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TOXICOLOGICAL REVIEW

OF

TRICHLOROETHYLENE

APPENDIX B

(CAS No. 79-01-6)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

September 2011

B. SYSTEMATIC REVIEW OF EPIDEMIOLOGIC STUDIES ON CANCER AND TCE EXPOSURE

B.1. INTRODUCTION

The epidemiologic evidence on TCE is large with over 50 studies and includes occupational cohort studies, case-control studies, both nested within a cohort (nested case-control study) or population-based, and geographic-based studies. The analysis of epidemiologic studies on cancer and TCE serves to document essential design features, exposure assessment approaches, statistical analyses, and potential sources of confounding and bias. These studies are described below and reviewed according to criteria to assess: (1) their ability to inform weight of evidence evaluation for TCE exposure and a cancer hazard and (2) their utility for examination using meta-analysis approaches. A secondary goal of the qualitative review is to provide transparency on study strengths and weaknesses, providing background for inclusion or exclusion of individual studies for quantitative treatment using meta-analysis approaches. Individual study qualities are discussed according to specific criteria in Sections B.2.1 to B.2.8., and rationale for studies examined using meta-analysis approaches, the systematic review, contained in Section B.2.9. Appendix C contains a full discussion of the meta-analysis, its analytical methodology, including sensitivity analyses, and findings. This analysis supports discussion of site-specific cancer observations in Chapter 4 where a presentation may be found of study findings with assessment and discussion of observations according to a study's weight of evidence and potential for alternative explanations, including bias and confounding.

B.2. METHODOLOGIC REVIEW OF EPIDEMIOLOGIC STUDIES ON CANCER AND TCE

Epidemiologic studies considered in this analysis assess the relationship between TCE exposure and cancer, and are identified using several sources and their utility for characterizing hazard and quantitative treatment is based on recommendations in NRC (2006). A thorough search of the literature was carried out through December 2010 without restriction on year of publication or language using the following approaches: a search of the bibliographic databases PubMed (http://www.ncbi.nlm.nih.gov/ pubmed/), TOXNET (http://toxnet.nlm.nih.gov/), and EMBASE (http://www.embase.com/) using the terms "trichloroethylene cancer epidemiology" and ancillary terms, "degreasers," "aircraft, aerospace or aircraft maintenance workers," "metal workers," and "electronic workers," "trichloroethylene and cohort," or "trichloroethylene and case-control;" bibliographies of reviews of the TCE epidemiologic literature such as those of the Institute of Medicine (IOM, 2003), NRC (2009, 2006), and Scott and Chiu (2006) and review of bibliographies of individual studies for relevant studies not identified in the previous two

approaches. The search strategy identified studies that were either published or available on-line (in press). NRC (2006) noted "a full review of the literature should identify all published studies in which there was a possibility that TCE was investigated, even though results per se may not have been reported."

Additional steps of U.S. EPA staff to identify studies not published in the literature included contacting primary investigators for case-control studies of liver, kidney and lymphoma and occupation, asking for information on analyses examining TCE uniquely and a review of ATSDR or state health department community health surveys or statistics reviews for information on TCE exposure and cancer incidence or mortality.

The breadth of the available epidemiologic database on TCE and cancer is wide compared to that available for other chemicals assessed by U.S. EPA. However, few studies were designed with the sole, or primary, objective of this report—to characterize the magnitude of underlying association, if such exists, between TCE and cancer. Yet, many studies in the body of evidence can provide information for identifying cancer hazard and dose-response inferences. The weight a study contributes to the overall evidence on TCE and cancer depends on a number of characteristics regarding the design, exposure assessment, and analysis approaches. Epidemiologic studies were most informative for analysis if they approached ideals described below, as evaluated using objective criteria for identifying a cancer hazard.

Seventy-five studies potentially relevant to health assessment of TCE exposure and cancer and identified from the above comprehensive search are presented in Tables B-1, B-2, and B-3. The studies vary widely in their approaches to study design, exposure assessment, and statistical analysis; for these reasons, studies vary in their usefulness for identifying cancer hazard. Studies are reviewed according to a set of a priori guidelines of their utility for assessing TCE exposure and cancer according to the below criteria. Studies approaching criteria ideals contribute greater weight in the weight of evidence analysis than studies with significant deficiencies. These criteria are not meant to be used to "accept" or "reject" a particular study for identifying cancer hazard. Rather, they are to be used as measurement tools for evaluating a study's ability to identify TCE exposure and cancer outcomes. Studies suitable for meta-analysis treatment are selected according to specific criteria identified in Section B.2.9.4. Individual study descriptions and abstract sheets according to these criteria are found in Section B.3. Appendix C describes meta-analysis methods and findings.

Table B-1. Description of epidemiologic cohort and PMR studies assessing cancer and TCE exposure

Reference	Description	Study group (N) Comparison group (N)	Exposure assessment and other information
Aircraft and aerospace workers			
Radican et al. (2008), Blair et al. (1998)	Civilian aircraft-maintenance workers with at least 1 yr in 1952–1956 at Hill Air Force Base, Utah. Vital status (VS) to 1990 (Blair et al., 1998) or 2000 (Radican et al., 2008); cancer incidence 1973–1990 (Blair et al., 1998).	14,457 (7,204 ever exposed to TCE). Incidence (Blair et al., 1998) and mortality rates (Radican et al., 2008; Blair et al., 1998) of nonchemical exposed subjects.	Most subjects (n = 10,718) with potential exposure to 1–25 solvents. Cumulative TCE assigned to individual subjects using JEM. Exposure-response patterns assessed using cumulative exposure, continuous or intermittent exposures, and peak exposure. TCE replaced in 1968 with 1,1,1-trichloroethane and was discontinued in 1978 in vapor degreasing activities. Median TCE exposures were about 10 ppm for rag and bucket; 100–200 ppm for vapor degreasing. Poisson regression analyses controlled for age, calendar time, sex (Blair et al., 1998), or Cox proportional hazard model for age and race.
Krishnadasan et al. (2007)	Nested case-control study within a cohort of 7,618 workers employed for between 1950 and 1992, or who had started employment before 1980 at Boeing/Rockwell/ Rocketdyne (SSFL [the UCLA cohort of (Morgenstern et al., 1997)]). Cancer incidence 1988–1999.	326 prostate cancer cases, 1,805 controls. Response rate: Cases, 69%; Controls, 60%.	JEM for TCE, hydrazine, PAHs, benzene, and mineral oil constructed from company records, walk-through, or interviews. Lifestyle factors obtained from living subjects through mail and telephone surveys. Conditional logistic regression controlled for cohort, age at diagnosis, physical activity, SES and other occupational exposure (benzene, PAHs, mineral oil, hydrazine).
Zhao et al. (2005); Ritz et al. (1999a)	Aerospace workers with >2 yrs of employment at Rockwell/ Rocketdyne (now Boeing) and who worked at SSFL, Ventura, California, from 1950 to 1993 (the UCLA cohort of (Morgenstern et al., 1997)). Cancer mortality as of December 31, 2001. Cancer incidence 1988–2000 for subjects alive as of 1988.	6,044 (2,689 with high cumulative exposure to TCE). Mortality rates of subjects in lowest TCE exposure category. 5,049 (2,227 with high cumulative exposure to TCE). Incidence rates of subjects in lowest TCE exposure category.	JEM for TCE, hydrazine, PAHs, mineral oil, and benzene. IH ranked each job title ranked for presumptive TCE exposure as high (3), medium (2), low (1), or no (0) exposure for 3 time periods (1951–1969, 1970–1979, 1980–1989). Cumulative TCE score: low (≤3), medium (>3–12), high (>12) assigned to individual subjects using JEM. Cox proportional hazard, controlled for time, since 1st employment, SES, age at diagnosis, and hydrazine.

Table B-1. Description of epidemiologic cohort and PMR studies assessing cancer and TCE exposure (continued)

Reference	Description	Study group (N) Comparison group (N)	Exposure assessment and other information
Boice et al. (2006b)	Aerospace workers with >6 months employment at Rockwell/ Rocketdyne (SSFL and nearby facilities) from 1948 to 1999 (IEI cohort, IEI [2005]). VS to 1999.	41,351, 1,642 male hourly test stand mechanics (1,111 with potential TCE exposure). Mortality rates of U.S. population and California population. Internal referent groups including male hourly nonadministrative Rocketdyne workers; male hourly, nonadministrative SSFL workers; and test stand mechanics with no potential exposure to TCE.	Potential TCE exposure assigned to test stands workers only whose tasks included the cleaning or flushing of rocket engines (engine flush) (n = 639) or for general utility cleaning (n = 472); potential for exposure to large quantities of TCE was much greater during engine flush than when TCE used as a utility solvent. JEM for TCE and hydrazine without semiquantitative intensity estimates. Exposure to other solvents not evaluated due to low potential for confounding (few exposed, low exposure intensity, or not carcinogenic). Exposure metrics included employment duration, employment decade, years worked with potential TCE exposure, and years worked with potential TCE exposure via engine cleaning, weighted by number of tests. Lifetable (SMR); Cox proportional hazard controlling for birth year, hire year, and hydrazine exposure.
Boice et al. (1999)	Aircraft-manufacturing workers with at least 1 yr >1960 at Lockheed Martin (Burbank, California). VS to 1996.	77,965 (2,267 with potential routine TCE exposures and 3,016 with routine or intermittent TCE exposure). Mortality rates of U.S. population (routine TCE exposed subjects) and non-exposed internal referents (routine and intermittent TCE exposed subjects).	12% with potential routine mixed solvent exposure and 30% with route or intermittent solvent exposure. JEM for potential TCE exposure on: (1) routine basis; or (2) intermittent or routine basis without semiquantitative intensity estimate. Exposure-response patterns assessed by any exposure or duration of exposure and internal control group. Vapor degreasing with TCE before 1966 and perchloroethylene, afterwards. Lifetable analyses (SMR); Poisson regression analysis adjusting for birth date, starting employment date, finishing employment date, sex, and race.
Morgan et al. (1998)	Aerospace workers with >6 months 1950–1985 at Hughes (Tucson, Arizona). VS to 1993.	20,508 (4,733 with TCE exposures). Mortality rates of U.S. population for overall TCE exposure; mortality rates of all-other cohort subjects (internal referents) for exposure-response analyses.	TCE exposure intensity assigned using JEM. Exposure-response patterns assessed using cumulative exposure (low vs. high) and job with highest TCE exposure rating (peak, medium/high exposure vs. no/low exposure). "High exposure" job classification defined as >50 ppm. Vapor degreasing with TCE 1952–1977, but limited IH data <1975. Limited IH data before 1975 and medium/ low rankings likely misclassified given temporal changes in exposure intensity not fully considered (NRC, 2006).
Costa et al. (1989)	Aircraft manufacturing workers employed 1954–1981 at plant in Italy. VS to 1981.	8,626 subjects Mortality rates of the Italian population.	No exposure assessment to TCE and job titles grouped into one of four categories: blue- and white-collar workers, technical staff, and administrative clerks. Lifetable (SMR).

Table B-1. Description of epidemiologic cohort and PMR studies assessing cancer and TCE exposure (continued)

Reference	Description	Study group (N) Comparison group (N)	Exposure assessment and other information
Garabrant et al. (1988)	Aircraft manufacturing workers >4 yrs employment and who had worked at least 1 d at San Diego, California, plant 1958–1982. VS to 1982.	14,067 Mortality rates of U.S. population.	TCE exposure assessment for 70 of 14,067 subjects; 14 cases of esophageal cancer and 56 matched controls. For these 70 subjects, company work records identified 37% with job title with potential TCE exposure without quantitative estimates. Lifetable (SMR).
Cohorts identified from biological monitoring (U-TCA)			
Hansen et al. (2001)	Workers biological monitored using U-TCA and air-TCE, 1947–1989. Cancer incidence from 1964 to 1996.	803 total Cancer incidence rates of the Danish population.	712 with U-TCA, 89 with air-TCE measurement records, 2 with records of both types. U-TCA from 1947 to 1989; air TCE measurements from 1974. Historic median exposures estimated from the U-TCA concentrations were: 9 ppm for 1947–1964, 5 ppm for 1965–1973, 4 ppm for 1974–1979, and 0.7 ppm for 1980–1989. Air TCE measurements from 1974 onward were 19 ppm (mean) and 5 ppm (median). Overall, median TCE exposure to cohort as extrapolated from air TCE and U-TCA measurements was 4 ppm (arithmetic mean, 12 ppm). Exposure metrics: year 1st employed, employment duration, mean exposure, cumulative exposure. Exposure metrics: employment duration, average TCE intensity, cumulative TCE, period 1st employment. Lifetable analysis (SIR).
Anttila et al. (1995)	Workers biological monitored using U-TCA, 1965–1982. VS 1965–1991 and cancer incidence 1967–1992.	3,974 total (3,089 with U-TCA measurements). Mortality and cancer incidence rates of the Finnish population.	Median U-TCA, 63 µmol/L for females and 48 µmol/L for males; mean U-TCA was 100 µmol/L. Average 2.5 U-TCA measurements per individual. Using the Ikeda et al. (1972) relationship for TCE exposure to U-TCA, TCE exposures were roughly 4 ppm (median) and 6 ppm (mean). Exposure metrics: years since 1st measurement. Lifetable analysis (SMR, SIR).
Axelson et al. (1994)	Workers biological monitored using U-TCA, 1955–1975. VS to 1986 and cancer incidence 1958–1987.	1,4,21 males Mortality and cancer incidence rates of Swedish male population.	Biological monitoring for U-TCA from 1955 and 1975. Roughly ¾ of cohort had U-TCA concentrations equivalent to <20 ppm TCE. Exposure metrics: duration exposure, mean U-TCA. Lifetable analysis (SMR, SIR).

Table B-1. Description of epidemiologic cohort and PMR studies assessing cancer and TCE exposure (continued)

Reference	Description	Study group (N) Comparison group (N)	Exposure assessment and other information
Other cohorts			
Clapp and Hoffman (2008)	Deaths between 1969 and 2001 among employees >5 yrs employment duration at an IBM facility (Endicott, New York).	360 deaths Proportion of deaths among New York residents during 1979 to 1998.	No exposure assessment to TCE. PMR analysis.
Sung et al. (2008; 2007)	Female workers 1st employed 1973–1997 at an electronics (RCA) manufacturing factory (Taoyuan, Taiwan). Cancer incidence 1979–2001 (Sung et al., 2007). Childhood leukemia 1979–2001 among first born of female subjects in (Sung et al., 2008)	63,982 females and 40,647 females with 1st live born offspring. Cancer incidence rates of Taiwan population (Sung et al., 2007). Childhood leukemia incidence rates of first born live births of Taiwan population (Sung et al., 2008).	No exposure assessment. Chlorinated solvents including TCE and perchloroethylene found in soil and groundwater at factory site. Company records indicated TCE not used 1975–1991 and perchloroethylene 1975–1991 and perchloroethylene after 1981. No information for other time periods. Exposure-response using employment duration. Lifetable analysis (SMR, SIR) (Sung et al., 2007; Chang et al., 2005; Chang et al., 2003) or Poisson regression adjusting for maternal age, education, sex, and birth year (Sung et al., 2008).
Chang et al. (2005; 2003)	Male and female workers employed 1978–1997 at electronics factory as studied by Sung et al. (2007). VS from 1985 to 1997 and cancer incidence 1979–1997.	86,868 total Incidence (Chang et al., 2005) or mortality (Chang et al., 2003) rates Taiwan population.	
ATSDR (2004a)	Workers 1952–1980 at the View-Master factory (Beaverton, Oregon).	616 deaths 1989–2001 Proportion of deaths between 1989 and 2001 in Oregon population.	No exposure information on individual subjects. TCE and other VOCs detected in well water at the time of the plant closure in 1998 were TCE, 1,220–1,670 µg/L; 1,1-DCE, up to 33 µg/L; and, perchloroethylene up to 56 µg/L. PMR analysis.
Raaschou-Nielsen et al. (2003)	Blue-collar workers employed >1968 at 347 Danish TCE-using companies. Cancer incidence through 1997.	40,049 total (14,360 with presumably higher level exposure to TCE). Cancer incidence rates of the Danish population.	Employers had documented TCE usage but no information on individual subjects. Blue-collar vs. white-collar workers and companies with <200 workers were variables identified as increasing the likelihood for TCE exposure. Subjects from iron and metal, electronics, painting, printing, chemical, and dry cleaning industries. Median exposures to TCE were 40–60 ppm for the years before 1970, 10–20 ppm for 1970–1979, and approximately 4 ppm for 1980–1989. Exposure metrics: employment duration, year 1st employed, and # employees in company. Lifetable (SIR).

Table B-1. Description of epidemiologic cohort and PMR studies assessing cancer and TCE exposure (continued)

Reference	Description	Study group (N) Comparison group (N)	Exposure assessment and other information
Ritz (1999a)	Male uranium-processing plant workers >3 months employment 1951–1972 at DOE facility (Fernald, Ohio). VS 1951–1989, cancer.	3,814 white males monitored for radiation (2,971 with potential TCE exposure). Mortality rates of the U.S. population; non-TCE exposed internal controls for TCE exposure-response analyses.	JEM for TCE, cutting fluids, kerosene, and radiation generated by employees and industrial hygienists. Subjects assigned potential TCE according to intensity: light (2,792 subjects), moderate (179 subjects), heavy (no subjects). Lifetable (SMR) and conditional logistic regression adjusted for pay status, date first hire, radiation.
Henschler et al. (1995)	Male workers >1 yr 1956–1975 at cardboard factory (Arnsberg region, Germany). VS to 1992.	169 exposed; 190 unexposed. Mortality rates from German Democratic Republic (broad categories) or RCC incidence rates from Danish population, German Democratic, or non-TCE exposed subjects.	Walk-through surveys and employee interviews used to identify work areas with TCE exposure. TCE exposure assigned to renal cancer cases using workman's compensation files. Lifetable (SMR, SIR) or Mantel-Haenszel.
Greenland et al. (1994)	Cancer deaths, 1969–1984, among pensioned workers employed <1984 at GE transformer manufacturing plant (Pittsfield, Massachusetts), and who had job history record; controls were noncancer deaths among pensioned workers.	512 cases, 1,202 controls. Response rate: Cases, 69%; Controls, 60%.	Industrial hygienist assessment from interviews and position descriptions. TCE (no/any exposure) assigned to individual subjects using JEM. Logistic regression.
Sinks et al. (1992)	Workers employed 1957–1980 at a paperboard container manufacturing and printing plant (Newnan, Georgia). VS to 1988. Kidney and bladder cancer incidence through 1990.	2,050 total Mortality rates of the U.S. population, bladder and kidney cancer incidence rates from the Atlanta-SEER registry for the years 1973–1977.	No exposure assessment to TCE; analyses of all plant employees including white- and blue-collar employees. Assignment of work department in case-control study based upon work history; Material Safety Data Sheets identified chemical usage by department. Lifetable (SMR, SIR) or conditional logistic regression adjusted for hire date and age at hire, and using 5- and 10-yr lagged employment duration.
Blair et al. (1989)	Workers employed 1942–1970 in U.S. Coast. VS to 1980.	3,781 males of whom 1,767 were marine inspectors (48%). Mortality rates of the U.S. population. Mortality rates of marine inspectors also compared to that of noninspectors.	No exposure assessment to TCE. Marine inspectors worked in confined spaces and had exposure potential to multiple chemicals. TCE was identified as one of 10 potential chemical exposures. Lifetable (SMR) and directly adjusted RRs.

