings for female breast cancer should be applicable to male breast cancer as well.

5-year survival % (SEER): Male=82.7% Female=89.4%

Mortality Studies: Morgan 1998, Radican 2008, Lipworth 2011, Constantini 2009, Calvert 2011, Blair 2003, Linet 2015, Bove 2014

Incidence Studies: Raaschou-Nielsen 2003, Hansen 2013, Chang 2005, Gallagher 2011, Selden 2011, Oddone 2014, Glass 2015

Bladder cancer

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Vlaanderen 2014 IARC **meta-analysis**	PCE (Dry cleaning worker studies)	summary RR = 1.08 (0.82, 1.42) for 3 PCE workers studies summary RR = 1.47 (1.16, 1.85) for 7 dry cleaning workers studies	In one dry cleaner study (Lynge et al 2006), RR = 1.5 was observed for an exposure duration of ≤one year	Exposure-response gradients were observed in the dry cleaning workers studies. Elevated risks were observed even at low to moderate exposure levels.
Aschengrau 1993	PCE in drinking water	OR = 1.55 (0.74, 3.01)		Low: OR=1.16 (0.48, 2.48) High: OR=6.04 (1.32, 21.84)
Hansen 2013	TCE	SIR=1.21 (0.91, 1.58), males only		
Lipworth 2011	Aircraft manufacturing TCE	SIR=1.03 (0.72, 1.43)		
Christensen 2013	TCE	OR < 1.0 for any or "substantial"		
Silver 2014	Microelectronics plant TCE PCE			Cumulative exposure (5 exposure-yrs) RR < 1.0 RR < 1.0
Radican 2008	Aircraft maintenance TCE	RR=1.05 (0.47, 2.35) (males only)	Cumulative exposure score (unit-yrs): 0-5: RR=0.96 5-25: RR=1.77 >25: RR=0.65	Low, intermittent RR=1.03 Low, continuous RR=1.32 Peak, infrequent RR=0.59 Peak, frequent RR=0.82
Zhao 2005	Aerospace TCE Incidence data			Cumulative exposure score (RRs) Zero lag 20 year lag Medium: 1.8 (0.6, 5.2) 1.8 (0.6, 5.1) High: 3.8 (1.0, 14.8) 3.7 (0.9, 15.5)
Anttila 1995	TCE	SIR=0.82 (0.27, 1.90)		
Axelson 1994	TCE	SIR=1.02 (0.44, 2.00)		
Morgan 1998	TCE subcohort	SMR=1.36 (0.59, 2.68)		Low TCE: SMR=0.51 High TCE: SMR=1.79 Peak (medium/high): RR=1.41 Low cumulative: RR=0.69 High cumulative: RR=2.71
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water	No association		
Bove 2014 (Camp Lejeune Civilian workers)	VOC contaminated drinking water	No association		

* Exposures are occupational unless otherwise noted.

Summary for PCE and bladder cancer

The IARC meta-analysis (Vlaanderen et al 2014) evaluated potential confounding by smoking and concluded: "Among the subgroup of dry-cleaning workers only, the mRR [meta-relative risk] for the case-control studies that adjusted for tobacco smoking was similar to the mRR for the cohort studies, indicating that there is little evidence of confounding by tobacco smoking." The meta-analysis study concluded: "Our meta-analysis demonstrates an increased risk of bladder cancer in dry cleaners, reported in both cohort and case–control studies, and some evidence for an exposure–response relationship." Three key dry cleaning cohort studies conducted by NCI, NIOSH and Nordic researchers that were included in the meta-analysis found positive associations. The Nordic study (Lynge et al 2006) obtained RRs of 1.44 (1.07, 1.93) and 1.69 (1.18, 2.43) for all Nordic countries and analyses restricted to Denmark and Norway, respectively. The NCI study (Blair et al 2003) obtained an SMR of 1.5 (0.6, 3.1) among those with medium or high exposure. The NIOSH study (Calvert et al 2011) obtained an SMR of 2.59 (1.24, 4.76) for workers who worked in shops where PCE was the primary cleaning solvent but also worked in shops for which the primary solvent was unidentified (but likely PCE), which increased to an SMR of 4.08 (2.13, 7.12) for those with 5 or more years employment and at least 20 years from first employment.

ATSDR Assessment: ATSDR concludes that the results of the meta-analysis conducted by the IARC workgroup support a classification of sufficient evidence of causation for PCE and bladder cancer. In particular, the results of meta-analysis were not affected by confounding due to smoking, and an exposure-response gradient was evident in some of the dry cleaning worker studies. At this time there is no animal data or mechanistic data that support the epidemiological findings, but ATSDR believes the epidemiological studies provide sufficient evidence for causation.

Summary for TCE and bladder cancer

The epidemiological evidence provides limited/suggestive evidence of an association between TCE and bladder cancer. The Camp Lejeune mortality studies did not find increased risks for bladder cancer. This is likely due to the fact that bladder cancer has a high survival rate and the Camp Lejeune cohorts were relatively young so there were few deaths due to bladder cancer in the Camp Lejeune studies. A full evaluation of bladder cancer risk at Camp Lejeune must await the cancer incidence study and later mortality follow-up.

5-year survival % (SEER): 77.4%

Mortality Studies: Morgan 1998, Radican 2008, Lipworth 2011, Silver 2014, Bove 2014

Incidence Studies: Aschengrau 1993, Axelson 1994, Anttila 1995, Zhao 2005, Hansen 2013, Christensen 2013

Parkinson's disease

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
McDonnell 2003	Solvents	OR = 1.53 (0.81, 2.87)	<10 years: OR=1.2 (0.5, 2.7) 10 - <20 years: OR=1.1 (0.4, 3.2) 20 - <30 years: OR=1.3 (0.3, 5.3) 30 + years: OR=3.6 (1.3, 10.3)	–
Goldman 2012	TCE PCE	OR = 6.1 (1.2, 33) for TCE OR = 10.5 (0.97, 113) for PCE	Exposure-response trend for duration	Exposure-response trend for cumulative exposure
Pezzoli 2013 **Meta-analysis**	Solvents	summary OR = 1.35 (1.09, 1.67) summary OR = 1.58 (1.23, 2.04) for higher quality studies	–	–
Feldman 2011	Organic solvents	RR < 1.0 for any solvent exposure RR = 1.4 (0.6, 2.9) for high probability of solvent exposure	–	–
Brouwer 2015	Aromatic and chlorinated solvents	No associations for aromatic or chlorinated solvents	–	–
Van der Mark 2015	Aromatic and chlorinated solvents	OR ≤ 1 for ever exposure to aromatic or chlorinated solvents	OR=1.39 (0.88, 2.20), >24 years exposure to chlorinated solvents OR=1.26 (0.80, 1.97), >24 years exposure to aromatic solvents	3rd tertile cumulative exposure: OR=1.15 (0.72, 1.84), chlorinated solvents OR=1.33 (0.86, 2.05), aromatic solvents
Bove 2014 (Camp Lejeune Civilian worker)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	SMR = 2.19 (0.71, 5.11) RR = 3.13 (0.76, 12.86)	The cases at Lejeune had at least 18 months of exposure	Four of five deaths had above the median cumulative exposure to TCE and PCE

* Exposures are occupational unless otherwise noted.