Table B-1. Description of epidemiologic cohort and PMR studies assessing cancer and TCE exposure (continued)

Reference	Description	Study group (N) Comparison group (N)	Exposure assessment and other information
Shannon et al. (1988)	Workers employed ≥6 months at GE lamp manufacturing plant, 1960–1975. Cancer incidence from 1964 to 1982.	1,870 males and females, 249 (13%) in coiling and wire-drawing area. Cancer incidence rates from Ontario Cancer Registry.	No exposure assessment to TCE. Workers in coiling and wire drawing (CWD) had potential exposure to many chemicals including metals and solvents. A 1955-dated engineering instruction sheet identified TCE used as degreasing solvent in CWD. Lifetable (SMR).
Shindell and Ulrich (1985)	Workers employed >3 months at a TCE manufacturing plant 1957–1983. VS to 1983.	2,646 males and females Mortality rates of the United States population.	No exposure assessment to TCE; job titles categorized as either white- or blue-collar. Lifetable analysis (SMR).
Wilcosky et al. (1984)	Respiratory, stomach, prostate, lymphosarcoma, and lymphatic leukemia cancer deaths 1964–1972 among 6,678 active and retired production workers at a rubber plant (Akron, Ohio); controls were a 20% age-stratified random sample of the cohort.	183 cases (101 respiratory, 33 prostate, 30 stomach, 9 lymphosarcoma and 10 lymphatic leukemia cancer deaths).	JEM without quantitative intensity estimates for 20 exposures including TCE. Exposure metric: ever held job with potential TCE exposure.

DOE = U.S. Department of Energy; IEI = International Epidemiology Institute; Los Angeles; VS = vital status.

Table B-2. Case-control epidemiologic studies examining cancer and TCE exposure

Reference	Population	Study group (N) Comparison group (N) Response rates	Exposure assessment and other information
Bladder			
Pesch et al. (2000a)	Histologically confirmed urothelial cancer (bladder, ureter, renal pelvis) cases from German hospitals (five regions) in 1991–1995; controls randomly selected from residency registries matched on region, sex, and age.	1,035 cases 4,298 controls Cases, 84%; controls, 71%	Occupational history using job title or self-reported exposure. JEM and JTEM to assign exposure potential to metals and solvents (chlorinated solvents, TCE, perchloroethylene). Lifetime exposure to TCE exposure examined as 30th, 60th, and 90th percentiles (medium, high, and substantial) of exposed control exposure index. Duration used to examine occupational title and job task duties and defined as 30th, 60th, and 90th percentiles (medium, long, and very long) of exposed control durations. Logistic regression with covariates for age, study center, and smoking.
Siemiatycki (1994), (1991)	Male bladder cancer cases, age 35–75 yrs, diagnosed in 16 large Montreal-area hospitals in 1979–1985 and histologically confirmed; controls identified concurrently at 18 other cancer sites; age-matched, population-based controls identified from electoral lists and random digit dialing.	484 cases 533 population controls; 740 other cancer controls Cases, 78%; controls, 72%	JEM to assign 294 exposures including TCE on semiquantitative scales categorized as any or substantial exposure. Other exposure metrics included exposure duration in occupation or job title. Logistic regression adjusted for age, ethnic origin, SES, smoking, coffee consumption, and respondent status [occupation or job title] or Mantel-Haenszel stratified on age, income, index for cigarette smoking, coffee consumption, and respondent status (TCE).
Brain			
De Roos et al. (2001); Olshan et al. (1999)	Neuroblastoma cases in children of <19 yrs selected from Children's Cancer Group and Pediatric Oncology Group with diagnosis in 1992–1994; population controls (random digit dialing) matched to control on birth date.	504 cases 504 controls Cases, 73%; controls, 74%	Telephone interview with parent using questionnaire to assess parental occupation and self-reported exposure history and judgment-based attribution of exposure to chemical classes (halogenated solvents) and specific solvents (TCE). Exposure metric was any potential exposure. Logistic regression with covariate for child's age and material race, age, and education.
Heineman et al. (1994)	White, male cases, age >30 yrs, identified from death certificates in 1978–1981; controls identified from death certificates and matched for age, year of death, and study area.	300 cases 386 controls Cases, 74%; controls, 63%	In-person interview with next-of-kin; questionnaire assessing lifetime occupational history using job title and JEM of Gomez et al. (1994). Cumulative exposure metric (low, medium, or high) based on weighted probability and duration. Logistic regression with covariates for age and study area.

Table B-2. Case-control epidemiologic studies examining cancer and TCE exposure (continued)

Reference	Population	Study group (N) Comparison group (N) Response rates	Exposure assessment and other information
Colon and rectum			
Goldberg et al. (2001); Siemiatycki (1991)	Male colon cancer cases, 35–75 yrs, from 16 large Montreal-area hospitals in 1979–1985 and histologically confirmed; controls identified concurrently at 18 other cancer sites; age-matched, population-based controls identified from electoral lists and random digit dialing.	497 cases 533 population controls and 740 cancer controls Cases, 82%; controls, 72%	In-person interviews (direct or proxy) with segments on work histories (job titles and self-reported exposures); analyzed and coded by a team of chemists and industrial hygienists (294 exposures on semiquantitative scales); potential TCE exposure defined as any or substantial exposure. Logistic regression adjusted for age, ethnic origin, birthplace, education, income, parent's occupation, smoking, alcohol consumption, tea consumption, respondent status, heating source SES, smoking, coffee consumption, and respondent status [occupation, some chemical agents] or Mantel-Haenszel stratified on age, income, index for cigarette smoking, coffee consumption, and respondent status [TCE].
Dumas et al. (2000); Simeiatycki (1991)	Male rectal cancer cases, age 35–75 yrs, diagnosed in 16 large Montreal-area hospitals in 1979–1985 and histologically confirmed; controls identified concurrently at 18 other cancer sites; age-matched, population-based controls identified from electoral lists and random digit dialing.	292 cases 533 population controls and 740 other cancer controls Cases, 78%; controls, 72%	In-person interviews (direct or proxy) with segments on work histories (job titles and self-reported exposures); analyzed and coded by a team of chemists and industrial hygienists (294 exposures on semiquantitative scales); potential TCE exposure defined as any or substantial exposure. Logistic regression adjusted for age, education, respondent status, cigarette smoking, beer consumption, and BMI [TCE] or Mantel-Haenszel stratified on age, income, index for cigarette smoking, coffee consumption, ethnic origin, and beer consumption [TCE].
Fredriksson et al. (1989)	Colon cancer cases aged 30–75 yrs identified through the Swedish Cancer Registry among patients diagnosed in 1980–1983; population-based controls were frequency-matched on age and sex and were randomly selected from a population register.	329 cases 658 controls Not available	Mailed questionnaire assessing occupational history with telephone interview follow-up. Self-reported exposure to TCE defined as any exposure. Mantel-Haenszel stratified on age, sex, and physical activity.

Table B-2. Case-control epidemiologic studies examining cancer and TCE exposure (continued)

Reference	Population	Study group (N) Comparison group (N) Response rates	Exposure assessment and other information
Esophagus			
Parent et al. (2000a), Siemiatycki (1991)	Male esophageal cancer cases, 35–75 yrs, diagnosed in 19 large Montreal-area hospitals in 1979–1985 and histologically confirmed; controls identified concurrently at 18 other cancer sites; age-matched, population-based controls identified from electoral lists and random digit dialing.	292 cases 533 population controls; 740 subjects with other cancers Cases, 78%; controls, 72%	In-person interviews (direct or proxy) with segments on work histories (job titles and self-reported exposures); analyzed and coded by a team of chemists and industrial hygienists (294 exposures on semiquantitative scales); potential TCE exposure defined as any or substantial exposure. Logistic regression adjusted for age, education, respondent status, cigarette smoking, beer consumption, and BMI [solvents] or Mantel-Haenszel stratified on age, income, index for cigarette smoking, coffee consumption, ethnic origin, and beer consumption [TCE].
Lymphoma			
Purdue et al. (2011);	Cases aged 20–74 with histologically-confirmed NHL (B-cell diffuse and follicular, T-cell, lymphoreticular) without HIV in 1998–2000 and identified from four SEER areas (Los Angeles County and Detroit metropolitan area, random sample; Seattle_Puget Sound and Iowa, all consecutive cases); population controls aged 20–74 yrs with no previous diagnosis of HIV infection or NHL, identified through: (1) if >65 yrs of age, random digit dialing; or (2) if ≥65 yrs, identified from Medicare eligibility files and stratified on geographic area, age, and race.	1,321 cases 1,057 controls Cases, 76%; controls, 78%	In-person interview using questionnaire or computer-assisted personal interview questionnaire specific for jobs held for >1 yr since the age of 16 yrs, hobbies, and medical and family history. For occupational history, 32 job- or industry-specific interview modules asked for detailed information on individual jobs and focused on solvents exposure, including TCE, assessment by expert industrial hygienist blinded to case and control status by levels of probability, frequency, and intensity. Exposure metric of overall exposure, average weekly exposure, years exposed, average exposure intensity, and cumulative exposure. Logistic regression adjusted for sex, age, race, education, and SEER site.

Table B-2. Case-control epidemiologic studies examining cancer and TCE exposure (continued)

Reference	Population	Study group (N) Comparison group (N) Response rates	Exposure assessment and other information
Gold et al.(2011)	Cases aged 35–74 with histologically-confirmed multiple myeloma in 2000–2002 and identified from SEER areas (Detroit, Seattle-Puget Sound); population controls.	181 cases 481 controls Cases, 71%; controls, 52%	In-person interview using computer-assisted personal interview questionnaire for jobs held ≥1 yr since 1941 (cases) or 1946 (controls) and since age 18 yrs. For occupational history, 20 occupations, job- or industry-specific interview modules asked for detailed information on individual jobs held at least 2 yrs and focused on solvents exposure, including TCE, assessment by expert industrial hygienist blinded to case and control status by levels of probability, duration, and cumulative exposure. Logistic regression adjusted for sex, age, race, education, and SEER site.
Cocco et al. (2010)	Cases aged ≥17 yrs with lymphoma (B-cell, T-cell, CLL, multiple myeloma, Hodgkin) in 1998–2004 and residents of referral areas from seven European countries (Czech Republic, Finland, France, Germany, Ireland, Italy, and Spain); hospital (four participating countries) or population controls (all others); controls from: (1) Germany and Italy selected by random digit dialing from general population and matched (individually in German and group-based in Italy) to cases by sex, age and residence area, and; (2) for all other countries, matched hospital controls with diagnoses other than cancer, infectious diseases and immundeficient diseases.	2,348 cases 2,462 controls Cases, 88%; controls, 81% hospital and 52% population	In-person interviews using same structured questionnaire translated to the local language for information on sociodemographic factors, lifestyle, health history, and all full-time job held ≥1 yr. Assessment by industrial hygienists in each participating center to 43 agents, including TCE, by confidence, exposure intensity, and exposure frequency. Exposure metric of overall TCE exposure and cumulative TCE exposure for subjects assessed with high degree of confidence (defined as low, medium, and high). Logistic regression adjusted for age, gender, education and study center.
German centers: Seidler et al. (2007); Mester et al. (2006); Becker et al. (2004)	NHL and Hodgkin lymphoma cases aged 18–80 yrs identified through all hospitals and ambulatory physicians in six regions of Germany between 1998 and 2003; population controls were identified from population registers and matched on age, sex, and region.	710 cases 710 controls Cases, 87%; controls, 44%	In-person interview using questionnaire assessing personal characteristics, lifestyle, medical history, UV light exposure, and occupational history of all jobs held for ≥1 yr. Exposure of a prior interest were assessed using job task-specific supplementary questionnaires. JEM used to assign cumulative quantitative TCE exposure metric, categorized according to the distribution among the control persons (50^{th} and 90^{th} percentile of the exposed controls). Conditional logistic regression adjusted for age, sex, region, smoking, and alcohol consumption.

Table B-2. Case-control epidemiologic studies examining cancer and TCE exposure (continued)

Reference	Population	Study group (N) Comparison group (N) Response rates	Exposure assessment and other information
Wang et al. (2009)	Cases among females aged 21 and 84 yrs with NHL in 1996–2000 and identified from Connecticut Cancer Registry; population-based female controls: (1) if <65 yrs of age, having Connecticut address stratified by 5-yr age groups identified from random digit dialing; or (2) >65 yrs of age, by random selection from Centers for Medicare and Medicaid Service files.	601 cases 717 controls Cases, 72%; controls, 69% (<65 yrs), 47% (>65 yrs)	In-person interview with using questionnaire assessment specific jobs held for >1 yr. Intensity and probability of exposure to broad category of organic solvents and to individual solvents, including TCE, estimated using JEM (Dosemeci et al., 1999; Gómez et al., 1994) and assigned blinded. Exposure metric of any exposure, exposure intensity (low, medium/high), and exposure probability (low, medium/high). Logistic regression adjusted for age, family history of hematopoietic cancer, alcohol consumption and race.
Costantini et al. (2008); Miligi et al. (2006)	Cases aged 20–74 with NHL, including CLL, all forms of leukemia, or multiple myeloma (MM) in 1991–1993 and identified through surveys of hospital and pathology departments in study areas and in specialized hematology centers in eight areas in Italy; population-based controls stratified by 5-yr age groups and by sex selected through random sampling of demographic or of National Health Service files.	1,428 NHL + CLL, 586 Leukemia, 263, MM 1,278 controls (leukemia analysis) 1,100 controls (MM analysis) Cases, 83%; controls, 73%	In-person interview primarily at interviewee's home (not blinded) using questionnaire assessing specific jobs, extra occupational exposure to solvents and pesticides, residential history, and medical history. Occupational exposure assessed by job-specific or industry-specific questionnaires. JEM used to assign TCE exposure and assessed using intensity (two categories) and exposure duration (two categories). All NHL diagnoses and 20% sample of all cases confirmed by panel of three pathologists. Logistic regression with covariates for sex, age, region, and education. Logistic regression for specific NHL included an additional covariate for smoking.
Persson and Fredriksson (1999); Combined analysis of NHL cases in Persson et al. (1993); Persson et al. (1989)	Histologically confirmed cases of B-cell NHL, age 20–79 yrs, identified in two hospitals in Sweden: Oreboro in 1964–1986 (Persson et al., 1989) and in Linkoping between 1975 and 1984 (Persson et al., 1993); controls were identified from previous studies and were randomly selected from population registers.	199 NHL cases, 479 controls Cases, 96% (Oreboro), 90% (Linkoping); controls, not reported	Mailed questionnaire to assess self reported occupational exposures to TCE and other solvents. Mantel-Haenszel χ^2.

Table B-2. Case-control epidemiologic studies examining cancer and TCE exposure (continued)

Reference	Population	Study group (N) Comparison group (N) Response rates	Exposure assessment and other information
Nordstrom et al. (1998)	Histologically-confirmed cases in males of hairy-cell leukemia reported to Swedish Cancer Registry in 1987–1992 (includes one case latter identified with an incorrect diagnosis date); population-based controls identified from the National Population Registry and matched (1:4 ratio) to cases for age and county.	111 cases 400 controls Cases, 91%; controls, 83%	Mailed questionnaire to assess self reported working history, specific exposure, and leisure time activities. Univariate analysis for chemical-specific exposures (any TCE exposure).
Fritschi and Siemiatycki (1996a); Siemiatycki (1991)	Male NHL cases, age 35–75 yrs, diagnosed in 16 large Montreal-area hospitals in 1979–1985 and histologically confirmed; controls identified concurrently at 18 other cancer sites; age-matched, population-based controls identified from electoral lists and random digit dialing.	215 cases 533 population controls (Group 1) and 1,900 subjects with other cancers (Group 2) Cases, 83%; controls, 71%	In-person interviews (direct or proxy) with segments on work histories (job titles and self-reported exposures); analyzed and coded by a team of chemists and industrial hygienists (294 exposures on semiquantitative scales). Exposure metric defined as any or substantial exposure. Logistic regression adjusted for age, proxy status, income, and ethnicity (solvents) or Mantel-Haenszel stratified by age, BMI, and cigarette smoking (TCE).
Hardell et al. (1994; 1981)	Histologically-confirmed cases of NHL in males, age 25–85 yrs, admitted to Swedish (Umea) hospital between 1974 and 1978; living controls (1:2 ratio) from the National Population Register, matched to living cases on sex, age, and place of residence; deceased controls from the National Registry for Causes of Death, matched (1:2 ratio) to dead cases on sex, age, place of residence, and year of death.	105 cases 335 controls Response rate not available	Self-administered questionnaire assessing self-reported solvent exposure; phone follow-up with subject, if necessary. Mantel-Haenszel χ^2.