Summary

IOM: Review of VA Clinical Guidance for the Health Conditions identified by the Camp Lejeune Legislation: "…Parkinson's disease is a neurobehavioral effect that may result from exposure to TCE and/or PCE."

Parkinson's disease is a disease occurring in older populations and has a long latency period (10-40 years).

ATSDR Assessment: A few studies have evaluated solvents in general and separately for chlorinated and organic solvents, and elevated risks for Parkinson's disease have been observed. Positive associations have been observed for TCE and PCE and Parkinson's disease in a well-

conducted twin study. Although the Camp Lejeune mortality study of marines could not evaluate Parkinson's disease because the cohort was too young, mortality among civilian workers was elevated both compared to Camp Pendleton and the U.S. population. Four out of the 5 deaths had above the median cumulative exposure to TCE and PCE in this study. The evidence is stronger for TCE since there have been case reports of Parkinson's disease and Parkinsonism among TCE-exposed workers. Moreover, a plausible mechanism exists since TCE has been found to be a mitochondrial neurotoxin in animal studies and mitochondrial dysfunctions in substantia nigra dopamine neurons is considered to cause the disease (Gash et al 2008). However, because only two study have focused on TCE exposure, there is insufficient evidence of causation for TCE and Parkinson's disease. ATSDR concludes that there is modest evidence for causation for TCE when the epidemiological evidence is combined with the animal and mechanistic study evidence.

Kidney disease

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Boice 2006	Any TCE	SMR=2.07 (0.67,4.82)		
Radican 2006	Aircraft maintenance TCE PCE	ESRD: RR=1.86 (1.02, 3.39) RR=0.97 (0.27, 3.52)	Person-years exposure: <2.5: RR=1.99 2.5-10: RR=1.52 >10: RR=2.05	Cumulative TCE exposure (unit-years) <5: RR=1.73 5-25: RR=2.48 >25: RR=1.65
Jacob 2007	TCE	RR = 2.5.(0.9, 6.5) for ESRD		RR=2.7 (0.7, 10.1) for high TCE exposures
Lipworth 2011	Aircraft manufacturing TCE PCE	Nephritis and nephrosis: SMR =1.13 (0.81, 1.54) SMR= 1.11 (0.74, 1.60)	–	
Silver 2014	Microelectronics plant TCE PCE	Non-malignant chronic renal disease	–	Cumulative exposure (5 exposure-years) RR =1.07 (0.70, 1.63) RR < 1.0
Calvert 2011	Dry cleaning PCE only PCE plus PCE only PCE plus PCE only PCE plus PCE only PCE plus	Acute glomerulonephritis/nephrotic syndrome/acute renal failure: SMR = 2.60 (0.31, 9.39 SMR=1.18 (0.14, 4.27) Total ESRD: SIR = 1.30 (0.67, 2.26) SIR = 1.37 (0.81, 2.17) Systemic ESRD: SIR=1.64 (0.85, 2.86) SIR=1.48 (0.83, 2.44) Hypertensive ESRD SIR=2.66 (1.15, 5.23) SIR=1.53 (0.62, 3.16)	–	–
Blair 2003	Dry cleaning	SMR = 1.1 (0.6, 1.8) for chronic nephritis	–	SMR = 1.4 (0.7, 2.5) for medium to high exposures to dry cleaning solvents (most likely PCE)
Bove 2014 (Camp Lejeune Civilian worker)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=0.78 (0.34, 1.54) RR=1.23 (0.39, 3.87)	3 deaths had exposure durations of ≤6 months, and the other 4 deaths had exposure duration ≥33 months.	
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=0.50 (0.35, 0.68) RR=1.0 (0.63, 1.63)	–	–

* Exposures are occupational unless otherwise noted. ESRD: End stage renal disease

Summary

The IOM report, Review of VA Clinical Guidance for the Health Conditions Identified by the Camp Lejeune Legislation, concluded: "While there is some evidence for increased mortality from solvent-induced hypertensive end-stage renal disease (ESRD), the association between TCE and PCE and chronic kidney disease is less clear, although there does appear to be an association between exposures to high levels of these solvents and ESRD."

EPA toxicological review of PCE (2012): "Taken together, the epidemiologic studies support an association between tetrachloroethylene and chronic kidney disease, as measured by urinary excretion of renal proteins and ESRD incidence."

The EPA toxicological review of TCE (2011) concluded that high levels of TCE exposure caused proximal tubule damage and increases in various biomarkers of kidney toxicity or ESRD including β2-microglublin, total protein, NAG, and α1-microglobulin. Animal studies provide evidence that TCE exposure causes renal toxicity in the form of cytomegaly and karyomegaly of the renal tubules. Studies of TCE metabolites have demonstrated a potential role for DCVC, TCOH and TCA in TCE-induced kidney toxicity.

ATSDR Assessment: Most of the studies listed in the table found positive associations between kidney diseases, including ESRD, and TCE and/or PCE exposures. Among Camp Lejeune workers, there was an excess of kidney disease deaths when compared to Camp Pendleton. ATSDR concludes that there is modest evidence of causation for TCE and kidney disease and ESRD based on the combined evidence from epidemiological studies, biomarker studies, animal studies and mechanistic information. The evidence for PCE and kidney disease is weaker but ATSDR concurs with the EPA assessment that there is sufficient evidence for an association for PCE and kidney disease and ESRD.