Table B-2. Case-control epidemiologic studies examining cancer and TCE exposure (continued)

Reference	Population	Study group (N) Comparison group (N) Response rates	Exposure assessment and other information
Persson et al. (1993); Persson et al. (1989)	Histologically confirmed cases of Hodgkin lymphoma, age 20–80 yrs, identified in two hospitals in Sweden: Oreboro in 1964–1986 (Persson et al., 1989) and in Linkoping between 1975 and 1984 (Persson et al., 1993); controls randomly selected from population registers.	54 cases (1989 study); 31 cases (1993 study) 275 controls (1989 study); 204 controls (1993 study) Response rate not available	Mailed questionnaire to assess self reported occupational exposures to TCE and other solvents. Logistic regression with adjustment for age and other exposure; unadjusted Mantel-Haenszel χ^2.
Childhood leukemia			
Shu et al. (2004; 1999)	Childhood leukemia cases, <15 yrs, diagnosed between 1989 and 1993 by a Children's Cancer Group member or affiliated institute; population controls (random digit dialing), matched for age, race, and telephone area code and exchange.	1,842 cases 1,986 controls Cases, 92%; controls, 77%	Telephone interview with mother, and whenever available, fathers using questionnaire to assess occupation using job-industry title and self-reported exposure history. Questionnaire included questions specific for solvent, degreaser, or cleaning agent exposures. Logistic regression with adjustment for maternal or paternal education, race, and family income. Analyses of paternal exposure also included age and sex of the index child.
Costas et al. (2002); MDPH (1997b)	Childhood leukemia (<19 yrs of age) diagnosed in 1969–1989 and who were resident of Woburn, Massachusetts; controls randomly selected from Woburn public School records, matched for age.	19 cases 37 controls Cases, 91%; controls, not available	Questionnaire administered to parents separately assessing demographic and lifestyle characteristics, medical history information, environmental and occupational exposure, and use of public drinking water in the home. Hydraulic mixing model used to infer delivery of TCE and other solvents water to residence. Logistic regression with composite covariate, a weighted variable of individual covariates.
McKinney et al. (1991)	Incident childhood leukemia and NHL cases, 1974–1988, ages not identified, from three geographical areas in England; controls randomly selected from children of residents in the three areas and matched for sex and birth health district.	109 cases 206 controls Cases, 72%; controls, 77%	In-person interview with questionnaire with mother to assess maternal occupational exposure history, and with father and mother, as surrogate, to assess paternal occupational exposure history. No information provided in paper whether interviewer was blinded as to case and control status. Matched pair design using logistic regression for univariate and multivariate analysis.

Table B-2. Case-control epidemiologic studies examining cancer and TCE exposure (continued)

Reference	Population	Study group (N) Comparison group (N) Response rates	Exposure assessment and other information
Lowengart et al. (1987)	Childhood leukemia cases aged <10 yrs and identified from the Los Angeles (California) Cancer Surveillance Program in 1980–1984; controls selected from random digit dialing or from friends of cases and matched on age, sex, and race.	123 cases 123 controls Cases, 79%; controls, not available	Telephone interview with questionnaire to assess parental occupational and self-reported exposure history. Matched (discordant) pair analysis.
Melanoma			
Fritschi and Siemiatycki (1996b); Siemiatycki (1991)	Male melanoma cases, age 35–75 yrs, diagnosed in 16 large Montreal-area hospitals in 1979–1985 and histologically confirmed; controls identified concurrently at 18 other cancer sites; age-matched, population-based controls identified from electoral lists and random digit dialing.	103 cases 533 population controls and 533 other cancer controls Cases, 78%; controls, 72%	In-person interviews (direct or proxy) with segments on work histories (job titles and self-reported exposures); analyzed and coded by a team of chemists and industrial hygienists (294 exposures on semiquantitative scales); potential TCE exposure defined as any or substantial exposure. Logistic regression adjusted for age, education, and ethnic origin (TCE) or Mantel-Haenszel stratified on age, income, index for cigarette smoking, and ethnic origin (TCE).
Prostate			
Aronson et al. (1996); Siemiatycki (1991)	Male prostate cancer cases, age 35–75 yrs, diagnosed in 16 large Montreal-area hospitals in 1979–1985 and histologically confirmed; controls identified concurrently at 18 other cancer sites; age-matched, population-based controls identified from electoral lists and random digit dialing.	449 cases 533 population controls (Group 1) and other cancer cases from same study (Group 2) Cases, 81%; controls, 72%	In-person interviews (direct or proxy) with segments on work histories (job titles and self-reported exposures); analyzed and coded by a team of chemists and industrial hygienists (294 exposures on semiquantitative scales). Logistic regression adjusted for age, ethnic origin, SES, Quetlet, and respondent status (occupation) or Mantel-Haenszel stratified on age, income, index for cigarette smoking, ethnic origin, and respondent status (TCE).

Table B-2. Case-control epidemiologic studies examining cancer and TCE exposure (continued)

Reference	Population	Study group (N) Comparison group (N) Response rates	Exposure assessment and other information
Renal cell			
Moore et al. (2010)	Cases aged 20–74 yrs from four European countries (Czech Republic, Poland, Russia, Romania) with histologically-confirmed kidney cancer in 1999–2003; hospital controls with diagnoses unrelated to smoking or genitourinary disorders in 1998–2003 and frequency matched by sex, age, and study center.	1,097 cases (825 renal cell carcinomas) 1,184 controls Cases, 90–99%; controls, 90.3–96%	In-person interview using questionnaire for information on lifestyle habits, smoking, antopometric measures, personal and family medical history, and occupational history. Specialized job-specific questionnaire for specific jobs or industries of interest focused on solvents exposure, including.TCE, with exposure assignment by expert blinded to case and control status by frequency, intensity and confidence of TCE exposure. Exposure metric of overall exposure, duration (total hours, years) and cumulative exposure. Logistic regression adjusted for sex, age, and study center. BMI, hypertension, smoking, and residence location also included in initial models but did not alter ORs by >10%.
Charbotel et al. (2009; 2006)	Cases from Arve Valley region in France identified from local urologists files and from area teaching hospitals; age- and sex-matched controls chosen from file of same urologist as who treated case or recruited among the patients of the case's general practitioner.	87 cases 316 controls Cases, 74%; controls, 78%	Telephone interview with case or control, or, if deceased, with next-of-kin (22% cases, 2% controls). Questionnaire assessing occupational history, particularly, employment in the screw cutting jobs, and medical history. Semiquantitative TCE exposure assigned to subjects using a task/TCE-Exposure Matrix designed using information obtained from questionnaires and routine atmospheric monitoring of workshops or biological monitoring (U-TCA) of workers carried out since the 1960s. Cumulative exposure, cumulative exposure with peaks, and TWA. Conditional logistic regression with covariates for tobacco smoking and BMI.
Brüning et al. (2003)	Histologically-confirmed cases 1992–2000 from German hospitals (Arnsberg); hospital controls (urology department) serving area, and local geriatric department, for older controls, matched by sex and age.	134 cases 401 controls Cases, 83%; controls, not available	In-person interviews with case or next-of-kin; questionnaire assessing occupational history using job title. Exposure metrics included longest job held, JEM of Pannett et al. (1985) to assign cumulative exposure to TCE and perchloroethylene, and exposure duration. Logistic regression with covariates for age, sex, and smoking.
Pesch et al. (2000b)	Histologically-confirmed cases from German hospitals (five regions) in 1991–1995; controls randomly selected from residency registries matched on region, sex, and age.	935 cases 4,298 controls Cases, 88%; controls, 71%	In-person interview with case or next-of-kin; questionnaire assessing occupational history using job title (JEM approach), self-reported exposure, or job task (JTEM approach) to assign TCE and other exposures. Logistic regression with covariates for age, study center, and smoking.

Table B-2. Case-control epidemiologic studies examining cancer and TCE exposure (continued)

Reference	Population	Study group (N) Comparison group (N) Response rates	Exposure assessment and other information
Parent et al. (2000a); Siemiatycki (1991)	Male RCC cases, age 35–75 yrs, diagnosed in 16 large Montreal-area hospitals in 1979–1985 and histologically confirmed; controls identified concurrently at 18 other cancer sites; age-matched, population-based controls identified from electoral lists and random digit dialing.	142 cases 533 population controls (Group 1) and other cancer controls (excluding lung and bladder cancers) (Group 2) Cases, 82%; controls, 71%	In-person interviews (direct or proxy) with segments on work histories (job titles and self-reported exposures); analyzed and coded by a team of chemists and industrial hygienists (about 300 exposures on semiquantitative scales); TCE defined as any or substantial exposure. Mantel-Haenszel stratified by age, BMI, and cigarette smoking (TCE) or logistic regression adjusted for respondent status, age, smoking, and BMI (occupation, job title).
Dosemeci et al. (1999)	Histologically-confirmed cases, 1988–1990, white males and females, 20–85 yrs, from Minnesota Cancer Registry; controls stratified for age and sex using random digit dialing, 21–64 yrs, or from HCFA records, 64–85 yrs.	438 cases 687 controls Cases, 87%; controls, 86%	In-person interviews with case or next-of-kin; questionnaire assessing occupational history of TCE using job title and JEM of Gomez et al. (1994). Exposure metric was any TCE exposure. Logistic regression with covariates for age, smoking, hypertension, and BMI.
Vamvakas et al. (1998)	Cases who underwent nephrectomy in 1987–1992 in a hospital in Arnsberg region of Germany; controls selected accident wards from nearby hospital in 1992.	58 cases 84 controls Cases, 83%; controls, 75%	In-person interview with case or next-of-kin; questionnaire assessing occupational history using job title or self-reported exposure to assign TCE and perchloroethylene exposure. Logistic regression with covariates for age, smoking, BMI, hypertension, and diuretic intake.
Multiple or other sites			
Lee et al. (2003)	Liver, lung, stomach, colorectal cancer deaths in males and females between 1966 and 1997 from two villages in Taiwan; controls were cardiovascular and cerebral-vascular disease deaths from same underlying area as cases.	53 liver, 39 stomach, 26 colorectal, and 41 lung cancer cases; 286 controls Response rate not reported	Residence as recorded on death certificate. Mantel-Haenszel stratified by age, sex, and time period.
Kernan et al. (1999)	Pancreatic deaths, 1984–1993, in 24 states; noncancer death and non-pancreatic disease death controls, frequency matched to cases by age, gender, race, and state.	63,097 pancreatic cancer cases 252,386 noncancer population controls Response rate not reported	Usual occupation and industry on death certificate coded to standardized occupation codes and industry codes for 1980 U.S. census. Potential exposure to 11 chlorinated hydrocarbons, including TCE, assessed using JEM of Gomez et al. (1994). Logistic regression adjusted for age, marital status, gender, race, and metropolitan and residential status.

Table B-2. Case-control epidemiologic studies examining cancer and TCE exposure (continued)

Reference	Population	Study group (N) Comparison group (N) Response rates	Exposure assessment and other information
Siemiatycki (1991)	Male cancer cases, 1979–1985, 35–75 yrs, diagnosed in 16 Montreal-area hospitals, histologically confirmed; cancer controls identified concurrently; age-matched, population-based controls identified from electoral lists and random digit dialing.	857 lung and 117 pancreatic cancer cases 533 population controls (Group 1) and other cancer cases from same study (Group 2) Cases, 79% (lung), 71% (pancreas); controls, 72%	In-person interviews (direct or proxy) with segments on work histories (job titles and self-reported exposures); analyzed and coded by a team of chemists and industrial hygienists (294 exposures on semiquantitative scales); TCE defined as any or substantial exposure. Mantel-Haenszel stratified on age, income, index for cigarette smoking, ethnic origin, and respondent status (lung cancer) and age, income, index for cigarette smoking, and respondent status (pancreatic cancer).

HCFA = Health Care Financing Administration; NCI =; UV = ultra-violet

Table B-3. Geographic-based studies assessing cancer and TCE exposure

Reference	Description	Analysis approach	Exposure assessment
Broome County, New York studies			
ATSDR (2006a, 2008b)	Total, 22 site-specific, and childhood cancer incidence from 1980 to 2001 among residents in two areas in Endicott, New York.	SIR among all subjects (ATSDR, 2006a) or among white subjects only (ATSDR, 2008b) with expected numbers of cancers derived using age-specific cancer incidence rates for New York State, excluding New York City. Limited assessment of smoking and occupation using medical and other records in lung and kidney cancer subjects (ATSDR, 2008b).	Two study areas, Eastern and Western study areas, identified based on potential for soil vapor intrusion exposures as defined by the extent of likely soil vapor contamination. Contour lines of modeled VOC soil vapor contamination levels based on exposure model using GIS mapping and soil vapor sampling results taken in 2003. The study areas were defined by 2000 Census block boundaries to conform to model predicted areas of soil vapor contamination. TCE was the most commonly found contaminant in indoor air in Eastern study area at levels ranging from 0.18 to 140 $\mu g/m^3$, with tetrachloroethylene, cis-1,2-dichloroethene, 1,1,1-trichloroethane, 1,1-DCE, 1,1-dichloroethane, and Freon 113 detected at lower levels. Perchloroethylene was most common contaminant in indoor air in Western study area with other VOCs detected at lower levels.
Maricopa County, Arizona studies			
Aickin et al. (1992); Aickin (2004)	Cancer deaths, including leukemia, 1966–1986, and childhood (≤19 yrs old) leukemia incident cases (1965–1986), Maricopa County, Arizona.	Standardized mortality rate ratio from Poisson regression modeling. Childhood leukemia incidence data evaluated using Bayes methods and Poisson regression modeling.	Location of residency in Maricopa County, Arizona, at the time of death as surrogate for exposure. Some analyses examined residency in West Central Phoenix and cancer. Exposure information is limited to TCE concentration in two drinking water wells in 1982.
Pima County, Arizona studies			
ADHS (1995, 1990)	Cancer incidence in children (≤19 yrs old) and testicular cancer in 1970–1986 and 1987–1991, Pima County, Arizona.	Standardized incidence RR from Poisson regression modeling using method of Aickin et al. (1992). Analysis compares incidence in Tucson Airport Area to rate for rest of Pima County.	Location of residency in Pima, County, Arizona, at the time of diagnosis or death as surrogate for exposure. Exposure information is limited to monitoring since 1981 and include VOCs in soil gas samples (TCE, perchloroethylene, 1,1-DCE, 1,1,1-trichloroacetic acid); PCBs in soil samples, and TCE in municipal water supply wells.

Table B-3. Geographic-based studies assessing cancer and TCE exposure (continued)

Reference	Description	Analysis approach	Exposure assessment
Other			
Coyle et al. (2005)	Incident breast cancer cases among men and women, 1995–2000, reported to Texas Cancer Registry.	Correlation study using rank order statistics of mean average annual breast cancer rate among women and men and atmospheric release of 12 hazardous air pollutants.	Reporting to EPA Toxic Release Inventory the number of pounds released for 12 hazardous air pollutants, (carbon tetrachloride, formaldehyde, methylene chloride, styrene, tetrachloroethylene, TCE, arsenic, cadmium, chromium, cobalt, copper, and nickel).
Morgan and Cassady (2002)	Incident cancer cases, 1988–1989, among residents of 13 census tracts in Redlands area, San Bernardino County, California.	SIR for all cancer sites and 16 site-specific cancers; expected numbers using incidence rates of site-specific cancer of a four-county region between 1988 and 1992.	TCE and perchlorate detected in some county wells; no information on location of wells to residents, distribution of contaminated water, or TCE exposure potential to individual residents in studied census tracts.
Vartiainen et al. (1993)	Total cancer and site-specific cancer cases (lymphoma sites and liver) from 1953 to 1991 in two Finnish municipalities.	SIR with expected number of cancers and site-specific cancers derived from incidence of the Finnish population.	Monitoring data from 1992 indicated presence of TCE, tetrachloroethylene and 1,1,1-trichloroethane in drinking water supplies in largest towns in municipalities. Residence in town used to infer exposure to TCE.
Cohn et al. (1994b); Fagliano et al. (1990)	Incident leukemia and NHL cases, 1979–1987, from 75 municipalities and identified from the New Jersey State Cancer Registry. Histological type classified using WHO scheme and the classification of NIH Working Formulation Group for grading NHL.	Logistic regression modeling adjusted for age.	Monitoring data from 1984 to 1985 on TCE, trihalomethanes, and VOCs concentrations in public water supplies, and historical monitoring data conducted in 1978–1984.
Mallin (1990)	Incident bladder cancer cases and deaths, 1978–1985, among residents of nine northwestern Illinois counties.	SIR and SMR by county of residence and zip code; expected numbers of bladder cancers using age-race-sex specific incidence rates from SEER or bladder cancer mortality rates of the U.S. population from 1978 to 1985.	Exposure data are lacking for the study population with the exception of noting one of two zip code areas with observed elevated bladder cancer rates also had groundwater supplies contaminated with TCE, perchloroethylene, and other solvents.
Isacson et al. (1985)	Incident bladder, breast, prostate, colon, lung, and rectal cancer cases reported to Iowa cancer registry between 1969 and 1981.	Age-adjusted site-specific cancer incidence in Iowa towns with populations of 1,000–10,000 and who were serviced by a public drinking water supply.	Monitoring data of drinking water at treatment plant in each Iowa municipality with populations of 1,000–10,000 used to infer TCE and other VOC concentrations in finished drinking water supplies.

Category A: Study Design

- Clear articulation of study objectives or hypothesis. The ideal is a clearly stated hypothesis or study objectives and the study is designed to achieve the identified objectives.
- Selection and characterization in cohort studies of exposure and control groups and of cases and controls (case-control studies) is adequate. The ideal is for selection of cohort and referents from the same underlying population and differences between these groups are due to TCE exposure or level of TCE exposure and not to physiological, health status, or lifestyle factors. Controls or referents are assumed to lack or to have background exposure to TCE. These factors may lead to a downward bias including one of which is known as "healthy worker bias," often introduced in analyses when mortality or incidence rates from a large population such as the U.S. population are used to derive expected numbers of events. The ideal in case-control studies is cases and controls are derived from the same population and are representative of all cases and controls in that population. Any differences between controls and cases are due to exposure to TCE itself and not to confounding factors related to both TCE exposure and disease. Additionally, the ideal is for controls to be free of any disease related to TCE exposure. In this latter case, potential bias is toward the null hypothesis.