Esophageal Cancer

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Raaschou-Nielsen 2003	TCE (20 year exposure lag)	Adenocarcinomas: SIR=1.8 (1.2, 2.7) SIR=1.7 (0.8, 3.0)	Duration of employment (years): <1: SIR=1.7 1-4.9: SIR=1.9 ≥5: SIR=1.9	An exposure lag period of 10-19 years had the highest risk: SIR=2.3 (0.9, 5.0)
Boice 2006	Any TCE	SMR=0.88 (0.18, 2.58)		
Radican 2008	Aircraft maintenance TCE (cumulative exposure & intensity, men only)	RR=1.88 (0.61, 5.79) Men: RR=1.66 (0.48, 5.74) Women: RR=2.81 (0.25, 31.1)	Cumulative exposure score (unit-yr) 0-5: RR=1.8 5-25: RR=1.3 >25: RR=1.7	Low, intermittent: RR=1.9 Low, continuous: RR=1.0 Peak, infrequent: RR=2.2 Peak, frequent: RR=1.6
Lipworth 2011	Aircraft manufacturing TCE PCE	 SMR=0.65 (0.39, 1.01) SMR=1.13 (0.72, 1.68)	Years exposed (PCE): <1: RR=2.3 1-4 RR=1.3 ≥5 RR=0.7	
Santibañez 2008	Chlorinated solvents	High (>0.83 ppm): OR=1.8 (0.4, 7.7)		
Hansen 2013	TCE	Men: SIR=1.30 (0.65, 2.32) (1 case among women)	Slightly higher SIRs as the exposure lag increases	U-TCA (mg/L) Ref: <5 5-25: RR=0.5 >25 0
Calvert 2011	Dry cleaning (All) PCE only PCE plus	SMR=2.44 (1.40, 3.97) SMR=2.68 (0.98, 5.83) SMR=2.32 (1.11, 4.27)	Duration of employment (years) <5: SMR=2.16 ≥5: SMR=4.78	
Blair 2003	Dry cleaning	SMR=2.2 (1.5, 3.3)		Little/no exposure: SMR=2.1 (0.9, 4.4) Medium/high exposure: SMR=2.2 (1.2, 3.5)
Linet 2015	Benzene	RR=1.6 (1.0, 2.5)		
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=0.85 (0.59, 1.18) HR=1.43 (0.85, 2.38)	Duration of exposure (months) 1-3: RR < 1.0 4-6: RR=2.4 7-12: RR=1.9 >12: RR <1.0	
Bove 2014 (Camp Lejeune Civilian Workers)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=0.64 (0.18, 1.65) HR=0.58 (0.15, 2.22)		

* Exposures are occupational unless otherwise noted.

Note: Lynge et al 2006 is omitted because a majority of the cases were unclassifiable on exposure status. If all the unclassifiable were exposed, then RR=1.19 (0.67, 2.12). If all the unclassifiable were unexposed, then RR=0.66 (0.30, 1.45).
Note: Selden and Ahlborg 2011 is omitted because there were no male cases and 3 female cases among dry cleaners.
Note: Christensen et al 2013 is omitted because there were no PCE-exposed cases and only one TCE-exposed case.

Summary

The NCI and NIOSH dry cleaning studies found strong associations with esophageal cancer. The Lipworth et al 2011 study also found an increased risk of esophageal cancer among PCE-exposed workers. TCE was associated with esophageal cancer in three cohort studies including the pooled Nordic study (Hansen 2013). An elevated RR was also observed in the Camp Lejeune mortality study of marines and navy personnel.

ATSDR Assessment: ATSDR concludes that there is sufficient evidence of an association for TCE and PCE exposure and esophageal cancer based on the dry cleaning and TCE cohort studies.

5-year survival % (SEER): 17.9%

Mortality Studies: Boice 2006, Radican 2008, Lipworth 2011, Calvert 2011, Blair 2003, Linet 2015, Bove 2014

Incidence Studies: Raaschou-Nielsen 2003, Santibañez 2008 Hansen 2013

Lung Cancer

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Morgan 1998	TCE subcohort	SMR=1.10 (0.89, 1.34)		Low TCE: SMR=1.49 High TCE: SMR=0.90 Peak (median/high): SMR=1.07 Low cumulative: RR=1.47 High cumulative: RR=0.96
Anttila 1995	TCE PCE	SIR=0.92 (0.59, 1.35) SIR=1.92 (0.62, 4.48)		U-TCA (µmol/L): <100 SIR=1.02 (0.58, 1.66) 100 + SIR=0.83 (0.33, 1.71)
Axelson 1994	TCE	SIR=0.69 (0.31, 1.30)		
Raaschou-Nielsen 2003	TCE	Men, SIR=1.4 (1.3, 1.5) Women, SIR=1.9 (1.5, 2.4)	Duration of employment (years): Men Women <1: SIR=1.6 SIR=2.5 1-4.9: SIR=1.3 SIR=1.6 ≥5: SIR=1.4 SIR=1.6	20 year exposure lag: Men: SIR=1.4 (1.2, 1.6) Women: SIR=1.6 (1.0, 2.3)
Zhao 2005	Aerospace TCE Incidence data			Cumulative exposure Medium: RR=1.36 (0.86, 2.14) High: RR=1.11 (0.60, 2.06)
Chang 2005	Chlorinated organic solvents	Men: SMR=0.90 (0.48, 1.53) Women: SMR=1.01 (0.65, 1.49)		
Radican 2008	Aircraft maintenance TCE	RR=0.83 (0.63, 1.08)		
Lipworth 2011	Aircraft manufacturing TCE PCE	 SMR=0.80 (0.71, 0.90) SMR=0.94 (0.81, 1.07)		
Hansen 2013	TCE	SIR=1.08 (0.90, 1.29) Men: SIR=1.05 (0.85, 1.28) Women: SIR=1.28 (0.77, 2.00)		
Silver 2014	Microelectronics plant TCE		1.03 (0.87, 1.22) for 5 exposure-yrs.	
Calvert 2011	Dry cleaning (All) PCE only PCE plus	SMR=1.31 (1.04, 1.64) SMR=1.25 (0.82, 1.83) SMR=1.35 (1.00, 1.77)	Duration of employment (years)€ <5: SMR=1.75 ≥5: SMR=1.08	
Blair 2003	Dry cleaning	SMR=1.4 (1.1, 1.6)		Little/no exposure: SMR=1.0 (0.7, 1.4) Medium/High exposure: SMR=1.5 (1.2, 1.9)
Selden 2011	Dry Cleaning: PCE subcohort	Men: SIR=1.30 (0.82, 1.94) Women: SIR=1.09 (0.76, 1.51)		

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Corbin 2011	Dry Cleaning	OR=1.39 (0.59, 3.28)		
Mattei 2014		Men Women		Cumulative exposure score (PCE) Men Women
	TCE (ever, JEM)	OR=1.0 (0.8, 1.2) OR=1.4 (0.9, 2.3)		Low: OR=1.14 OR=3.80
	TCE (ever, self-report)	OR=1.1 (0.9, 1.3) OR=1.0 (0.5, 1.8)		High: OR=1.36 OR=1.43
	PCE (ever, JEM)	OR=1.3 (0.9, 1.8) OR=2.7 (1.2, 6.1)		
	PCE (ever, self-report)	OR=3.2 (1.2, 8.4) OR=3.6 (0.5, 24)		
	TCE + PCE (JEM)	OR=1.3 (0.6, 3.0) OR=2.4 (0.5, 12)		
Vizcaya 2013 (pooled analysis)	Exposure Any "Substantial"			
	TCE	OR=1.7 (0.9, 3.4) OR=1.1 (0.5, 2.7)		
	PCE	OR=2.5 (1.2, 5.6) OR=2.4 (0.8, 7.7)		
Boffetta 2003 **Meta-analysis**	Vinyl chloride	SMR=0.90 (0.77, 1.06)		
Scelo 2004	Vinyl chloride	OR=1.05 (0.68, 1.62)	ORs ≤ 1.0 except longest duration >2.25 Wt-yrs, OR=1.27 >14 years, OR=1.56	ORs < 1.0 except for highest cumulative exposure: OR=1.51 (0.65, 3.47)
Gennaro 2008	Vinyl chloride			
	PVC baggers	RR=3.13 (0.96, 10.28)		
	PVC compound	RR=1.90 (0.62, 5.80)		
Linet 2015	Benzene	RR=1.5 (1.2, 1.9)		
Paulu 1999	PCE contaminated drinking water	OR=1.9 (0.9, 4.1) for >median exposure, 7 year latency OR=6.2 (1.1, 31.6) for >90th percentile exposure, 7 year latency		
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water		Duration of exposure (months)	
	vs U.S. population	SMR=0.92 (0.80, 1.04)	1-3 RR=1.44	
	vs. Camp Pendleton	RR=1.16 (0.96, 1.40)	4-6 RR=1.90	
			7-12 RR=1.21	
			>12 RR=1.15	
Bove 2014 (Camp Lejeune Civilian Workers)	VOC contaminated drinking water			
	vs U.S. population	SMR=1.09 (0.87, 1.36)		
	vs. Camp Pendleton	RR=1.25 (0.89, 1.75)		

* Exposures are occupational unless otherwise noted.

€ ≥20 years since time of first employment.

Summary

Several studies found associations between PCE and lung cancer. Although the NCI and NIOSH dry cleaning studies did not control for smoking, other studies that found associations (Corbin 2011, Vizcaya 2013 and Mattei 2014) adjusted for smoking. Elevated risks were also observed for exposure to PCE-contaminated drinking water and lung cancer in the Cape Cod study. The findings for TCE do not support an association. The findings for vinyl chloride are mixed with an early meta-analysis indicating no association and a recent study finding strong associations. For benzene, there is one study that observed an elevated risk for lung cancer but not for other smoking-related cancers, suggesting that smoking was not a confounder in this study. The Camp Lejeune mortality studies found elevated risks for lung cancer when the marines and civilian worker cohorts were compared to Camp Pendleton cohorts.

ATSDR Assessment: Based on the findings for PCE in the dry cleaning and other studies, there is sufficient evidence of an association for PCE and lung cancer.

5-year survival % (SEER): 17.4%

Mortality Studies: Morgan 1998, Radican 2008, Gennaro 2008, Lipworth 2011, Zhao 2005, Silver 2014, Calvert 2011, Blair 2003, Linet 2015, Bove 2014

Incidence Studies: Anttila 1995, Paulu 1999, Raaschou-Nielsen 2003, Scelo 2004, Zhao 2005, Chang 2005, Selden 2011, Corbin 2011, Hansen 2013, Vizcaya 2013, Mattei 2014

Rectal Cancer

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Morgan 1998	TCE subcohort	SMR=1.06 (0.39, 2.31)		Low TCE: SMR=0.49 (0.01, 2.74) High TCE: SMR=1.38 (0.45, 3.21)
Anttila 1995	TCE	SIR=1.71 (0.88, 2.98)		U-TCA (µmol/L): <100 SIR=2.34 (1.07, 4.44) 100 + SIR=0.85 (0.10, 3.07)
Raaschou-Nielsen 2003	TCE	Men, SIR=1.1 (1.0, 1.4) Women, SIR=1.1 (0.6, 1.8)		
Chang 2005	Chlorinated organic solvents	Men: SMR=0.73 (0.08, 2.65) Women: SMR=1.67 (0.89, 2.85)	Duration of Employment (years): ≤1: SMR=1.81 for women 1-≤5: SMR=1.01 for women >5: SMR=2.50 for women	
Radican 2008	Aircraft maint. TCE	RR=0.65 (0.22, 1.93)		
Lipworth 2011	Aircraft manufacturing TCE PCE	 SMR=0.96 (0.59, 1.49) SMR=0.82 (0.39, 1.50)		
Christensen 2013	TCE Any PCE	Any: OR=1.8 (0.9, 3.6) "Substantial": OR=0.7 (0.2, 2.6) OR=1.5 (0.5, 5.0)		
Hansen 2013	TCE	SIR=1.06 (0.78, 1.43) Men: SIR=1.11 (0.76, 1.56) Women: SIR=0.94 (0.45, 1.73)		
Calvert 2011	Dry cleaning (All) PCE only PCE plus	SMR=1.26 (0.51, 2.59) SMR=0 (no cases) SMR=1.81 (0.73, 3.74)		
Blair 2003	Dry cleaning	SMR=1.3 (0.7, 2.2)		
Paulu 1999	PCE contaminated drinking water	OR=2.6 (0.8, 6.7) for ever exposed, 11 year latency		
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=0.81 (0.52, 1.21) RR=1.60 (0.83, 3.07)	Duration of exposure (months) 1-3 RR=1.37 4-6 RR=0.99 7-12 RR=1.03 >12 RR=1.42	
Bove 2014 (Camp Lejeune Civilian Workers)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=1.06 (0.29, 2.72) RR=1.65 (0.36, 7.44)		

* Exposures are occupational unless otherwise noted.