Category B: Endpoint Measured

- Levels of health outcome assessed. Three levels of health outcomes are considered in assessing the human health risks associated with exposure to TCE: biomarkers of effects and susceptibility, morbidity, and mortality. Both morbidity as enumerated by incidence and mortality as identified from death certificates are useful indicators in risk assessment for hazard identification. The ideal is for accurate and predictive indicator of disease. Incidence rates are generally considered to provide an accurate indication of disease in a population and cancer incidence is generally enumerated with a high degree of accuracy in cancer registries. Death certifications are readily available and have complete national coverage but diagnostic accuracy is reduced and can vary by specific diagnosis. Furthermore, diagnostic inaccuracies can contribute to death certificates as a poor surrogate for disease incidence. Incidence, when obtained from population-based cancer registries, is preferred for identifying cancer hazards.
- Changes in diagnostic coding systems for lymphoma, particularly NHL. Classification of lymphomas today is based on morphologic, immunophenotypic, genotypic, and clinical features and is based upon the WHO classification, introduced in 2001, and incorporation of WHO terminology into International Classification of Disease (ICD)-0-3. ICD Versions 7 and earlier had rubrics for general types of lymphatic and hematopoietic cancer, but no categories for distinguishing specific types of cancers, such as acute leukemia. Epidemiologic studies based on causes of deaths as coded using these older ICD classifications typically grouped together lymphatic neoplasms instead of examining individual types of cancer or specific cell types. Before the use of immunophenotyping, these grouping of ambiguous diseases such as NHL and Hodgkin lymphoma may be have misclassified. Lymphatic tumors coding, starting in 1994 with the introduction of the Revised European-American Lymphoma classification, the basis of the current WHO

classification, was more similar to that presently used. Misclassification of specific types of cancer, if unrelated to exposure, would have attenuated estimate of RR and reduced statistical power to detect associations. When the outcome was mortality, rather than incidence, misclassification would be greater because of the errors in the coding of underlying causes of death on death certificates (IOM, 2003). Older studies that combined all lymphatic and hematopoietic neoplasms must be interpreted with care.

Category C: TCE-Exposure Criteria

- Adequate characterization of exposure. The ideal is for TCE exposure potential known for each subject and quantitative assessment (job-exposure-matrix approach) of TCE exposure assessment for each subject as a function of job title, year exposed, duration, and intensity. Consideration of job task as additional information supplementing job title strengthens assessment increases specificity of TCE assignment. The assessment approach is accurate for assigning TCE intensity (TCE concentration or a TWA) to individual study subjects and estimates of TCE intensity are validated using monitoring data from the time period. The objective for cohort and case-controls studies is to differentiate TCE exposed subjects from subjects with little or no TCE exposure. A variety of dose-metrics may be used to quantify or classify exposures for an epidemiologic study. They include precise summaries of quantitative exposure, concentrations of biomarkers, cumulative exposure, and simple qualitative assessments of whether exposure occurred (yes or no). Each method has implicit assumptions and potential problems that may lead to misclassification. Exposure assessment approaches in which it was unclear that the study population was actually exposed to TCE are considered inferior since there may be a lower likelihood or degree of exposure to study subjects compared to approaches that assign known TCE exposure potential to each subject.

Category D: Follow-up (Cohort)

- Loss to follow-up. The ideal is complete follow-up of all subjects; however, this is not achievable in practice, but it seems reasonable to expect loss to follow-up not to exceed 10%. The bias from loss to follow-up is indeterminate. Random loss may have less effect than if subjects who are not followed have some significant characteristics in common.
- Follow-up period allows full latency period for over 50% of the cohort. The ideal to follow all study subjects until death. Short of the ideal, a sufficient follow-up period to allow for cancer induction period or latency over 15 or 20 years is desired for a large percentage of cohort subjects.

Category E: Interview Type (Case-control)

- Interview approach. The ideal interviewing technique is face-to-face by trained interviewers with >90% of interviews with cases and control subjects conduced face-to-

face. The effect on the quality of information from other types of data collection is unclear, but telephone interviews and mail-in questionnaires probably increase the rate of misclassification of subject information. The bias is toward the null hypothesis if the proportion of interview by type is the same for case and control, and of indeterminate direction otherwise.

- Blinded interviewer. The ideal is for the interviewer to be unaware whether the subject is among the cases or controls and the subject to be unaware of the purpose and intended use of the information collected. Although desirable for case-control studies, blinding is usually not possible to fully accomplish because subject responses during the interview provide clues as to subject status. In face-to-face and telephone interviews, potential bias may arise from the interviewer expects regarding the relationship between exposure and cancer incidence. The potential for bias from face-to-face interviews is probably less than with mail-in interviews. Some studies have assigned exposure status in a blinded manner using a JEM and information collected in the unblinded interview. The potential for bias in this situation is probably less with this approach than for nonblinded assignment of exposure status.

Category F: Proxy Respondents

- Proxy respondents. The ideal is for data to be supplied by the subject because the subject generally would be expected to be the most reliable source; <10% of either total cases or total controls for case-control studies. A subject may be either deceased or too ill to participate, however, making the use of proxy responses unavoidable if those subjects are to be included in the study. The direction and magnitude of bias from use of proxies is unclear, and may be inconsistent across studies.

Category G: Sample Size

- The ideal is for the sample size is large enough to provide sufficient statistical power to ensure that any elevation of effect in the exposure group, if present, would be found, and to ensure that the confidence bounds placed on RR estimates can be well-characterized.

Category H: Analysis Issues

- Control for potentially confounding factors of importance in analysis. The ideal in cohort studies is to derive expected numbers of cases based on age-sex- and time-specific cancer rates in the referent population and in case-control studies by matching on age and sex in the design and then adjusting for age in the analysis of data. Age and sex are likely correlated with exposure and are also risk factors for cancer development. Similarly, other factors such as cigarette smoking and alcohol consumption are risk factors for several site-specific cancers reported as associative with TCE exposure. To be a confounder of TCE, exposure to the other factor must be correlated, and the association of the factor with the site-specific cancer must be causal. The expected effect from controlling for confounders is to move the estimated RR estimate closer to the true value.

- Statistical methods are appropriate. The ideal is that conclusions are drawn from the application of statistical methods that are appropriate to the problem and accurately interpreted.
- Evaluation of exposure-response. The ideal is an examination of a linear exposure-response as assessed with a quantitative exposure metric such as cumulative exposure. Some studies, absent quantitative exposure metrics, examine exposure response relationships using a semiquantitative exposure metric or by duration of exposure. A positive dose-response relationship is usually more convincing of an association as causal than a simple excess of disease using TCE dose-metric. However, a number of reasons have been identified for a lack of linear exposure-response finding and the failure to find such a relationship means little from an etiological viewpoint and does not minimize an observed association with overall TCE exposure.
- Documentation of results. The ideal is for analysis observations to be completely and clearly documented and discussed in the published paper, or provided in supplementary materials accompanying publication.

B.2.1. Study Designs and Characteristics

The epidemiologic designs investigating TCE exposure and cancer include cohort studies of occupationally exposure populations, population case-control studies, and geographic studies of residents in communities with TCE in water supplies or ambient air. Analytical epidemiologic studies, which include case-control and cohort designs, are generally relied on for identifying a causal association between human exposure and adverse health effects (U.S. EPA, 2005b) due to their clear ability to show exposure precedes disease occurrence. In contrast, ecologic studies such as health surveys of cancer incidence or mortality in a community during a specified time period (i.e., geographic-based studies identified in Table B-3, provide correlations between rates of cancer and exposure measured at the geographic level).

An epidemiologic study's ability to inform a question on TCE and cancer depends on clear articulation of study objective or hypothesis and adequate selection of exposed and control group in cohort studies and cases and controls in case-control studies are important. As the body of evidence on TCE has grown over the past 20 years, so has the number of studies with clearly articulated hypothesis. All Nordic cohort studies (Raaschou-Nielsen et al., 2003; Hansen et al., 2001; Anttila et al., 1995; Axelson et al., 1994) are designed to examine cancer and TCE, albeit some with limited statistical power, as are recent cohort studies of U.S. occupationally exposed populations (Radican et al., 2008; Boice et al., 2006b; Zhao et al., 2005; Boice et al., 1999; Ritz, 1999a). Exposure assessment approaches in these studies distinguished subjects with varying potentials for TCE exposure, and in some cases, assigned a semiquantitative TCE exposure surrogate to individual study subjects. Three case-control studies nested in cohorts, furthermore, examined TCE exposure and site-specific cancer, albeit a subject's potential and overall prevalence of TCE exposure greatly varied between these studies (Krishnadasan et al., 2007; Greenland et al., 1994; Wilcosky et al., 1984). Typically, studies of all workers at a plant or

manufacturing facility (Clapp and Hoffman, 2008; 2008; 2007; Chang et al., 2005; 2004a; Chang et al., 2003; Sinks et al., 1992; Blair et al., 1989; Costa et al., 1989; Garabrant et al., 1988; Shannon et al., 1988; Shindell and Ulrich, 1985) are not designed to evaluate cancer and TCE specifically, given their inability to identify varying TCE exposure potential for individual study subjects; rather, such studies evaluate the health status of the entire population working at that facility. Bias associated with exposure misclassification is greater in these studies, and for this and other reasons more fully discussed below, they are of limited utility for informing evaluations on TCE exposure and cancer.

Recent case-control studies with hypotheses specific for TCE exposure include the kidney cancer case-control studies of Vamvakas et al. (1998), Brüning et al. (2003), and Charbotel et al. (2009; 2006). More common, population-based, case-control studies assess occupational exposure to organic solvents, using a JEM approach for exposure assessment to examine organic solvent categories (i.e., aliphatic hydrocarbons, or specific solvents such as TCE). The case-control studies of Costas et al. (2002) and Lee et al. (2003) were also designed to examine possible association with contaminated drinking water containing TCE and other solvents detected at lower concentrations. The hypothesis of Siemiatycki (1991) and ancillary publications (Goldberg et al., 2001; Dumas et al., 2000; Parent et al., 2000a; Fritschi and Siemiatycki, 1996a; Siemiatycki et al., 1994) explored possible association between 20 site-specific cancers and occupational title or chemical exposures, including TCE exposure, using a contemporary exposure assessment approach for more focused research investigation.

Cases and control selection in most population-based case-control studies of TCE exposure are considered a random sample and representative of the source population [Gold et al., 2011; Cocco et al., 2010; Moore et al., 2010; Charbotel et al., 2009; Seidler et al., 2007; Charbotel et al., 2006; Miligi et al., 2006; Shu et al., 2004; Brüning et al., 2003; Lee et al., 2003; Costas et al., 2002; De Roos et al., 2001; Pesch et al., 2000a, 2000b; Dosemeci et al., 1999; Kernan et al., 1999; Persson and Fredrikson, 1999; Nordström et al., 1998; Hardell et al., 1994; Heineman et al., 1994; McKinney et al., 1991; Lowengart et al., 1987Siemiatycki et al., 1991 (and related publications: Siemiatycki et al., 1994; Aronson et al., 1996; Fritschi and Siemiatycki 1996b; Dumas et al., 2000; Parent et al., 2000b; Goldberg et al., 2001, and Fritschi and Siemiatycki, 1996a)].

Case and control selection in Vamvakas et al. (1998), a study conducted in the Arnsberg area of Germany, is subject to criticism regarding possible selection bias resulting from differences in selection criteria, cases worked in small industries and controls from a wider universe of industries; differences in age, controls being younger than cases with possible lower exposure potentials; and temporal difference in case and control selection, controls selected only during the last year of the study period with possible lower exposure potential if exposure has decreased over period of the study (NRC, 2006). The potential for selection bias in Brüning et al. (2003), another study in the same area as Vamvakas et al. (1998) but of later period of

observation, was likely reduced compared to Vamvakas et al. (1998) due to the broader region of southern Germany from which cases were identified and interviewing cases and controls during the same time. One case-control study nested in a cohort (Greenland et al., 1994) included subjects whose deaths were reported to and known by the employer, e.g., occurred among vested or pensioned employees or among currently employees. A 10–15-year employment period was required for subjects in this study to receive a pension; deaths among employees who left employment before this time were not known to the employer and not included the study. Survivor bias, a selection bias, may be introduced by excluding nonpensioned workers or those who leave employment before becoming vested in a company's retirement plan is more likely than in a study of all employees with complete follow-up. The use of pensioned deaths as controls, as was done in this study, would reduce potential bias if both cases and control had the same likelihood of becoming pensioned. That is, the probability for becoming a pensioned worker is similar for all deaths and unrelated to the likelihood of exposure or magnitude of exposure and disease. No information was available in (Greenland et al., 1994) to evaluate this assumption.

Geographic-based and ecological studies of TCE contaminated water supplies typically focus on estimating cancer or other disease rates in geographically circumscribed populations who are geospatially located with a source containing TCE, e.g., a hazardous waste site, well water, or air. These studies are often less informative for studying cancer due to their inability to estimate incidence rate ratios, essential for causal inferences, inferior exposure assessment approach, and to possible selection biases. Ecological studies also are subject to bias known as "ecological fallacy" since variables of exposure and outcome measured on an aggregate level do not represent association at the individual level. Consideration of this bias is important for diseases with more than one risk factor, such as the site-specific cancers evaluated in this assessment.

B.2.2. Outcomes Assessed in TCE Epidemiologic Studies

The epidemiologic studies consider at least three levels of health outcomes in their examinations of human health risks associated with exposure to TCE: biomarkers of effects and susceptibility, morbidity, and mortality (NRC, 2006). Few susceptibility biomarkers have been examined and these are not specific to TCE (NRC, 2006). By far, the bulk of the literature on cancer and TCE exposure is of cancer morbidity (Gold et al., 2011; Purdue et al., 2011; Cocco et al., 2010; Moore et al., 2010; Charbotel et al., 2009; Wang et al., 2009; Sung et al., 2008; Seidler et al., 2007; ATSDR, 2006a; Charbotel et al., 2006; Miligi et al., 2006; Coyle et al., 2005; Aickin, 2004; Shu et al., 2004; Brüning et al., 2003; Raaschou-Nielsen et al., 2003; Costas et al., 2002; Morgan and Cassady, 2002; De Roos et al., 2001; Hansen et al., 2001; Dumas et al., 2000; Pesch et al., 2000a, 2000b; Dosemeci et al., 1999; Persson and Fredrikson, 1999; Nordström et al., 1998; Vamvakas et al., 1998; ADHS, 1995; Anttila et al., 1995; Axelson et al., 1994;. Cohn

et al., 1994b;; Hardell et al., 1994; Persson et al., 1993; Vartiainen et al., 1993; McKinney et al., 1991; Siemiatycki, 1991; ADHS, 1990; Fredriksson et al., 1989; Shannon et al., 1988; Lowengart et al., 1987; Isacson et al., 1985), mortality (Clapp and Hoffman, 2008; Radican et al., 2008; Boice et al., 2006b; ATSDR, 2004a; Lee et al., 2003; Boice et al., 1999; Kernan et al., 1999; Ritz, 1999a; Morgan et al., 1998; Greenland et al., 1994; Heineman et al., 1994; Aickin et al., 1992; Blair et al., 1989; Costa et al., 1989; Garabrant et al., 1988; Shindell and Ulrich, 1985; Wilcosky et al., 1984), or both (Sung et al., 2007; Chang et al., 2005; Zhao et al., 2005; Chang et al., 2003; Blair et al., 1998; Henschler et al., 1995; Sinks et al., 1992).

Mortality is readily identified from death certificates; however, diagnostic accuracy from death certificates varies by the specific diagnosis (Brenner and Gefeller, 1993). Incident cancer cases are enumerated more accurately by tumor registries and by hospital pathology records and cases identified from these sources are considered to have less bias resulting from disease misclassification than cause or underlying cause of death as noted on death certificates. Studies of incidence are preferred, particularly for examining association with site-specific cancers having high 5-year survival rates or which may be misclassified on death certificate. Misclassification of the cause of death as noted on death certificates attenuates statistical power through errors of outcome identification. This nondifferential misclassification of outcome in cohort studies will lead to attenuation of rate ratios, although the magnitude of is difficult to predict (NRC, 2006). Cancer registries are used for cases diagnosed in more recent time periods and cohorts whose entrance dates are 30 or 40 years may miss many incident cancers and reduced statistical power as a consequence. Two studies examine both cancer incidence and mortality (Zhao et al., 2005; Blair et al., 1998). The lapse of ≥20 years in Blair et al. (1998) and 38 years in Zhao et al. (2005) between date of cohort identification and cancer incidence ascertainment suggests these studies are missing cases and limits incidence examinations.

B.2.3. Disease Classifications Adopted in TCE Epidemiologic Studies

Disease coding and changes over time are important in epidemiologic evaluations, particularly in evaluation of heterogeneity or consistency of observations from a body of evidence. The ICD, published by WHO, is used to code underlying and contributing cause of death on death certificates and is updated periodically, adding to diagnostic inconsistency for cross-study comparisons (NRC, 2006). Tumor registries use the International Classification of Diseases-Oncology (ICD-O) for coding the site and the histology of neoplasms, principally obtained from a pathology report.

The epidemiologic studies of TCE exposure have used a number of different classification systems (Scott and Chiu, 2006). A number of studies classified neoplasms according to ICD-O (Gold et al., 2011; Purdue et al., 2011; Moore et al., 2010; Chang et al., 2005; Costas et al., 2002; Siemiatycki, 1991) or to ICD-9 (Zhao et al., 2005; Kernan et al., 1999; Ritz, 1999a; Nordström et al., 1998). Other ICD revisions used in recent studies include ICDA-8

(Blair et al., 1998; Greenland et al., 1994; Blair et al., 1989), ICD-7 (Raaschou-Nielsen et al., 2003; Hansen et al., 2001; Anttila et al., 1995; Axelson et al., 1994), or several ICD revisions, whichever was in effect at the date of death (Radican et al., 2008; Morgan et al., 2000; Boice et al., 1999; Morgan et al., 1998; Garabrant et al., 1988). In this latter case, changes in disease classification over revisions are not harmonized or recoded to a common classification; and diagnostic inconsistencies and disease misclassification errors leads to a greater likelihood for bias in these studies. Greatest weight is placed on studies where all cases or deaths are classified using current classification systems. However, association in studies adopting older revisions, ICD 7 (Raaschou-Nielsen et al., 2003; Hansen et al., 2001; Anttila et al., 1995; Axelson et al., 1994), for example, is noteworthy given the narrow consideration of lymphoid neoplasms compared to contemporary classification systems. Consistency examinations of the overall body of evidence using meta-analysis methods and examination of heterogeneity will need to consider study differences in coding in interpreting findings.

A major shift in thinking occurred around 1995 with the Revised European-American Lymphoma (REAL) classification of grouping diseases of the blood and lymphatic tissues along their cell lines compared to previous approaches to group lymphomas by a cell's physical characteristics. It was increasing recognized that some NHLs and corresponding lymphoid leukemias were different phases (solid and circulating) of the same disease entity (Morton et al., 2007). Many concepts of contemporary knowledge of lymphomas are incorporated in the WHO Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues, an international consensus scheme for classifying leukemia and lymphoma now in use and the predecessor to REAL (IARC, 2001). Both the ICD-O, 3rd edition, and ICD-10 have adopted the WHO classification framework.