Summary

The NCI and NIOSH dry cleaning studies found elevated risks for rectal cancer. A case-control study (Christensen et al 2013) also observed an elevated risk for PCE but had only four cases exposed and one case with "substantial" exposure. The Cape Cod drinking water study found an elevated risk for those exposed to PCE-contaminated drinking water. The evidence supporting an association with TCE is mixed. Both Camp Lejeune mortality studies observed an excess rectal cancer when the Camp Lejeune cohorts were compared to Camp Pendleton.

ATSDR Assessment: Although there are relatively few studies that evaluated PCE and rectal cancer, ATSDR concludes that there is sufficient evidence of an association for PCE and rectal cancer based on the epidemiological evidence.

5-year survival % (SEER): 66.6%

Mortality Studies: Morgan 1998, Radican 2008, Lipworth 2011, Calvert 2011, Blair 2003, Bove 2014

Incidence Studies: Anttila 1995, Paulu 1999, Raaschou-Nielsen 2003, Chang 2005, Hansen 2013, Christensen 2013

Cervical Cancer

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Anttila 1995	TCE PCE	SIR=2.42 (1.05, 4.77) SIR=3.20 (0.39, 11.6)		U-TCA (µmol/L): <100 SIR=1.86 (0.38, 5.45) 100 + SIR=4.35 (1.41, 10.1)
Weiderpass 2001	Chlorinated solvents	Low: RR=1.3 (1.0, 1.7) High: RR=1.2 (0.9, 1.6)		
Raaschou-Nielsen 2003	TCE 20 year exposure lag	SIR=1.9 (1.4, 2.4) SIR=1.5 (0.7, 2.9)	Duration of employment (years) <1: SIR=2.5 (1.7, 3.5) 1-4.9: SIR=1.6 (1.0, 2.4) ≥5: SIR=1.3 (0.6, 2.4)	
Chang 2005	Chlorinated organic solvents	SMR=0.80 (0.49, 1.22)		
Radican 2008	Aircraft maintenance TCE	RR=1.67 (0.54, 5.22)	Excess entirely in >25 unit yrs	Low, intermittent: RR=1.8 Low, continuous: RR=1.1 Peak, infrequent: RR=4.4 Peak, frequent: RR=2.3
Charbotel 2013¥	TCE PCE	OR=1.51 (0.42, 5.41) OR=1.25 (0.19, 8.46)	Exposure Duration (years) TCE <5 OR=4.32 5-10 OR=1.36 ≥10 OR=0.08	Cumulative Exposure (ppm-years) TCE Low (1-90) OR=2.21 (0.37, 13.3) Medium (91-250) OR=1.62 (0.16, 16.8) High (>250) OR=0.80 (0.10, 6.63)
Hansen 2013	TCE	SIR=2.31 (1.32, 3.75)	SIRs were similarly elevated for 0, 10 yr and 20 yr exposure lags with the highest risk for no lag: SIR=2.3	U-TCA (mg/L): 5-25: RR=1.54 (0.38, 6.26) >25-50: RR=2.41 (0.49, 11.98) >50: RR=3.28 (0.73, 14.91)
Lynge 2006	PCE (dry cleaning) Others in dry cleaning	RR=0.98 (0.65, 1.47) RR=1.73 (1.00, 2.97)	Length of employment (years) ≤1: RR=2.68 2-4: RR=0.78 5-9: RR=0.47 ≥10: RR=1.18	
Calvert 2011	Dry cleaning (All) PCE only PCE plus	SMR=1.84 (0.98, 3.14) SMR=2.10 (0.68, 4.90) SMR=1.70 (0.74, 3.36)	Duration of employment (years) "Latency"€: <20 years ≥20 years <5: SMR=0.84 SMR=2.75 ≥5: SMR=2.63 SMR=2.08	
Blair 2003	Dry cleaning	SMR=1.6 (1.0, 2.3)		Little/no exposure: SMR=1.5 (0.8, 2.7) Medium/high exposure: SMR=1.4 (0.7, 1.7)
Reference	**Exposure***	**RR (SIR, SMR, OR) & 95% CI**	**Exposure Duration information**	**Exposure intensity/cumulative exposure**

				information
Selden 2011	Dry Cleaning: PCE subcohort	SIR=1.19 (0.64, 1.93)	Duration of employment (years): <1: SIR=0.32 1-4: SIR=1.72 >4: SIR=1.24	
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	SMR=1.03 (0.33, 2.39) RR=1.33 (0.24, 7.32)	Duration of exposure (months) 1-3 RR=3.4 4-6 RR <1.0 7-12 RR <1.0 >12 RR <1.0	

* Exposures are occupational unless otherwise noted.

€ "Latency": time since first employment.

¥ Only 6 of the 67 cases were cervical cancer. The rest were severe cervical dysplasia cases.

Note: There was 1 death due to cervical cancer in the Camp Lejeune civilian worker cohort and no deaths in the Camp Pendleton civilian worker cohort.

Summary

Cervical cancer was consistently associated with both TCE and PCE in the occupational studies. An excess risk was also observed in the Camp Lejeune mortality study for marines and navy personnel compared to the U.S. population and the Camp Pendleton cohort.

ATSDR Assessment: ATSDR concludes that there is sufficient evidence of an association for TCE and PCE and cervical cancer based on the consistent positive findings in the epidemiological studies.

5-year survival % (SEER): 67.8%

Mortality Studies: Radican 2008, Calvert 2011, Blair 2003, Bove 2014

Incidence Studies: Anttila 1995, Raaschou-Nielsen 2003, Chang 2005, Lynge 2006, Selden 2011, Hansen 2013, Charbotel 2013

Brain (Central Nervous System) Cancer

Reference	Exposure*	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Morgan 1998	TCE subcohort	SMR=0.55 (0.15, 1.40)		Low TCE: SMR=0.73 (0.09, 2.64) High TCE: SMR=0.44 (0.05, 1.58)
Anttila 1995	TCE PCE	SIR=1.09 (0.50, 2.07) SIR=1.15 (0.14, 4.15)		U-TCA (µmol/L): <100 SIR=1.52 (0.61, 3.13) 100 + SIR=0.76 (0.09, 2.74)
Raaschou-Nielsen 2003	TCE	Men, SIR=1.0 (0.8, 1.2) Women, SIR=1.1 (0.7, 1.7)	Duration of employment (years): <1: men, RR=1.3; women, RR=2.8 1-4.9: men, RR=1.0; women, RR=4.1 ≥5: men, RR=1.1; women, RR=1.3	Similar SIRs for lag time of zero and 20 years.
Zhao 2005	Aerospace TCE			Medium/high cumulative exposure: RRs < 1.0 based on 3 incident cases and 6 deaths
Chang 2005	Chlorinated organic solvents	Men: SMR=0.48 (0.01, 2.66) Women: SMR=0.91 (0.33, 1.99)		
Radican 2008	Aircraft maintenance TCE (men only)	RR=1.26 (0.43, 3.75)	Cumulative exposure score (unit-yr) 0-5: RR=1.5 5-25: RR=1.7 >25: RR=0.7	Low, intermittent: RR=0.9 Low, continuous: RR=1.4 Peak, infrequent: RR=3.0 Peak, frequent: RR=0.9
Lipworth 2011	Aircraft manufacturing TCE PCE	 SMR=0.85 (0.52, 1.32) SMR=1.00 (0.57, 1.63)		
Hansen 2013	TCE	SIR=0.79 (0.51, 1.17) Men: SIR=0.82 (0.47, 1.34) Women: SIR=0.73 (0.31, 1.43)		
Silver 2014	Microelectronics plant TCE PCE	 RR < 1.0 RR < 1.0		
Neta 2012	TCE (probable exposure) PCE (probable exposure)	RRs ≤1.0 for glioma RR=1.5 (0.4, 6.3) for meningioma RR=1.2 (0.4, 3.8) for glioma, men RR=0.5 (0.1, 1.7) for glioma, women RR=0.3 (0.1, 1.7) for meningioma	High duration vs low duration TCE: OR=4.5 (0.5, 39.7) Comparing high and low duration with unexposed, ORs ≤ 1.0 for TCE and PCE	Cumulative exposures: ORs ≤1.0 for TCE and PCE.
Ruder 2013	TCE PCE	ORs < 1.0 ORs < 1.0		
Blair 2003	Dry cleaning	SMR=0.6 (0.2, 1.4)		
Reference	**Exposure***	**RR (SIR, SMR, OR) & 95% CI**	**Exposure Duration information**	**Exposure intensity/cumulative exposure**

				information
Boffetta 2003 **Meta-analysis**	Vinyl chloride	SMR=1.26 (0.98, 1.62)		
Linet 2015	Benzene	RR=0.8 (0.4, 1.6)		
Paulu 1999	PCE contaminated drinking water	ORs ≤ 1.0		
Bove 2014 (Camp Lejeune Marines/Navy)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=0.83 (0.65, 1.04) RR=0.93 (0.67, 1.30)		
Bove 2014 (Camp Lejeune Civilian Workers)	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	 SMR=1.05 (0.42, 2.16) RR=0.65 (0.21, 2.04)		

* Exposures are occupational unless otherwise noted.

Summary

There is some evidence for an association between vinyl chloride and brain cancer based on the meta-analysis. The evidence for an association between either TCE or PCE and brain cancer is weak.

ATSDR Assessment: Based on the meta-analysis, ATSDR concludes that there is sufficient evidence of an association between vinyl chloride and brain cancer. For TCE and PCE, the present state of the evidence is insufficient to support an association for TCE and PCE.

5-year survival % (SEER): 33.3%

Mortality Studies: Morgan 1998, Zhao 2005, Radican 2008, Lipworth 2011, Blair 2003, Silver 2014, Bove 2014, Linet 2015

Incidence Studies: Anttila 1995, Paulu 1999, Raaschou-Nielsen 2003, Chang 2005, Zhao 2005, Neta 2012, Hansen 2013, Ruder 2013

Scleroderma/Systemic Sclerosis

Summary

Three case-control studies based their assessments of occupational exposures to TCE on industrial hygienist review of job histories. Two of the studies evaluated men and women while a third study evaluated women only. A pooled analysis by EPA researchers (Cooper GS et al 2009) obtained an **OR for men of 2.46 (1.13, 5.38)** and an **OR for women of 1.22 (0.58, 2.57)**.

EPA attempted to explain the difference in the pooled ORs for men and women: "The incidence of systemic sclerosis among men is very low (approximately 1 per 100,000 per year), and is approximately 10 times lower than the rate seen in women…. Thus, the human data, at this time, do not allow for the determination of whether the difference in effect estimates between men and women reflects the relatively low background risk of scleroderma in men, gender-related differences in exposure prevalence or in the reliability of exposure assessment…, a gender-related difference in susceptibility to the effects of TCE, or chance." (pages 4-427 and 4-428, EPA 2011). The EPA concluded that "human and animal studies of TCE and immune-related effects provide strong evidence for a role of TCE in autoimmune disease…."

A recent case-control study (Marie I et al 2014) obtained an OR of 2.26 (0.95, 5.26) for TCE and scleroderma which increased to 3.63 (1.15, 12.09) for high cumulative exposure score. For any exposure to TCE, males had a higher risk (OR=2.77, 95% CI: 0.80, 9.35) than females (OR=1.36, 95% CI: 0.30, 5.04). Exposure to aromatic solvents was also associated with scleroderma with an OR of 8.17 (2.29, 36.5) for any exposure and a similar risk at high cumulative exposure score, with an OR of 7.40 (1.65, 45.3) with a much stronger risk in females (OR=26.4) than males (OR=2.05). The authors concluded that the findings support a strong association between TCE and systemic sclerosis.

ATSDR Assessment: Although it is unclear why the findings for men differ greatly from those for women, ATSDR concludes that there is modest evidence for causation for TCE and systemic sclerosis/scleroderma based on the findings from the pooled analysis, the recent case-control study and supporting evidence from animal studies indicating associations between TCE and autoimmune disorders.