The only study coding NHLs using the WHO classification is (Cocco et al., 2010). Other NHL studies have adopted older lymphoma classification systems, either the NCI's Working Formulation (Costantini et al., 2008; Miligi et al., 2006) or other systems coding lymphomas according to NCI's Working Formulation (i.e., International Classification of Disease-Oncology, 2nd Edition (Gold et al., 2011; Purdue et al., 2011; Wang et al., 2009)]) that divided lymphomas into low-grade, intermediate-grade and high grade, with subgroups based on cell type and presentation, or Rappaport (Hardell et al., 1994; 1981), with groupings based on microscopic morphology (Lymphoma Information Network, 2008). Both Purdue et al. (2011) and Gold et al. (2011) provide equivalent ICD-O-3 morphology codes (http://www.seer.cancer.gov/tools/conversion/ICDO2-3manual.pdf, accessed April 6, 2011,). Lowengart et al. (1987), Persson et al. (1993; 1989), McKinney et al. (1991), and Persson and Fredriksson (1999) do not provide information in their published articles on lymphomas classification systems used in these studies.

Implications of classification changes are most significant for NHL. As noted by the IOM (2003), in Revision 7 and earlier editions of the ICD, all lymphatic and hematopoietic

neoplasms were grouped together instead of treated as individual types of cancer (such as Hodgkin lymphoma) or specific cell types (such as acute lymphocytic leukemia). One limitation of this treatment was the amalgamation of these relatively rare cancers would increase the apparent sample size but could also result in diluted estimates of effect if etiologic heterogeneity of different lymphoma subtypes existed (i.e., different sites of cancer were not associated in similar ways with the exposures of interest). Additionally, immunophenotyping was not available, leading to decreased ability to distinguish ambiguous diseases, and diagnoses of these cancers may have been misclassified; for example, NHL may have been grouped with other lymphatic and hematopoietic cancers to increase statistical power or misclassified as Hodgkin lymphoma, for example. Examination of distinct lymphoma subtypes is expected to reduce disease misclassification bias. Five case-control studies on NHL include analysis of lymphoma subtype and TCE exposure (Gold et al., 2011; Purdue et al., 2011; Cocco et al., 2010; Costantini et al., 2008; Miligi et al., 2006).

A change in liver cancer coding occurred between ICDA-8 and ICD-9 and is important to consider in examinations of liver cancer observations across the TCE studies. With ICD-9, liver cancer "not specified as primary or secondary" was moved from the grouping of secondary malignant neoplasms and added to the larger class of malignant liver neoplasms. Thus, a similar grouping of liver cancer causes is necessary to cross-study comparisons. For example, an examination of liver cancer, based on ICDA-8, would need to include codes for liver and intrahepatic bile duct (code 155) and liver, not specified as primary or secondary (code 197.8), but, for ICD-9, would include liver and intrahepatic bile duct (code 155) only. The effect of adding "liver cancer, not specified as primary or secondary" to the larger liver and intrahepatic bile duct category in ICD-9 was a twofold increase in the overall liver cancer mortality (Percy et al., 1990).

B.2.4. Exposure Classification

Adequacy of exposure assessment approaches and their supporting data are a critical determinant of a study's contribution in a weight-of-evidence evaluation (Checkoway et al., 1989). Exposure assessment approaches in studies of TCE and cancer vary greatly. At one extreme, studies assume subjects are exposed by residence in a defined geographic area (ATSDR, 2008b, 2006a; Coyle et al., 2005; Aickin, 2004; Lee et al., 2003; Morgan and Cassady, 2002; ADHS, 1995; Cohn et al., 1994b; Vartiainen et al., 1993; Aickin et al., 1992; ADHS, 1990; Isacson et al., 1985) or by employment in a plant or job title (Clapp and Hoffman, 2008; Sung et al., 2008; Sung et al., 2007; Chang et al., 2005; ATSDR, 2004a; Chang et al., 2003; Blair et al., 1989; Costa et al., 1989; Garabrant et al., 1988; Shannon et al., 1988; Shindell and Ulrich, 1985). This is a poor exposure surrogate given potential for TCE exposure can vary in these broad categories depending on job function, year, use of personal protection, and, for residential exposure, pollutant fate and transport, water system distribution characteristics, percent of time

per day in residence, presence of mitigation devices, drinking water consumption rates, and showering times. Another example comprises measurement from a subset of workers with jobs where TCE is routinely used to infer TCE exposure and TCE intensity to all subjects. In both examples, exposure misclassification potential may be extensive and with a downward bias in risk estimates.

At the other extreme and preferred given a reduced likelihood for misclassification bias, quantitative exposure assessment based upon a subject's job history, job title, and monitoring data are used to develop estimates of TCE intensity and cumulative exposure (quantitative exposure metrics or measures) and is known as JEM approaches. Peak exposure is also well characterized. Addition to JEM approaches of information on job tasks (JTEM) associated with exposure such as that done by Pesch et al. (2000a, 2000b) is expected to reduce potential exposure misclassification. In between these two extremes, semiquantitative estimates of low, medium, and high TCE exposure are assigned to subjects. Twenty-one studies assigned a quantitative or semiquantitative TCE surrogate metrics to individual subjects using a JEM, JTEM, or expert knowledge: (Siemiatycki, 1991) (and related publications (Goldberg et al., 2001; Dumas et al., 2000; Parent et al., 2000a; Aronson et al., 1996; Fritschi and Siemiatycki, 1996a, b; Siemiatycki et al., 1994); Blair et al. (1998) and follow-up by Radican et al. (2008); Morgan et al. (1998), Vamvakas et al. (1998), Kernan et al. (1999), Ritz (1999a), Pesch et al. (2000a, 2000b), Brüning et al. (2003), Zhao et al. (2005), Miligi et al. (2006), Charbotel et al. (2009; 2006), Krishnadansen et al. (2007), Seidler et al. (2007), Costantini et al. (2008), Wang et al. (2009), Cocco et al. (2010), Gold et al. , Moore et al. (2010), and Purdue et al. (2011).

Thirteen other studies assigned a qualitative TCE surrogate metric (ever exposed or never exposed), less preferred to a semi-quantitative exposure surrogate given greater likelihood for error associated exposure misclassification, using general job classification of job title by reference to industrial hygiene records indicating a high probability of TCE use, individual biomarkers, JEMs, water distribution models, for cohort studies, or obtained from subjects using questionnaire for case-control studies. The 13 studies were: Wilcosky et al. (1984), Lowengart et al. (1987), McKinney et al. (1991), Greenland et al. (1994), Hardell et al. (1994), Nordstrom et al. (1998), Shu et al. (1999), Boice et al. (2006b; 1999), Dosemeci et al. (1999), Persson and Fredriksson (1999), Costas et al. (2002), and Raaschou-Nielsen et al. (2003). Without quantitative measures, however, it is not possible to quantify exposure difference between groupings nor is it possible to compare similarly named categories across studies. Exposure misclassification for dichotomous exposure defined in these studies, if nondifferential, would downward bias resulting risk estimates.

Zhao et al. (2005), Krishnadansen et al. (2007), and Boice et al. (2006b) are studies with overlap in some subjects, but with different exposure assessment approaches, more fully discussed in Section B.3.1.1, with implication on study ability to identify cancer hazard. While these studies used job title to assign TCE exposure potential, Zhao et al. (2005) and

Krishnadansen et al. (2007) developed a semiquantitative estimate of TCE exposure potential, whereas Boice et al. (2006b) classified subjects as either "exposed" or "unexposed" using a qualitative surrogate. These studies, furthermore, identify TCE exposure potentially differently for possibly similar job titles. For example, jobs as instrument mechanics, inspectors, test stand engineers, and research engineers are identified with medium potential exposure in Zhao et al. (2005) and Krishnadansen et al. (2007); however, these job titles were considered in Boice et al. (2006b) as having background exposure and were combined with unexposed subjects, the referent population in Cox Proportional Hazard analyses.

Three Nordic cohorts have TCE exposure as indicated from biological markers, assigning TCE exposure to subjects using either concentration of TCA in urine or TCE in blood (Hansen et al., 2001; Anttila et al., 1995; Axelson et al., 1994). The utility of a biomarker depends on it selectivity and the exposure situation. Urinary TCA (U-TCA) is a nonselective marker since other chlorinated solvents besides TCE are metabolized to TCA and resultant urinary elimination. If TCE is the only exposure, urinary TCE may be a useful marker; however, in setting with mixed exposure, urinary TCA may serve as an integrated exposure marker of several chlorinated solvents. The Nordic studies used the linear relationship found for average inhaled TCE vs. U-TCA: TCE (mg/m^3) = 1.96; U-TCA (mg/L) = 0.7 for exposures <375 mg/m^3 (69.8 ppm) (Ikeda et al., 1972). This relationship shows considerable variability among individuals, which reflects variation in urinary output and activity of metabolic enzymes. Therefore, the estimated inhalation exposures are only approximate for individuals but can provide reasonable estimates of group exposures. There is evidence of nonlinear formation of U-TCA above about 400 mg/m^3 or 75 ppm of TCE. The half-life of U-TCA is about 100 hours. Therefore, the U-TCA value represents roughly the weekly average of exposure from all sources, including skin absorption. The Ikeda et al. (1972) relationship can be used to convert urinary values into approximate airborne concentration, which can lead to misclassification if tetrachloroethylene and 1,1,1-trichloroethane are also being used because they also produce U-TCA. In most cases, the Ikeda et al. (1972) relationship provides a rough upper boundary of exposure to TCE.

B.2.5. Follow-up in TCE Cohort Studies

Cohort studies are most informative if vital status is ascertained for all cohort subjects and if the period of time for disease ascertainment is sufficient to allow for long latencies, particularly for cancer detection and death, in the case of mortality studies. Inability to ascertain vital status for all subjects, or, conversely, subjects who are loss-to-follow-up, can affect the validity of observations and lead to biased results. Both power and rate ratios estimated in cohort studies can be underestimated due to bias introduced if the follow-up period was not long enough to account for latency (NRC, 2006). The probability of loss to follow-up may be related to exposure, disease, or both. The multiple-stage process of cancer development occurs over

decades after first exposure and studies with full latent periods are considered to provide greater weight to the evaluation compared to cohort studies with shortened follow-up period and lower percentage of subjects whose vital status was known on the date follow-up ended. Vital status ascertainment for over 90% of all cohort studies and long mean follow-up periods, about 15 years of longer, characterized many occupational cohort studies on TCE and cancer (Blair et al., 1998; Anttila et al., 1995; Costa et al., 1989; Garabrant et al., 1988) and the follow-up study of Radican et al. (2008; Boice et al., 2006b; Zhao et al., 2005; Raaschou-Nielsen et al., 2003; Boice et al., 1999; Ritz, 1999a; Morgan et al., 1998). Information is lacking in two biomarker studies (Hansen et al., 2001; Axelson et al., 1994), additionally, to estimate the mean follow-up period for TCE-exposed subjects; although Hansen et al. (2001) state "some workers were followed for as long as 50 years after their exposure, which allowed the detection of cancers with long latency periods." Other studies of TCE and cancer did not identify a latent period, information for calculating a latent period, or contained other deficiencies in follow-up criteria (Sung et al., 2007; Chang et al., 2005; Henschler et al., 1995; Sinks et al., 1992; Blair et al., 1989; Costa et al., 1989; Shannon et al., 1988; Wilcosky et al., 1984). PMR studies, based only on deaths and which lack information on person-year structure as cohort studies, by definition, do not contain information on cancer latent periods or follow-up (Clapp and Hoffman, 2008; ATSDR, 2004a).

B.2.6. Interview Approaches in Case-Control Studies of Cancer and TCE Exposure

Interview approaches and the percentage of subjects with information obtained from proxy or next-of-kin respondents need consideration in interpreting population and hospital-based, case-control studies in light of possible biases. Biases resulting from proxy respondent or from low participation related to mailed questionnaires are not relevant to cohort or geographic studies since information is obtained from local, national, or corporate records. Both face-to-face and telephone interviews are common and valid approaches used in population or hospital-based case-control studies. Important to each is the use of a structured questionnaires combined with intensive training as ways to minimize a high potential for biases often associated with mailed questionnaires (Blatter et al., 1997; Schlesselman, 1982). Studies with information limited to job title, type of business and dates of employment and aided with computer or job-exposure-matrix approaches are preferred to studies of job title only; the added approaches can reduce exposure misclassification bias and improve disease risk estimates (Stewart et al., 1996). Moreover, interview with respondents other than the individual case or control, through proxy or next-of-kin respondents, may also introduce bias in case-control studies. Proxy respondents are used when cases or control are either too sick to respond or if deceased. This bias would dampen observed associations if proxy respondents did not fully provide accurate information. Boyle et al. (1992), for example, in their study of several site-specific cancers and occupational exposures found low sensitivity, or correct reporting, for occupational exposure to solvents among proxy

respondents. The weight-of-evidence analysis on TCE and cancer, for this reason, places greatest weight on observations from studies which obtain information on personal, medical, and occupational histories from each case and control with lesser weight is placed on studies where ≥10% of interviews are with proxy respondents.

Many of the more recent case-control studies include face-to-face (Gold et al., 2011; Purdue et al., 2011; Cocco et al., 2010; Moore et al., 2010; Wang et al., 2009; Seidler et al., 2007; Miligi et al., 2006; Brüning et al., 2003; Costas et al., 2002; Pesch et al., 2000a, 2000b; Dosemeci et al., 1999; Vamvakas et al., 1998; McKinney et al., 1991; Siemiatycki, 1991) or telephone (Charbotel et al., 2009; Charbotel et al., 2006; Shu et al., 2004; Shu et al., 1999; Lowengart et al., 1987) interviews. Few of these studies included interviewers who were blinded or did not know the identity of who is a case and who is a control. Although desirable for case-control studies, blinding is usually not possible to fully accomplish because subject responses during the interview provide clues as to subject status. For this reason, the lack of blinded interviewers is not considered a serious limitation. More importantly, most studies assigned exposure to cases and controls in a blinded manner

Information obtained from mailed questionnaire predominantly characterized older Nordic studies (Persson and Fredrikson, 1999; Nordström et al., 1998; Hardell et al., 1994; Persson et al., 1993; Fredriksson et al., 1989; Persson et al., 1989; Hardell et al., 1981). One case-control study did not ascertain information from a questionnaire or through interviews, instead using occupation coded on death certificates to infer TCE exposure potential (Kernan et al., 1999). In all studies except Costas et al. (2002) and Kernan et al. (1999), assignment of potential TCE exposure to cases and controls, to different degrees depending on each study, is based on self-reported information on job title, and in some cases, to specific chemicals.

More common to the case-control studies on TCE and cancer was possible bias related to a higher percentage of proxy interviews. Seven studies (Gold et al., 2011; Purdue et al., 2011; Moore et al., 2010; Wang et al., 2009; Pesch et al., 2000a, 2000b; Dosemeci et al., 1999) excluded subjects with proxy interviews and the percentage of proxy interview among subjects in one other study is <10% (Nordström et al., 1998). Charbotel et al. (2009; 2006) furthermore presents analyses for data they considered as better quality, including higher confidence exposure information and excluding proxy respondents, in addition to analyses using both living and proxy respondents. A consideration of proxy interviews in studies of childhood cancers, which include an examination of paternal occupational exposure, is needed given a greater likelihood for bias if fathers are not directly interviewed and the father's occupational information is provided only by the child's mother. A good practice is for statistical analyses examining paternal occupational exposure to include only cases and controls with direct information provided by the fathers, such as De Roos et al. (2001), the only childhood cancer study (neuroblastoma) to exclude the use of proxy information.

B.2.7. Sample Size and Approximate Statistical Power

Cancer is generally considered a rare disease compared to more common health outcomes such as cardiovascular disease. Of all site-specific cancers, endocrine cancers of the breast prostate and lung cancer are most common, with age-adjusted incidence rates of 126 per 100,000 women (breast), 163 per 100,000 men (prostate), and 63.9 per 100,000 men and women (lung) (Ries et al., 2008). Several site-specific cancers including kidney cancer, liver cancer, and NHL that are of interest to TCE are rarer and consideration of study size and the influence on statistical power are factors for judging a study's validity and assessment of a study's contribution to the overall weight of evidence for identifying a hazard. For example, the age-adjusted incidence rates of NHL, liver and intrahepatic bile duct cancer, and kidney, renal, and pelvis cancer in the United States population are 19.5 per 100,000, 6.4 per 100,000, and 13.2 per 100,000; rates vary by sex and race. Age-adjusted mortality rates for these cancers are lower: 7.3 per 100,000 (NHL), 5.0 per 100,000 (liver and intrahepatic bile duct), 4.2 per 100,000 (kidney and renal pelvis). Rates of the childhood cancer, acute lymphocytic leukemia, are even lower: 1.6 (incidence) and 0.5 (mortality) per 100,000 (Ries et al., 2008).

Only very large cohort or case-control studies would have a sufficient number of cases and statistical power to estimate excess risks and exposure-response relationships (NRC, 2006). Observations from studies with large numbers of TCE-exposed subjects, given consideration of exposure conditions and other criteria discussed in this section, can provide useful information on hazard and may provide quantitative information on possible upper bound TCE cancer risks. Alternatively, studies of small numbers of subjects or cases and controls, typically, studies with statistical power <80% to detect risk of a magnitude of ≤2, are not likely to provide useful evidence for or against the hypothesis that TCE is a human carcinogen.