Major cardiac defects

Reference	Exposure	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Gilboa 2012	Any occupational exposure: TCE PCE Chlorinated solvents	 1.06 (0.77, 1.45), all heart defects 1.10 (0.82, 1.47), all heart defects 1.2 (0.8, 2.0), conotruncal heart defects 1.7 (0.9, 3.4) D-Transposition of the great arteries		
Goldberg 1990	TCE drinking water	PR* = 2.58 (2.0, 3.4) for first trimester exposure		
Bove 1995	Drinking water TCE > 10 ppb PCE > 5 ppb Benzene > 0 ppb	 OR = 1.24 (90% CI: 0.5, 2.9) OR = 1.13 (90% CI: 0.6, 2.1) OR = 1.75 (90% CI: 0.7, 3.9)		
Masschusetts Dept of Health 1996 (Woburn, MA)	TCE Drinking water	No association for cardiac defects based on 4 cases ever exposed during the 1st trimester.		
Aschengrau 2009	Drinking water PCE >40 µg/L	OR=1.1 (0.4, 3.3)		
Forand 2012	Vapor intrusion: TCE PCE	RR = 2.40 (1.00-5.77) RR = 4.91 (1.58-15.24), conotruncal heart defects RR = 2.91 (0.73-+11.65) RR = 4.91 (0.69-34.90), conotruncal heart defects		

* Prevalence ratio calculated by Bove 2002.

Summary

Animal studies suggest that prenatal exposure to TCE and its metabolites results in increased numbers of congenital cardiac defects. Studies of pregnant rats found an exposure-response relationship between exposure to TCE in drinking water and congenital heart defects in their offspring (Dawson et al. 1990; Johnson et al. 2003). A study of chick embryos found that exposure to TCE when the heart was developing resulted in cardiac defects (Rufer at al. 2010). EPA (Chiu et al 2013) concluded that there was "strong evidence, based on weakly suggestive epidemiologic studies, limited experimental animal studies, and multiple mechanistic studies, that TCE causes fetal cardiac malformations" and "limited experimental evidence that oxidative metabolites, such as TCA and/or DCA, cause similar effects."

ATSDR Assessment: Few epidemiological studies have evaluated associations between cardiac defects and PCE, TCE, vinyl chloride or benzene. Nevertheless, two drinking water studies and a vapor intrusion study found associations between TCE and cardiac defects and provide support for an association. Strong evidence for causation is provided by the animal and mechanistic studies. Therefore, ATSDR concurs with EPA's assessment that there is sufficient evidence for causation for TCE and cardiac defects.

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Appendix

Evaluation of possible confounding due to smoking and other risk factors for the studies listed in the tables

Study	Smoking	Other Risk Factors*
't Mannetje 2015	No information	
Anttila 1995	No evident confounding for TCE: SIR < 1.0 for lung cancer	
Aschengrau 1993	Smoking prevalence was similar for cases and controls	SES, medical history
Axelson 1994	No evident confounding: SIR < 1.0 for lung cancer	
Bassig 2015	Adjusted for smoking	Alcohol, BMI, SES
Blair 2003	Confounding of up to 20% possible	
Boice 2006	Adjusted for smoking	SES, hydrazine exposure
Bove 2014 (marines)	Minimal confounding: RR=1.08 for COPD (Camp Lejeune vs Camp Pendleton)	SES, occupation
Bove 2014 (workers)	Minimal confounding: RR=1.21 for COPD, other smoking-related but not solvent-related diseases had RRs < 1.0 (Camp Lejeune vs Camp Pendleton)	SES, occupation
Brouwer 2015	Adjusted for smoking	Physical activity, BMI
Calvert 2011	Some evidence of potential confounding: SMR=1.33 for COPD among "PCE only"; SMR=1.35 for lung cancer among "PCE plus"	
Carreón 2014	Minimal confounding by smoking (<10%)	
Chang 2005	No evident confounding: SIRs < 1.0 for smoking-related cancers	
Charbotel 2013	No confounding by smoking	Sexual & gynecological history, BMI, parity
Christensen 2013	Adjusted for smoking	Alcohol, coffee, SES
Cocco 2010	N/A (case-control study of multiple myeloma and NHL)	SES
Cocco 2013	N/A (case-control study of NHL)	Study location
Cohn 1994	No information	
Corbin 2011	Adjusted for smoking	SES
Costantini 2008	No information	SES
Costantini 2009	No information	
Costas 2002	Adjusted for maternal smoking	SES, breast-feeding
Feldman 2011	Adjusted for smoking	SES
Gallagher 2011	No confounding observed after adjustment	Medical history, family history of breast cancer, pregnancy history
Gennaro 2008	No information	
Gilboa 2012	Adjusted for smoking	Folic acid supplement, SES
Glass 2015	No confounding due to smoking	Alcohol, BMI, HRT, family history, parity, age at menarche, age at first birth
Gold 2011	N/A (case-control study of multiple myeloma, which is not related to smoking)	SES
Goldman 2012	Adjusted for smoking	Hobby exposures, head injury (Twin study)
Hansen 2013	Confounding minimal: lung cancer SIR=1.08. U-TCA analysis is internal and not likely confounded by smoking	

Study	Smoking	Other Risk Factors*
Hsieh 2011	No evident confounding: SMRs < 1.0 for lung cancer	
Jacob 2007	No information	Hypertension, baseline proteinuria, SES
Krishnadasan 2007	No information (Smoking is not a strong risk factor for prostate cancer. A recent study¥ found an RR of 1.4 for prostate cancer deaths among current smokers)	SES, physical activity, other chemicals, prostate screening, diabetes, family history, obesity
Linet 2015	Some evidence of potential confounding: RR=1.5 for lung cancer, but RRs < 1.0 for smoking-related bladder and oral cancers	
Lipworth 2011	No evident confounding: SMRs < 1.0 for smoking-related cancers	
Lynge 2006	Adjusted for smoking	Alcohol
Marie 2014	Adjusted for smoking	
Mattei 2014	Adjusted for smoking	Asbestos, SES
McDonnell 2003	No information	
Miligi 2006	No confounding was observed for smoking	SES, disease history
Moore 2010	Smoking distribution was similar among cases and controls	BMI, hypertension
Morgan 1998	Minimal cofounding: SMR=1.10 for lung cancer in TCE subgroup	
Morton 2014	No information	
Neta 2012	No information	
Oddone 2014	Adjusted for smoking	Alcohol, BMI, SES, pregnancy history
Paulu 1999	Adjusted for smoking	SES, medical history
Peplonska 2010	No information	SES and risk factors specific to breast cancer
Raaschou-Nielsen 2003	Some evidence of possible confounding: lung cancer SIRs=1.4 males, 1.9 females (slightly lower SIRs for laryngeal cancer)	
Radican 2006, 2008	No evident confounding: RR < 1.0 for lung cancer. Internal analyses unlikely to be confounded by smoking	
Ruckart 2013	No confounding observed after adjustment	SES, pregnancy factors, Vietnam experience
Ruder 2013	No information	SES
Saberi Hosnijeh 2013	Adjusted for smoking	alcohol
Santibañez 2008	Adjusted for smoking	Alcohol, SES
Santibañez 2010	Adjusted for smoking	Alcohol, SES
Scelo 2004	Adjusted for smoking	Other lung carcinogens
Schnatter 2012	Evaluated smoking with limited data and found none	
Seidler 2007	Adjusted for smoking	Alcohol
Selden 2011	Some evidence of potential confounding: SMR=1.32 for lung cancer among dry cleaners + laundry workers (although excess risk may be due to laundry workers rather than dry cleaning workers)	
Silver 2014	No evident confounding: SMRs < 1.0 for smoking-related diseases	
Stenehjem 2015	Adjusted for smoking	Other benzene exposures
Van der Mark 2015	Adjusted for smoking	Coffee, SES
Vizcaya 2013	Adjusted for smoking	SES, occ. exposure to 8 lung carcinogens
Vlaanderen 2013	Internal analyses unlikely to be confounded by smoking	
Weiderpass 2001	No confounding by smoking was found	BMI, parity