Studies with either a large number of TCE-exposed subjects or with large numbers of total deaths, cancer deaths, or cancer cases among TCE-exposed subjects are the cohort studies of Blair et al. (1998), Raaschou-Nielsen et al. (2003), and Zhao et al. (2005), and the case-control studies of Pesch et al. (2000a, 2000b), Shu et al. (2004; 1999) [paternal exposure assessment, only]), Wang et al. (2009) and Cocco et al. (2010), with ≥50 TCE-exposed cases. The cohorts of Boice et al. (2006b; 1999) and Morgan et al. (1998), like that of Blair et al. (1998), comprised over 10,000 subjects both with and without potential TCE exposure; however, the number of subjects and the percentage of the larger cohort identified with TCE exposure in these studies was less than that in Blair et al. (1998); 23% of all subjects in Morgan et al. (1998), 3% in Boice et al. (1999), 2% in Boice et al. (2006b) compared to 50% in Blair et al. (1998). Moreover, although the cohorts of Garabrant et al. (1988), Chang et al. (2005) and Sung et al. (2007) are also of population sizes >10,000, these studies of employees at one manufacturing facility lack assignment of potential TCE exposure to individual subjects and include subjects with varying exposure potential, some of whom are likely with very low to no exposure potential to TCE. Rate ratios estimated from cohorts that include unexposed subjects would be underestimated,

although the magnitude of this bias cannot be calculated given the absence in individual studies of information on the percentage of subjects lacking potential TCE exposure.

Examination of the statistical power or ability to detect a rate ratio magnitude for site-specific cancer in an epidemiologic study informs weight-of-evidence evaluations and provides perspective on a study's validity and robustness of observations. Although statistical power calculations are traditionally carried out during the design phase for sample size estimation, examination of a study's statistical power post hoc is one of several tools to evaluate a study's validity; however, such calculations must be interpreted in context of exposure conditions in the study. Given the lower average exposure concentrations in the cohort studies and in population case-control studies, an assumption of low RRs is plausible. Approximate statistical power to detect a RR of 2.0 with $\alpha = 0.05$ was calculated for site-specific cancers in cohort and geographic-based studies according to the methods of Beaumont and Breslow (1981), as suggested by NRC (2006), and are found in Table B-4. Approximate statistical power was calculated for kidney, NHL, and liver cancers as examples. Radican et al. (2008), the previous follow-up of this cohort by Blair et al. (1998), and Raaschou-Nielsen et al. (2003) have over 80% statistical power to detect RR of 2.0 for kidney and liver cancers and NHL and overall TCE exposure. However, while these studies may appear sufficient for examining overall TCE exposure and RRs of 2.0, they have a greatly reduced ability to detect underlying risks of this magnitude in analyses using rank-ordered exposure- or duration-response analyses. Other studies with fewer TCE-exposed subjects and of similar or lower exposure conditions as Blair et al. (1998) will decreased statistical power to detect most site-specific cancer risks of <2.0. Statistical power in Morgan et al. (1998) and Boice et al. (1999) approaches that in Blair et al. (1998) and Raaschou-Nielsen et al. (2003). As further identified in Table B-4, Garabrant et al. (1988) and Morgan and Cassady (2002) each had over 80% statistical power to detect RRs of 2.0 for liver and kidney cancer and reflects the number of subjects in each of these studies. However, underlying risk in both studies and other studies such as these which lack characterization of TCE exposure to individual subjects is likely lower than 2.0 because of inclusion of subjects with varying exposure potential, including low exposure potential. Case-control studies such as Charbotel et al. (2006) and Brüning et al. (2003) examine higher level exposure to TCE than average exposure in the population case-control studies, and although these two studies contain fewer subjects than population case-control studies such as Cocco et al. (2010), a higher statistical power is expected related to the different and higher exposure conditions and to the higher prevalence of exposure.

Overall, except for a few studies noted above, the body of evidence has limited statistical power for evaluating low level cancer risk and TCE. For this reason, studies reporting statistically significant association between TCE and site-specific cancer are noteworthy if positive biases such as confounding are minimal.

Table B-4. Approximate statistical power (%) in cohort and geographic-based studies to detect an RR = 2

Exposure group		NHL	Kidney	Liver	Reference
Cohort studies—incidence					
Aerospace workers (Rocketdyne)					Zhao et al. (2005)
	Any exposure to TCE	Not reported	Not reported	Not reported	
	Low cumulative TCE score	Referent	Referent	Referent	
	Medium cumulative TCE score	97.0	43.8	Not reported	
	High TCE score	58.2	18.7	Not reported	
All employees at electronics factory (Taiwan)					Chang et al. (2005)
	Males	Not reported	Not reported	16.9	
	Females	Not reported	92.1[a]	15.4	
Danish blue-collar worker with TCE exposure					Raaschou-Nielsen et al. (2003)
	Any exposure, all subjects	100.0	100.0	100.0	
	Employment duration, males				
	<1 yr	98.4	96.6	85.2	
	1–4.9 yrs	99.4	98.4	92.7	
	≥5 yrs	97.7	97.0	93.1	
	Employment duration, females				
	<1 yr	40.3	30.1	27.3	
	1–4.9 yrs	48.4	37.1	34.1	
	≥5 yrs	39.6	31.9	30.5	

Table B-4. Approximate statistical power (%) in cohort and geographic-based studies to detect an RR = 2 (continued)

Exposure group		NHL	Kidney	Liver	Reference
Biologically-monitored Danish workers					Hansen et al. (2001)
	Any TCE exposure	37.9	47.9	35.7	
	Cumulative exposure (Ikeda)		Not reported	Not reported	
	<17 ppm-yr	17.9			
	≥17 ppm-yr	20.3			
	Mean concentration (Ikeda)		Not reported	Not reported	
	<4 ppm	21.0			
	4+ ppm	23.6			
	Employment duration		Not reported	Not reported	
	<6.25 yr	18.3			
	≥6.25	20.1			
Aircraft maintenance workers from Hill Air Force Base					Blair et al. (1998)
	TCE subcohort	Not reported	Not reported	Not reported	
	Males, cumulative exposure				
	0	Referent	Referent	Referent	
	<5 ppm-yr	79.5	67.8	58.2	
	5–25 ppm-yr	63.1	49.4	44.7	
	>25 ppm-yr	70.8	58.4	47.4	
	Females, cumulative exposure				
	0	Referent	Referent	Referent	
	<5 ppm-yr	28.2	0 cases	0 cases	
	5–25 ppm-yr	0 cases	0 cases	0 cases	
	>25 ppm-yr	34.1		0 cases	
Biologically-monitored Finnish workers					Anttila et al. (1995)
	All subjects	53.8	70.4	56.5	
	Mean air-TCE (Ikeda extrapolation)				
	<6 ppm	36.8	Not reported	23.2	
	6+ ppm	25.6	Not reported	17.4	

Table B-4. Approximate statistical power (%) in cohort and geographic-based studies to detect an RR = 2 (continued)

Exposure group		NHL	Kidney	Liver	Reference
Cardboard manufacturing workers in Arnsberg, Germany					Henschler et al. (1995)
	Exposed workers	Not reported	16.3	Not reported	
Biologically-monitored Swedish workers					Axelson et al. (1994)
	Any TCE exposure, males	43.5	59.6	40.1	
	Any TCE exposure, females	Not reported	Not reported	Not reported	
Cardboard manufacturing workers, Atlanta area, Georgia					Sinks et al. (1992)
	All subjects	Not reported	27.9	Not reported	
Cohort studies—mortality					
Aerospace workers (Rocketdyne)					
	Any TCE (utility/engine flush)	56.0	43.5	42.6	Boice et al. (2006b)
	Any exposure to TCE	Not reported	Not reported	Not reported	Zhao et al. (2005)
	Low cumulative TCE score	Referent	Referent	Referent	
	Medium cumulative TCE score	97.0	57.6	Not reported	
	High TCE score	55.4	26.4	Not reported	
View-Master employees					ATSDR (2004a)
	Males	40.9	17.3	23.4	
	Females	74.1	24.1	0 deaths	
All employees at electronics factory (Taiwan)					Chang et al. (2003)
	Males	49.8	0 deaths	16.9	
	Females	79.0	37.5	15.4	
United States uranium-processing workers (Fernald)					Ritz (1999a)
	Any TCE exposure				
	Light TCE exposure, >2 yrs duration	91.6[b]	59.7[c]	10.1	
	Modified TCE exposure, >2 yrs duration	20.9[b]	0 deaths[c]	0.08	
Aerospace workers (Lockheed)					Boice et al. (1999)
	Routine exposure	88.4	71.3	72.9	
	Duration of exposure, routine-intermittent				
	0 yrs	Referent	Referent	Referent	
	<1 yr	81.7	66.3	73.6	

Table B-4. Approximate statistical power (%) in cohort and geographic-based studies to detect an RR = 2 (continued)

Exposure group		NHL	Kidney	Liver	Reference
	1–4 yrs	73.5	60.3	63.5	
	≥5 yrs	78.5	63.8	67.3	
	p for trend				
Aerospace workers (Hughes)					Morgan et al. (1998)
	TCE subcohort	42.6, 79.6[d]	65.5	65.6	
	Low intensity (<50 ppm)	22.1	33.3	34.7	
	High intensity (>50 ppm)	31.8	50.1	49.2	
Aircraft maintenance workers (Hill Air Force Base, Utah)					Blair et al. (1998)
	TCE subcohort	92.7	81.5	87.9	
	Males, cumulative exposure				
	0				
	<5 ppm-yr	62.1	50.7	61.4	
	5–25 ppm-yr	43.1	37.1	44.7	
	>25 ppm-yr	54.8	44.9	52.8	
	Females, cumulative exposure				
	0				
	<5 ppm-yr	18.2	0 deaths	0 deaths	
	5–25 ppm-yr	0 deaths	8.4	0 deaths	
	>25 ppm-yr	22.0	11.5	19.1	
	TCE subcohort	99.9	94.4	99.7	Radican et al. (2008)
	Males, cumulative exposure				
	0				
	<5 ppm-yr	83.0	43.8	59.4	
	5–25 ppm-yr	64.9	53.0	70.6	
	>25 ppm-yr	75.7	33.4	50.9	
	Females, cumulative exposure				
	0				
	<5 ppm-yr	38.9	0 deaths	25.9	
	5–25 ppm-yr	0 deaths	12.4	0 deaths	

Table B-4. Approximate statistical power (%) in cohort and geographic-based studies to detect an RR = 2 (continued)

Exposure group		NHL	Kidney	Liver	Reference
	>25 ppm-yr	49.2	21.1	32.2	
Cardboard manufacturing workers in Arnsberg, Germany					Henschler et al. (1995)
	TCE exposed workers	19.6[b]	16.0	Not reported	
Cardboard manufacturing workers, Atlanta area, Georgia		45.3[b]	17.3	Not reported	Sinks et al. (1992)
Coast Guard employees (US)					Blair et al. (1989)
	Marine inspectors	31.8	31.8	38.6	
Aircraft manufacturing plant employees (Italy)					Costa et al. (1989)
	All subjects	94.1[b]	Not reported	63.1	
Aircraft manufacturing plant employees (San Diego, California)					Garabrant et al. (1988)
	All subjects	95.1[e], 74.2[f]	90.9	77.9	
Geographic-based studies					
Residents in two study areas in Endicott, New York		90.8	41.7	31.8	ATSDR (2006a)
Residents of 13 census tracts in Redlands, California		100	100.0	98.7	Morgan and Cassady (2002)
Finnish residents					Vartiainen et al. (1993)
	Residents of Hausjarvi	98.8	Not reported	84.2	
	Residents of Huttula	98.7	Not reported	83.2	

[a]Kidney cancer and other urinary organs, excluding bladder, as reported in Sung et al. (2008).
[b]All cancers of hematopoietic and lymphatic tissues.
[c]Bladder and kidney cancer, as reported in NRC (2006).
[d]Based on number of observed cases of NHL reported in Mandel et al. (2006).
[e]Lymphosarcoma and reticulosarcoma.
[f]Other lymphatic and hematopoietic tissue neoplasms.

B.2.8. Statistical Analysis and Result Documentation

Appropriate analysis approaches characterize most cohort and case-control studies on TCE cancer. Many studies clearly documented statistical analyses, evaluated possible confounding factors, and included an examination of exposure-response. In occupational cohort studies, potential confounding factors other than age, sex, race, and calendar year are, generally, not evaluated. Expected numbers of outcomes (deaths or incident cancers) were calculated using life table analysis and an external comparison group, national or regional population mortality or incidence rates (Sung et al., 2007; 2006b; Chang et al., 2005; ATSDR, 2004a; Chang et al., 2003; Raaschou-Nielsen et al., 2003; Boice et al., 1999; Blair et al., 1998; Morgan et al., 1998; Anttila et al., 1995; Henschler et al., 1995; Axelson et al., 1994; Sinks et al., 1992; Blair et al., 1989; Costa et al., 1989; Garabrant et al., 1988; Shannon et al., 1988; Shindell and Ulrich, 1985). Risk ratios are also presented in some cohort studies using proportional hazard and logistic regression statistical methods using mortality or incidence rates of non-TCE exposed cohort subjects as referent or internal controls (Radican et al., 2008; Boice et al., 1999; Ritz, 1999a; Blair et al., 1998). Use of a non-TCE exposed referent group employed at the same facility as exposed generally reduces downward bias or bias having potential associations masked by a healthy worker work or other factors such as smoking that may be more similar within an occupational cohort than between the cohort and the general population. However, the advantage is minimized if subjects with lower TCE exposure potential are included in the referent group as in Boice et al. (2006b). One referent group (the Santa Susanna Field Laboratory [SSFL] group) of Boice et al. (2006b) included individuals with low TCE potential, a treatment different from the overlapping study of Zhao et al. (2005) whose exposure assessment adopted a semi-quantitative approach, grouping subjects identified with low TCE exposure potential separately from subjects with no TCE exposure potential. A second referent group of all Rocketdyne workers in Boice et al. (2006b) for whom TCE exposure potential was not examined may, also, have potential for greater than background exposure since TCE use was widespread and rocket engine cleaning occurred at other locations besides at test sites (Morgenstern, 1998). The inclusion of nonexposed subjects in the low-exposure group can obscure resultant associations due to misclassification bias (Stewart and Correa-Villaseor, 1991).

Cohort studies additionally evaluate a limited number of other factors associated with employment which could be easily obtained from company and other records such as hire date, time since first employment, SES or pay status, and termination date (2006b; Zhao et al., 2005; Boice et al., 1999; Greenland et al., 1994), and three studies (Boice et al., 2006b; Zhao et al., 2005; Ritz, 1999a) included a limited evaluation of smoking using information collected by survey on smoking patterns from a subgroup of subjects. Neither analysis of Morgan et al. (1998) nor Zhao et al. (2005) control for race, although Morgan et al. (1998) stated that "data concerning race were too sparse to use." The direction of any bias introduced depends on proportion of nonwhites in the referent (internal) group compared to TCE-exposed and on

differences between racial groups in site-specific cancer incidence and mortality rates. Blair et al. (1998), furthermore, presumed all subjects of unknown race were white, an assumption with little associated error as shown later by Radican et al. (2008) whose RR estimates were adjusted for race in follow-up analysis of this cohort.

The case-control studies on TCE are better able than cohort studies to evaluate other possible confounders besides age and sex using logistic regression approaches since such information can be obtained directly through interview and questionnaires. The case-control studies of Hardell et al. (1994), Nordstrom et al. (1998), and Persson and Fredriksson (1999) lack evaluation of possible confounding factors other than age, sex, and other demographic information used to match control subjects to case subjects. RCC case-control studies included evaluation of suggested risk factors for RCC such as smoking (Charbotel et al., 2006; Brüning et al., 2003; Pesch et al., 2000b; Vamvakas et al., 1998; Siemiatycki, 1991), weight, or obesity (Charbotel et al., 2006; Dosemeci et al., 1999), and diuretics (Dosemeci et al., 1999; Vamvakas et al., 1998). Moore et al. (2010) examined the effect on RCC by smoking in univariate analyses and reported a change in their OR of <10% compared to that for TCE and RCC. They concluded that smoking was not a confounder of the observed association with TCE. NHL and childhood leukemia case-control studies included evaluation and control for possible confounding due to smoking (Seidler et al., 2007; Costas et al., 2002; Siemiatycki, 1991), alcohol consumption (Seidler et al., 2007; Costas et al., 2002), and education (Costantini et al., 2008; Miligi et al., 2006), although etiological factors for these cancers are not well identified other than a suggestion of a role of immune function and some infectious agents in NHL (Alexander et al., 2007b). Smoking was not controlled in other NHL case-control studies; however, neither smoking nor alcohol is a strong risk factor for NHL (Besson et al., 2006; Morton et al., 2005).

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Mineral oils such as cutting fluids or hydrazine common to some job titles with potential TCE exposure as machinists, metal workers, and test stand mechanics are included as covariates in statistical analyses of Zhao et al. (2005), Boice et al. (2006b), and Charbotel et al. (2009; 2006) or evaluated as a single exposure for cases and controls in Moore et al., 2010 (Moore et al., 2010) and Karami et al. (Karami et al., 2011; 2010). Two other kidney case-control studies of TCE exposure examined the effect of cutting oil as a single occupational exposure on kidney cancer risk (Karami et al., 2011; Brüning et al., 2003). In Brüning et al. (2003), cutting oil exposure did not appear highly correlated with TCE exposure as only five cases reported exposure to cutting oils compared to 25 cases reporting TCE exposure. Karami et al. (2011), who examined mineral oil or cutting fluid exposure among cases and controls in Moore et al. (2010), reported an OR of 0.8 (95% CI: 0.6, 1,1) and 1.1 (95% CI: 0.8, 1.4), for cutting oil mists or other mineral oil mists respectively, and provides little evidence for confounding in Moore et al. (2010) by cutting or mineral oil exposures. Moreover, cutting oils and mineral oils have not been associated with kidney cancer in other cohort or case-control studies (Mirer, 2010; NIOSH, 1998). In all other studies, exposure to cutting oils or to hydrazine did not greatly affect magnitude of risk estimates for TCE exposure.

Geographical studies do not examine possible confounding factors other than sex, age and calendar year. These studies are generally health surveys using publically-available records such as death certificates and lack information on other risk factors such as smoking and exposure to viruses, important to Lee et al. (2003), introduces uncertainties for informing evaluations of TCE and cancer.

B.2.9. Systematic Review for Identifying Cancer Hazards and TCE Exposure

The epidemiological studies on cancer and TCE are reviewed systematically and transparently using criteria to identify studies for meta-analysis. Section B.3 contains a description of and comment on 79 studies of varying qualities for identifying cancer hazard, a question complementary but separate from that examined using meta-analysis. This section identifies of the studies reviewed, studies in which there is a high likelihood of TCE exposure in individual study subjects (e.g., based on JEMs, biomarker monitoring, or industrial hygiene data indicating a high probability of TCE use) and were judged to have met the inclusion criteria identified below. Lack of inclusion of an individual study in the meta-analysis does not necessarily imply an inability to identify cancer hazard. Not all questions associated with identifying a cancer hazard are addressed using meta-analyses and the 79 studies with varying abilities approached, to sufficient degrees, the standards of epidemiologic design and analysis, identified in the beginning of Section B.2.

The NRC (2006) suggested U.S. EPA conduct a new meta-analysis of the epidemiologic data on TCE to synthesize the epidemiologic data on TCE exposure. Meta-analysis approaches are feasible for examining cancers of the liver, kidney, and NHL given most studies presented risks for these sites in their published papers and these cancer sites are of interest given observations in the animal studies. Examination of site-specific cancers other than kidney cancer, liver cancer, and NHL, such as for childhood leukemia, bladder cancer, esophageal cancer, or cervical cancer is more difficult and not recommended due to fewer available high-quality studies. NRC (2006) specifically suggested EPA to:

1. Document essential design features, exposure, and results from the epidemiologic studies—Information on study design, exposure assessment approach, statistical analysis, and other aspects important to interpreting observations in a weight of evidence evaluation for individual studies is found in Section B.3 and site-specific estimated RRs or measures of association are presented in Chapter 4;

2. Analyze the epidemiologic studies to discriminate the amount of exposure experience by the study population; exclude studies in meta-analysis based on objective criteria (e.g., studies in which it was unclear that the study population was exposed)—Section B.3. describes exposure assessment approach for individual studies and inclusion criteria for identifying studies for meta-analysis are identified below;

3. Classify studies in terms of objective characteristics, such as on the basis of the study's design characteristics or documentation of exposure—Section B.3. groups studies by study design, analytical designs and geographic-based designs, with discussion of factors important to study design, endpoint measured, exposure assessment approach, study size, and statistical analysis methods including adjustment for potential confounding exposures;

4. Assess statistical power of each study—Table B-4 presents power calculations for cohort studies;

5. Combine case-control and cohort studies in the analysis, unless it introduces substantial heterogeneity—Appendix C discusses the meta-analysis statistical methods and findings;

6. Testing of heterogeneity (e.g., fixed or random effect models)—Appendix C discusses the meta-analysis statistical methods and findings;

7. Perform a sensitivity analysis in which each study is excluded from the analysis to determine whether any study significantly influences the finding—Appendix C discusses the meta-analysis statistical methods and findings.

Studies selected for inclusion in the meta-analysis met the following criteria: (1) cohort or case-control designs; (2) evaluation of incidence or mortality; (3) adequate selection in cohort studies of exposure and control groups and of cases and controls in case-control studies; (4) TCE exposure potential inferred to each subject and quantitative assessment of TCE exposure for each subject by reference to industrial hygiene records indicating a high probability of TCE use, individual biomarkers, JEMs, water distribution models, or obtained from subjects using questionnaire (case-control studies); and (5) RR estimates for kidney cancer, liver cancer, or NHL adjusted, at minimum, for possible confounding of age, sex, and race. Table B-5 in Section B.2.9.4 identifies studies included in the meta-analysis and studies that did not meet the inclusion criteria and the primary reasons for their deficiencies.

B.2.9.1. Cohort Studies

The cohort studies (Radican et al., 2008; Sung et al., 2008; Krishnadasan et al., 2007; Sung et al., 2007; Boice et al., 2006b; Chang et al., 2005; Zhao et al., 2005; Chang et al., 2003; Raaschou-Nielsen et al., 2003; Hansen et al., 2001; Boice et al., 1999; Ritz, 1999a; Blair et al., 1998; Morgan et al., 1998; Anttila et al., 1995; Henschler et al., 1995; Axelson et al., 1994; Greenland et al., 1994; Sinks et al., 1992; Blair et al., 1989; Costa et al., 1989; Garabrant et al., 1988; Shannon et al., 1988; Shindell and Ulrich, 1985; Wilcosky et al., 1984), with data on the incidence or morality of site-specific cancer in relation to TCE exposure range in size (803 (Hansen et al., 2001) to 86,868 (Chang et al., 2005; Chang et al., 2003)), and were conducted in Denmark, Sweden, Finland, Germany, Taiwan, and the United States (see Table B-1). Three case-control studies nested within cohorts (Krishnadasan et al., 2007; Greenland et al., 1994; Wilcosky et al., 1984) are considered as cohort studies because the summary risk estimate from a nested case-control study, the OR, was estimated from incidence density sampling and is considered an unbiased estimate of the hazard ratio, similar to an RR estimate from a cohort study. Two studies of deaths within a cohort were included in the group, but these studies lacked information on the person-year structure (i.e., both are PMR studies, and did not satisfy the meta-

analysis inclusion criteria for analytical study design [(Clapp and Hoffman, 2008; ATSDR, 2004a)]).

Cohort and nested case-control study designs are analytical epidemiologic studies and are generally relied on for identifying a causal association between human exposure and adverse health effects (Zhou et al., 2003). Some subjects in the Hansen et al. study are also included in a study reported by Raaschou-Nielsen et al. (2003); however, any contribution from the former to the latter are minimal given the large differences in cohort sizes of these studies (Raaschou-Nielsen et al., 2003; Hansen et al., 2001). Similarly, some females in Chang et al. (2005; 2003), a large cohort of 70,735 female and 16,133 male subjects, are included in Sung et al. (2007), a cohort of 63,982 female electronic workers from the same factory who were followed an additional 4-year period than subjects in Chang et al. (2005; 2003). Cancer observations for female subjects in these studies are considered as equivalent since they are derived from essentially the same population. Krishnadasan et al. (2007) is a nested case-control study of prostate cancer with cases and controls drawn from subjects in a large cohort of aerospace workers as subjects in Zhao et al. (2005), who did not report on prostate cancer, and met all of the inclusion criteria except that for reporting an RR estimate for cancer of the kidney, liver or NHL.

Eleven of the cohort studies met all five inclusion criteria: the cohorts of Blair et al. (1998) and its further follow-up by Radican et al. (2008), Morgan et al. (1998), Boice et al. (2006b; 1999) and Zhao et al. (2005) of aerospace workers or aircraft mechanics; Axelson et al. (1994), Anttila et al. (1995), Hansen et al. (2001), and Raaschou-Nielsen et al. (2003) of Nordic workers in multiple industries with TCE exposure; and Greenland et al. (1994) of electrical manufacturing workers. All 11 cohort studies adopted statistical methods, e.g., life table analysis, Poisson regression analysis, or Cox Proportional Hazard analysis, that met epidemiologic standards, and were able to control for age, race, sex, and calendar time trends in cancer rates. Statistical analyses in Boice et al. (1999) adjusted for demographic variable such as age, race, and sex, and also included date of first employment and terminating date of employments, which may have decreased the statistical power of their analyses due to collinearity between age, first and last employment dates. Statistical analyses in Zhao et al. (2005) and Boice et al. (2006b) adjusted for potential effects by other occupational exposures on cancer and both Raaschou-Nielsen et al. (2003) and Zhao et al. (2005) examined possible confounding by smoking on TCE exposure and cancer risks using indirect approaches.

Of the 11 studies, 2 studies reported risk estimates for both site-specific cancer incidence and mortality (Zhao et al., 2005; Blair et al., 1998), 4 studies reported risk estimates for cancer incidence only (Krishnadasan et al., 2007; Raaschou-Nielsen et al., 2003; Hansen et al., 2001; Anttila et al., 1995; Axelson et al., 1994), and four studies reported risk estimates for mortality only (Radican et al., 2008; 2006b; Boice et al., 1999; Morgan et al., 1998). Incidence ascertainment in two cohorts began 21 (Blair et al., 1998) and 38 years (Zhao et al., 2005) after

the inception of the cohort. Specifically, Zhao et al. (2005) note "results may not accurately reflect the effects of carcinogenic exposure that resulted in nonfatal cancers before 1988." Because of the issues concerning case ascertainment raised by this incomplete coverage, incidence observations must be interpreted in light of possible bias reflecting incomplete ascertainment of incident cases. Furthermore, use of an internal referent population, nonexposed subjects drawn from the same or nearby facilities as exposed workers, in Blair et al. (1998) and Radican et al. (2008) for overall TCE exposure, and in Blair et al. (1998), Morgan et al. (1998), Boice et al. (1999), Zhao et al. (2005), Boice et al. (2006b), and Radican et al. (2008) for rank-ordered TCE exposure is expected to reduce bias associated with the healthy worker effect. Morgan et al. (1998) presents risk estimates for overall TCE exposure comparing mortality in their TCE subcohort to that expected using mortality rate of the U.S. population in an Environmental Health Strategies Final Report and sent to U.S. EPA by Paul Cammer, Ph.D., on behalf of the Trichloroethylene Issues Group (EHS, 1997). The final report also contained risk estimates from internal analyses of rank-order TCE exposure and published as Morgan et al. (1998). Both internal cohort analyses of the rank-ordered exposure, presented in both the final report of Environmental Health Strategies (1997) and Morgan et al. (1998), and overall TCE exposure, available in the final report or upon request, are based on the same group of internal referents, nonexposed TCE subjects employed at the same facility.

Subjects in these studies had a high likelihood or potential for TCE exposure, although estimated average exposure intensity for overall TCE exposure in some cohorts was considered as <10 or 20 ppm (TWA). The exposure assessment techniques used in these cohort studies included a detailed JEM (Blair et al., 1998; Greenland et al., 1994); its follow-up by Radican et al. (2008) (2008; Boice et al., 2006b; Zhao et al., 2005; Boice et al., 1999; Morgan et al., 1998); Radican et al. (2008), biomonitoring data (Hansen et al., 2001; Anttila et al., 1995; Axelson et al., 1994), or use of industrial hygiene data on TCE exposure patterns and factors that affect such exposure (Raaschou-Nielsen et al., 2003), with high probability of TCE exposure potential to individual subjects. The JEM in six studies provided rank-ordered surrogate metrics for TCE exposure (Hansen et al., 2001; Blair et al., 1998; Anttila et al., 1995; Axelson et al., 1994) and its follow-up by Radican et al. (2008; Zhao et al., 2005), a strength compared to use of duration of employment as an exposure surrogate, e.g., Boice et al. (2006b; 1999) or Raaschou-Nielsen et al. (2003), which is a poorer exposure metric given subjects may have differing exposure intensity with similar exposure duration (NRC, 2006). Rank-ordered TCE dose surrogates for low and medium exposure from the JEM of Morgan et al. (1998) are uncertain because of a lack of information on frequency of exposure-related tasks and on temporal changes (NRC, 2006); only the high category for TCE exposure is unambiguous. The nested case-control study of Greenland et al. (1994) examined TCE as one of seven exposures and potential assigned to individual cases and controls using a job-exposure-matrix approach. However, the low exposure prevalence, missing job history information for 34% of eligible subjects, and study of pensioned

workers only were other factors judged to lower this study's sensitivity for cancer hazard identification.

The remaining cohort studies (Chang et al., 2005; Chang et al., 2003; Ritz, 1999a; Henschler et al., 1995; Sinks et al., 1992; Blair et al., 1989; Costa et al., 1989; Garabrant et al., 1988; Shannon et al., 1988; Shindell and Ulrich, 1985; Wilcosky et al., 1984); Sung et al., (Sung et al., 2008; 2007) less satisfactorily meet inclusion criteria. These studies, while not meeting the meta-analysis inclusion criteria, can inform the hazard analysis although their findings are weighted less than for observations in the other studies, and observations may have alternative causes. Reasons for study insufficiencies varied. Nine studies do not assign TCE exposure potential to individual subjects (Clapp and Hoffman, 2008; Sung et al., 2008; Sung et al., 2007; Chang et al., 2005; ATSDR, 2004a; Chang et al., 2003; Sinks et al., 1992; Costa et al., 1989; Garabrant et al., 1988; Shindell and Ulrich, 1985) all subjects are presumed as "exposed" because of employment in the plant or facility although individual subjects would be expected to have differing exposure potentials.

TCE exposure potential is ambiguous in both Wilcosky et al. (1984) and Ritz (1999a), two studies of low potential, low intensity TCE exposure compared to studies using exposure assessment approaches supported by information on job titles, tasks, and industrial hygiene monitoring data. Furthermore, high correlation in Ritz (1999a) between TCE and other exposures, particularly cutting fluids and radiation, may not have been sufficiently controlled in statistical analyses. Ritz et al. (1999a), furthermore, did not report estimated RRs for kidney or NHL separately; rather, presenting RR estimates for kidney and bladder cancer combined and for all hemato- and lymphopoietic cancers.

Two studies do not sufficiently define the underlying cohort or there is uncertainty in cancer case or death ascertainment (Henschler et al., 1995; Shindell and Ulrich, 1985). Furthermore, magnitude of observed risk in Henschler et al. (1995), ATSDR (2004a), and Clapp and Hoffman (2008) must be interpreted in a weight-of-evidence evaluation in light of possible bias introduced through use of analysis of proportion of deaths (PMR) in ATSDR (2004a) and Clapp and Hoffman (2008), or to inclusion of index kidney cancer cases in Henschler et al. (1995).

B.2.9.2. Case-Control Studies

Case-control studies on TCE exposure are of several site-specific cancers and include bladder cancer (Pesch et al., 2000a; Siemiatycki et al., 1994; Siemiatycki, 1991); brain cancer (De Roos et al., 2001; Heineman et al., 1994); childhood lymphoma or leukemia (Shu et al., 2004; Costas et al., 2002; Shu et al., 1999; McKinney et al., 1991; Lowengart et al., 1987); colon cancer (Goldberg et al., 2001; Siemiatycki, 1991), esophageal cancer (Parent et al., 2000b; Siemiatycki, 1991); liver cancer (Lee et al., 2003); lung cancer (Siemiatycki, 1991); lymphoma (Hardell et al., 1994) [NHL, Hodgkin lymphoma], (Nordström et al., 1998; Fritschi and

Siemiatycki, 1996a; Siemiatycki, 1991), [hairy cell leukemia], (Persson and Fredrikson, 1999) [NHL], (Miligi et al., 2006) [NHL and CLL], (Seidler et al., 2007) [NHL, Hodgkin lymphoma], (Costantini et al., 2008) [leukemia types, CLL included in Miligi et al. (2006), Wang et al. (2009) [NHL], (Cocco et al., 2010) [NHL, CLL, MM]; (Gold et al., 2011) [MM]; Purdue et al. (2011) [NHL]; melanoma (Fritschi and Siemiatycki, 1996a; Siemiatycki, 1991); rectal cancer (Dumas et al., 2000; Siemiatycki, 1991); RCC, a form of kidney cancer (Moore et al., 2010; Charbotel et al., 2009; Charbotel et al., 2006; Brüning et al., 2003; Parent et al., 2000a; Pesch et al., 2000b; Dosemeci et al., 1999; Vamvakas et al., 1998; Siemiatycki, 1991); pancreatic cancer (Siemiatycki, 1991); and prostate cancer (Aronson et al., 1996; Siemiatycki, 1991). No case-control studies of reproductive cancers (breast or cervix) and TCE exposure were found in the peer-reviewed literature.

Several of the above publications are studies of cases and controls drawn from the same underlying population with a common control series. Miligi et al. (2006) and Costantini et al. (2008) presented observations from the Italian multicenter lymphoma population case-control study; Miligi et al. (2006) on occupation or specific solvent exposures and NHL, and who also included CLL and Hodgkin lymphoma in the overall NHL category, and Costantini et al. (2008) who examined leukemia subtypes, and included CLL as a separate disease outcome. Seidler et al. (2007) analyzed independently the German subjects of the six European country, multicenter lymphoma population case-control study (EPILYMPH study) of Cocco et al. (2010). Each study adopted a different approach to calculate cumulative exposure and apparent inconsistency in their conclusions may reflect the slightly different ranking of cases and controls in each study (personal communication from Pierluigi Cocco to Cheryl Siegel Scott). Gold et al. (2011) and Purdue et al. (2011) presented observations from the NCI-SEER population case-control studies and share a common control series; Purdue et al. (2011) of NHL in four SEER reporting areas and Gold et al. (2011) of multiple myeloma in two of the four SEER sites. Pesch et al. (2000a, 2000b), a multiple center population case- control study of urothelial cancers in Germany, presented observations on TCE and bladder cancer, including cancer of the ureter and renal pelvis, in Pesch et al. (2000a) and RCC in Pesch et al. (2000b). Siemiatycki (1991), a case-control of occupational exposures and several site-specific cancers (bladder, colon, esophagus, lung, rectum, pancreas, and prostate) and designed to generate hypotheses about possible occupational carcinogens, presents risk estimates associated with TCE exposure using Mantel-Haentszel methods. Subsequent publications examine either TCE exposure (analyses of melanoma and colon cancers) or job title/occupation (all other cancer sites) using logistic regression methods (Goldberg et al., 2001; Dumas et al., 2000; Parent et al., 2000a; Aronson et al., 1996; Fritschi and Siemiatycki, 1996b, a; Siemiatycki et al., 1994).

The population case-control studies with data on cancer incidence or mortality (Siemiatycki, 1991 [and related publications, Goldberg et al., 2001; Dumas et al., 2000; Parent et al., 2000a; Aronson et al., 1996; Fritschi and Siemiatycki, 1996b; Siemiatycki et al., 1994], Gold

et al., 2011; Purdue et al., 2011; Cocco et al., 2010; Moore et al., 2010; Wang et al., 2009; Costantini et al., 2008; Seidler et al., 2007; Charbotel et al., 2006; Miligi et al., 2006; Shu et al., 2004; Brüning et al., 2003; Lee et al., 2003; Costas et al., 2002; De Roos et al., 2001; Pesch et al., 2000a, 2000b; Dosemeci et al., 1999; Kernan et al., 1999; Persson and Fredrikson, 1999; Nordström et al., 1998; Vamvakas et al., 1998; Hardell et al., 1994; Heineman et al., 1994; McKinney et al., 1991; Lowengart et al., 1987) in relation to TCE exposure range in size, from small studies with <100 cases and control (Costas et al., 2002) to multiple-center studies large-scale studies of over 2,000 cases and controls (Costantini et al., 2008; Miligi et al., 2006; Shu et al., 2004; Pesch et al., 2000a, 2000b; Shu et al., 1999), and were conducted in Sweden, Germany, Italy, Taiwan, Canada, and the United States (see Table B-2).