Study	Smoking	Other Risk Factors*
Zhao 2005	Minimal confounding: RR=1.1 for lung cancer in high exposure group; RR < 1.1 for lung cancer deaths.	

* Risk factors in addition to age, sex, race/ethnicity, and calendar period.

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Below we summarize additional issues raised by either NTP or IARC in their assessments of specific studies that we have included in the tables.

NTP Comments

Vlaanderen et al. 2013. Limitations: Low prevalence of exposure (TCE) and exposure levels likely to be low. Considerable misclassification of exposure likely. TCE and PCE exposures were correlated. Strengths: long follow-up and large number of cases. NTP rating of **LOW utility**

Hansen et al 2013. Limitations: Low exposure levels and short exposure duration. Strengths: Biomonitorinig data {although ATSDR would add that there were small numbers of cases for some of the categorical U-TCA levels as evidenced by the wide confidence intervals, and biomonitoring for solvent exposure reflects recent exposures only}. NTP rating of **MODERATE utility**

Raaschou-Nielsen et al 2003: Limitations: Low levels of TCE from 1970 onward. Young cohort. Strengths: Large numbers of exposed cases. Subcohort with higher exposure potential was evaluated. NTP rating of **LOW/MODERATE utility**

Lipworth et al 2011: Limitations: Exposure levels not reported. Short duration of exposure. Few exposed deaths in subgroup analysis. No evaluation of exposure intensity. 70% had exposure to mixed solvents. Strengths: long FU, adequate # of cases and controls for "ever exposed" analysis. NTP rating of **LOW/MODERATE utility** {Given the limitations, ATSDR would consider this study of low utility}

Radican et al 2008: Limitations: Most workers are exposed to low levels therefore there is limited statistical power to evaluate higher exposures. Follow-up time (45 years) may be past induction time (i.e., may be too long). Possible confounding by co-exposures. Strengths: adequate semi-quantitative job-exposure matrix. Sufficiently long follow-up. Adequate statistical power for "ever exposed" analysis. NTP rating of **MODERATE utility**

Christensen 2013: Limitations: ≤2% of controls had "substantial" exposure & ≤3% had any exposure to TCE or PCE. The number of cases with "substantial" TCE exposure were 2, 3, and 1 for kidney cancer, non-Hodgkin lymphoma, and liver cancer, respectively. Only 2 bladder cancer cases had "substantial" exposure to PCE. The study had very low statistical power. NTP rating of **LOW/MODERATE utility**

Silver 2014: Limitations: Exposure levels not reported. <14% of cohort exposed to TCE and 15% exposed to PCE. Young cohort of which only 17% had died by the end of the study. NTP questioned the quality of the cumulative exposure score derivation. NTP rating of **LOW utility**

Cocco 2013: Limitations: 9% of the cases and controls were "ever exposed" to TCE; and 1% were considered to have "definite" TCE exposure. Reduced statistical power in NHL subtype analyses. Strengths: Analysis of NHL subtypes was conducted. NTP rating of **HIGH utility**

Moore 2010: Strengths: Large number of exposed cases. Intensity, duration and cumulative exposures were evaluated. {ATSDR would add that an additional strength was the evaluation of genetic polymorphisms for TCE metabolism} NTP rating of **HIGH utility**

Morgan 1998: Limitations: Few exposed cases. Strengths: Long follow-up and semi-quantitative exposure assessment. NTP ratings of **MODERATE (cancers of the liver & kidney) and LOW/MODERATE (NHL) utility**

Zhao 2005: Limitations: Exposure levels were not reported but presumed to be high. Few cases in subgroup analyses. Strengths: semi-quantitative exposure assessment.Multivariate exposure-response analysis adjusting for co-exposures. NTP rating of **HIGH utility**

Camp Lejeune Mortality Studies: Limitations: Young cohorts. Low percentage of the cohorts had died by the end of the studies. No information on individual water consumption. Correlated contaminants. Strengths: large cohort of marines. NTP rating of **LOW utility**

IARC Comments

Seidler 2007. Limitations: Participation rate among controls was half that of cases. Cumulative exposure appeared to be very low.

NCI dry cleaning cohort (Blair 2003). Strengths: Large cohort, and extended follow-up. {ATSDR notes that exposures to other solvents involved in dry cleaning, e.g., spot removal, likely occurred}

NIOSH dry cleaning cohort (Calvert 2011): Limitation: 2/3 of the cohort were exposed to solvents other than PCE. Strength: Monitoring data were used to verify exposure to PCE and other solvents and to exclude workers exposed to TCE and carbon tetrachloride.

Lynge 2006: Strength: The unexposed comparison group comprised laundry workers rather than the general population used for comparison in the US studies thereby minimizing potential confounding by smoking and minimizing healthy worker effect biases. {ATSDR notes that exposures to other solvents involved in dry cleaning, e.g., spot removal, likely occurred}

Selden 2011: Limitation: Low response rate for the questionnaire mailed to "washing establishments" in Sweden (<38%). {ATSDR notes that exposures to other solvents involved in dry cleaning, e.g., spot removal, likely occurred}