Fifteen of the case-control studies met the meta-analysis inclusion criteria identified in Section B.2.9 (Purdue et al., 2011; Cocco et al., 2010; Moore et al., 2010; Charbotel et al., 2009; Wang et al., 2009; Seidler et al., 2007; Charbotel et al., 2006; Miligi et al., 2006; Brüning et al., 2003; Pesch et al., 2000b; Dosemeci et al., 1999; Persson and Fredrikson, 1999; Nordström et al., 1998; Hardell et al., 1994; Siemiatycki, 1991). They were of analytical study design, cases and controls were considered to represent underlying populations and selected with minimal potential for bias; exposure assessment approaches included assignment of TCE exposure potential to individual subjects using information obtained from face-to-face, mailed, or telephone interviews; analyses methods were appropriate, well-documented, included adjustment for potential confounding exposures, with RR estimates and associated CIs reported for kidney cancer, liver cancer, or NHL. All thirteen studies evaluated TCE exposure potential to individual cases and controls and a structured questionnaire sought information on self-reported occupational history and specific exposures such as TCE. Three studies assigned TCE exposure potential to cases and controls using self-reported information (Nordström et al., 1998; Hardell et al., 1994) and two of these studies used judgment to assign potential exposure intensity (Persson and Fredrikson, 1999; Nordström et al., 1998). Persson and Fredriksson (1999) also assigned TCE exposure potential from both occupational and leisure use, the only study to do so. The 10 other studies assigned TCE exposure potential using self-reported job title and occupational history, a superior approach compared to use of a JEM supported by expert judgment and information on only self-reported information given its expect greater specificity (Purdue et al., 2011; Cocco et al., 2010; Moore et al., 2010; Charbotel et al., 2009; Wang et al., 2009; Seidler et al., 2007; Charbotel et al., 2006; Miligi et al., 2006; Brüning et al., 2003; Pesch et al., 2000b; Dosemeci et al., 1999; Siemiatycki, 1991). Pesch et al. (2000b) assigned TCE exposure potential using both JEM and JTEM. The inclusion of task information is considered superior to exposure assignment using only job title since it likely reduces potential misclassification and, for this reason, RR estimates in Pesch et al. (2000b) for TCE from a JTEM are preferred. All studies except Hardell et al. (1994) and Dosemeci et al. (1999) developed a semiquantitative or quantitative TCE exposure surrogate.

These studies to varying degrees were considered as stronger studies for weight-of evidence characterization of hazard. Both Brüning et al. (2003) and Charbotel et al. (2006), (2009) had a priori hypotheses for examining RCC and TCE exposure. Strengths of both studies are in their examination of populations with potential for high exposure intensity and in areas with high frequency of TCE usage and their assessment of TCE potential. An important feature of the exposure assessment approach of Charbotel et al. (2006) is their use of a large number of studies on biological monitoring of workers in the screw-cutting industry a predominant industry with documented TCE exposures as support. The other studies were either large multiple-center studies (Purdue et al., 2011; Cocco et al., 2010; Moore et al., 2010; Wang et al., 2009; Miligi et al., 2006; Pesch et al., 2000b); or reporting from one location of a larger international study (Seidler et al., 2007; Dosemeci et al., 1999). In contrast to Brüning et al. (2003) and Charbotel et al. (2009; 2006), two studies conducted in geographical areas with widespread TCE usage and potential for exposure to higher intensity, a lower exposure prevalence to TCE is found (any TCE exposure: 15% of cases [(Dosemeci et al., 1999); 6% of cases (Miligi et al., 2006); 13% of cases (Seidler et al., 2007); 13% of cases (Wang et al., 2009)]) and most subjects identified as exposed to TCE probably had minimal contact (3% of cases with moderate/high TCE exposure [(Miligi et al., 2006); 1% of cases with high cumulative TCE (Seidler et al., 2007); 2% of cases with high intensity, but of low probability TCE exposure (Wang et al., 2009)]). This pattern of lower exposure prevalence and intensity is common to community-based, population case-control studies (Teschke et al., 2002).

Fifteen case-control studies did not meet specific inclusion criterion (Gold et al., 2011; Costantini et al., 2008; Shu et al., 2004; Lee et al., 2003; Costas et al., 2002; Goldberg et al., 2001; Dumas et al., 2000; Parent et al., 2000a; Pesch et al., 2000a; Kernan et al., 1999; Shu et al., 1999; Vamvakas et al., 1998; Fritschi and Siemiatycki, 1996b; Siemiatycki, 1991). Costantini et al. (2008) and Gold et al. (2011) examined multiple myeloma or leukemias, not included in older NHL classification schemes, although these neoplasms are now considered as lymphomas under the WHO Lymphoma Classification. Vamvakas et al. (1998) has been subject of considerable controversy (Cherrie et al., 2001; Mandel, 2001; Green and Lash, 1999; McLaughlin and Blot, 1997; Bloemen and Tomenson, 1995; Swaen, 1995) with questions raised on potential for selection bias related to the study's controls. This study was deficient in the criterion for adequacy of case and control selection. Brüning et al. (2003), a study from the same region as Vamvakas et al. (1998), is considered a stronger study for identifying cancer hazard since it addresses many of the deficiencies of Vamvakas et al. (1998). Lee et al. (2003), in their study of hepatocellular cancer, assigns one level of exposure to all subjects in a geographic area, and inherent measurement error and misclassification bias because not all subjects are exposed uniformly. Additionally, statistical analyses in this study did not control for hepatitis viral infection, a known risk factor for hepatocellular cancer and of high prevalence in the study area. Ten of 12 studies reported RR estimates for site-specific cancers other than kidney, liver, and

NHL (Shu et al., 2004; Costas et al., 2002; Goldberg et al., 2001; Dumas et al., 2000; Parent et al., 2000b; Pesch et al., 2000a; Kernan et al., 1999; Shu et al., 1999; Aronson et al., 1996; Fritschi and Siemiatycki, 1996b; Siemiatycki et al., 1994; Garabrant et al., 1988).

B.2.9.3. Geographic-Based Studies

The geographic-based studies (ATSDR, 2008b, 2006a; Aickin, 2004; Morgan and Cassady, 2002; ADHS, 1995; Cohn et al., 1994b; Vartiainen et al., 1993; Aickin et al., 1992; ADHS, 1990; Mallin, 1990; Isacson et al., 1985) with data on cancer incidence (all studies) are correlation studies to examine cancer outcomes of residents living in communities with TCE and other chemicals detected in groundwater wells or in municipal drinking water supplies. These eight studies did not meet inclusion criteria and were deficient in a number of criteria.
All geographic-based studies are surveys of cancer rates for a defined time period among residents in geographic areas with TCE contamination in groundwater or drinking water supplies, or soil and are not of analytical designs such as cohort and case-control designs. A major shortcoming in all studies is, also, their low level of detail to individual subjects for TCE potential. The exposure surrogate is assigned to a community, town, or a geographically-defined area such as a contiguous grouping of census tracts as an aggregate level, typically based on limited number of water monitoring data from a recent time period and is a poor exposure surrogate because potential for TCE exposure can vary in these broad categories depending on job function, year, use of personal protection, and, for residential exposure, pollutant fate and transport, water system distribution characteristics, percent of time per day in residence, presence of mitigation devices, drinking water consumption rates, and showering times. Additionally, ATSDR (2008b), the only geographic-based study to examine other possible risk factors on individual subjects, reported that smoking patterns and occupational exposures may partly contribute to the observed elevated rates of kidney and renal pelvis cancer and lung cancer in subjects living in a community with contaminated groundwater and with TCE exposure potential from vapor intrusion into residences.

B.2.9.4. Recommendation of Studies for Treatment Using Meta-Analysis Approaches

All studies are initially considered for inclusion in the meta-analysis; however, as discussed throughout this section, some studies are better than others for inclusion in a quantitative examination of cancer and TCE. Twenty-six of the studies included in the meta-analysis (statistical methods and findings discussed in Appendix C) met the following five inclusion criteria: (1) cohort or case-control designs; (2) evaluation of incidence or mortality; (3) adequate selection in cohort studies of exposure and control groups and of cases and controls in case-control studies; (4) TCE exposure potential inferred to each subject and quantitative assessment of TCE exposure assessment for each subject by reference to industrial hygiene records indicating a high probability of TCE use, individual biomarkers, JEMs, water

distribution models, or obtained from subjects using questionnaire (case-control studies); and (5) RR estimates for kidney cancer, liver cancer, or NHL adjusted, at minimum, for possible confounding of age, sex, and race. The twenty-six studies that met these inclusion are: Siemiatycki (1991), Axelson et al. (1994), Greenland et al. (1994), Hardell et al. (1994), Anttila et al. (1995), Blair et al. (1998), Morgan et al. (1998), Nordstrom et al. (1998), Dosemeci et al. (1999), Boice et al. (2006b; 1999), Persson and Fredriksson (1999), Pesch et al. (2000b), Hansen et al. (2001), Brüning et al. (2003), Raaschou-Nielsen et al. (2003), Zhao et al. (2005), Miligi et al. (2006), Charbotel et al. (2006), Seidler et al. (2007), Radican et al. (2008), Wang et al. (2009), Cocco et al. (2010), Moore et al. (2010), and Purdue et al. (2011). Table B-5 identifies studies included in the meta-analysis and studies that did not meet the inclusion criteria and the primary reasons for their deficiencies.

Table B-5. Summary of rationale for study selection for meta-analysis

Decision outcome	Studies	Primary reason(s)
Studies recommended for meta-analysis:		
	Siemiatycki (1991); Axelson et al. (1994); Hardell (1994); Greenland et al. (1994); Anttila et al. (1995); Morgan et al. (1998); Nordstrom et al. (1998); Boice et al. (2006b; 1999); Dosemeci et al., (1999); Persson and Fredriksson, (1999); Pesch et al. (2000b); Hansen et al. (2001); Brüning et al. (2003); Raaschou-Nielsen et al. (2003); Zhao et al. (2005); Miligi et al. (2006); Charbotel et al. (2006); Radican et al. (2008) [Blair et al. (1998), incidence]; Wang et al. (2009); Cocco et al. (2010); Moore et al. (2010); Purdue et al. (2011)	Analytical study designs of cohort or case-control approaches; evaluation of cancer incidence or cancer mortality. Specifically identified TCE exposure potential to individual study subjects by reference to industrial hygiene records, individual biomarkers, JEMs, water distribution models, industrial hygiene data indicating a high probability of TCE use (cohort studies), or obtained information on TCE exposure from subjects using questionnaire (case-control studies). Reported results for kidney cancer, liver cancer, or NHL with RR estimates and corresponding CIs (or information to allow calculation).

Table B-5. Summary of rationale for study selection for meta-analysis (continued)

Decision outcome	Studies	Primary reason(s)
Studies not recommended for meta-analysis:		
	ATSDR (2004a); Clapp and Hoffman, (2008); Cohn et al. (1994b)	Weakness with respect to analytical study design (i.e., geographic-based, ecological, or PMR design)
	Wilcosky et al. (1984); Isacson et al. (1985); Shindell and Ulrich (1985); Garabrant et al. (1988); Shannon et al.(1988); Blair et al. (1989); Costa et al. (1989); ADHS (1995, 1990); Mallin (1990); Aickin et al. (1992); Sinks et al. (1992); Vartiainen et al. (1993); Morgan and Cassady (2002); Lee et al. (2003); Aickin (2004); Chang et al. (2005; 2003); Coyle et al. (2005); ATSDR (2008b, 2006a); Sung et al. (2008; 2007)	TCE exposure potential not assigned to individual subjects using JEM, individual biomarkers, water distribution models, or industrial hygiene data indicating a high probability of TCE use (cohort studies).
	Lowengart et al. (1987); Fredriksson et al. (1989); McKinney et al. (1991); Heineman et al. (1994); Siemiatycki et al. (1994); Aronson et al. (1996); Fritchi and Siemiatycki (1996b); Dumas et al. (2000); Kernan et al.(1999); Shu et al. (2004; 1999); Parent et al. (Parent et al., 2000b); Pesch et al., (2000a); De Roos et al. (2001); Goldberg et al. (2001); Costas et al. (2002); Krishnadasan et al. (2007); Costantini et al. (2008); Gold et al. (2011)	Cancer incidence or mortality reported for cancers other than kidney, liver, or NHL.
	Ritz (1999a)	Subjects monitored for radiation exposure with likelihood for potential confounding. Cancer mortality and TCE exposure not reported for kidney cancer and all hemato- and lymphopoietic cancer reported as broad category.
	Henschler et al. (1995)	Incomplete identification of cohort and index kidney cancer cases included in case series.
	Vamvakas et al. (1998)	Control selection may not represent case series with potential for selection bias.

There is some overlap between the cohorts of Zhao et al. (2005) and Boice et al. (2006b); each cohort is identified from a population of workers, but these studies differ on cohort definition, cohort identification dates, disease outcome examined, and exposure assessment approach. Zhao et al. (2005), who adopted a semiquantitative approach for TCE exposure assessment, is preferred to Boice et al. (2006b), whose TCE subcohort included subjects with a

lower likelihood for TCE exposure and duration of exposure, a poor exposure metric given that subjects may have differing exposure intensity with similar exposure duration (NRC, 2006). Additionally, a larger number of site-specific cancer deaths identified with potential TCE exposure is observed by Zhao et al. (2005) compared to Boice et al. (2006b); e.g., 95 lung cancer cases with medium or high TCE exposure (Zhao et al., 2005) and 51 lung cancer cases with any TCE exposure (Boice et al., 2006b) (see further discussion in Section B.3.1.1.1.3). Radican et al. (2008) studied the same subjects as Blair et al. (1998), adding an additional 10 years of follow-up and updating mortality. Observed site-specific cancer mortality risk estimates in Radican et al. (2008) did not change appreciably and were consistent with those reported in Blair et al. (1998) and is preferred. Blair et al. (1998) who also presented incidence RR estimates is recommended for inclusion in sensitivity analyses. Charbotel et al. (2006) is preferred to Charbotel et al. (2009), who examined kidney cancer risk and TCE exposure at the existing French occupational exposure limit for cases and controls from their earlier publication (Charbotel et al., 2009); the earlier publication contained more extensive analyses and included exposure-response analyses using several exposure metrics and multiple exposure categories. Cocco et al. (2010) is preferred to Seidler et al. (2007), whose subjects are included in the larger multicenter population case-control study. In conclusion, twenty-four studies in which there is a high likelihood for TCE exposure and judged to have met, to a sufficient degree, the standards of epidemiologic design and analysis, are identified in a systematic review of the epidemiologic literature and for examination using meta-analysis.

B.3. INDIVIDUAL STUDY REVIEWS AND ABSTRACTS

B.3.1. Cohort Studies

B.3.1.1. Studies of Aerospace Workers

Seven papers reported on cohort studies of aerospace or aircraft maintenance and manufacturing workers in large facilities.

B.3.1.1.1. Studies of SSFL workers.

TCE exposure to workers at SSFL, an aerospace facility located nearby Los Angeles, California, operated by Rocketdyne/Atomics International, formerly a division of Boeing and currently owned by Pratt-Whitney, is subject of two research efforts: (1) the University of California at Los Angeles (UCLA) study, overseen by the California Department of Health Services and funded by the U.S. Department of Energy (DOE) (Morgenstern et al., 1999; Ritz et al., 1999; Morgenstern et al., 1997), with two publications on TCE exposure and cancer incidence (Krishnadasan et al., 2007; Zhao et al., 2005) and mortality (Zhao et al., 2005) and (2) the International Epidemiology Institute study (IEI), funded by Boeing after publication of the initial UCLA reports, of all Rocketdyne employees which included a mortality analysis of TCE exposure in a subcohort of SSFL test stand mechanics (Boice et al., 2006b). In addition to

chemical exposure, both groups examine radiation exposure and cancer among Rocketdyne workers monitored for radiation (Boice et al., 2006a; Ritz et al., 2000).

B.3.1.1.1.1. International Epidemiology Institute study of Rocketdyne workers.

B.3.1.1.1.1.1. Boice et al. (2006b).

B.3.1.1.1.1.1.1. Author's abstract.

Objective: The objective of this study was to evaluate potential health risks associated with testing rocket engines. **Methods**: A retrospective cohort mortality study was conducted of 8372 Rocketdyne workers employed 1948 to 1999 at the Santa Susanna Field Laboratory (SSFL). Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) were calculated for all workers, including those employed at specific test areas where particular fuels, solvents, and chemicals were used. Dose-response trends were evaluated using Cox proportional hazards models. **Results:** SMRs for all cancers were close to population expects among SSFL workers overall (SMR = 0.89; CI = 0.82-0.96) and test stand mechanics in particular (n = 1651; SMR = 1.00; CI = 0.86-1.1.6), including those likely exposure to hydrazines (n = 315; SMR = 1.09; CI = 0.75-1.52) or trichloroethylene (TCE) (n=1111; SMR = 1.00; CI = 0.83-1.19). Nonsignificant associations were seen between kidney cancer and TCE, lung cancer and hydrazines, and stomach cancer and years worked as a test stand mechanic. No trends over exposure categories were statistically significant. **Conclusion:** Work at the SSFL rocket engine test facility or as a test stand mechanic was not associated with a significant increase in cancer mortality overall or for any specific cancer.

B.3.1.1.1.1.1.2. Study description and comment.

Boice et al. (2006b) examined all cause, all cancer and site-specific mortality in a subcohort of 1,651 male and female test stand mechanics who had been employed on or after 1949 to 1999, the end of follow-up, for at least 6 months at SSFL. Subjects were identified from 41,345 male and female Rocketdyne workers at SSFL (n = 8.372) and two nearby facilities (32,979). Of the 1,642 male test stand mechanics, 9 females were excluded due to few numbers, personnel listing in company phone directories were used to identify test stand assignments (and infer potential specific chemical exposures) for 1,440 subjects, and of this group, 1,111 male test stand mechanics were identified with potential TCE exposure either from the cleaning of rocket engines between tests or from more generalized use as a utility degreasing solvent. Cause-specific mortality is compared to several referents: (1) morality rates of the U.S. population; (2) mortality rates of California residents; (3) hourly nonadministrative workers at SSFL and two nearby facilities; and (4) 1,598 SSFL hourly workers; however, the published paper does not

clearly present details of all analyses. For example, the referent population is not identified for the SMR analysis of the 1,111 male subjects with TCE potential exposure and analyses examining exposure duration present point estimates and p-values from tests of linear trend, but not always CIs (e.g., Boice et al. (2006b) Table 7, table footnotes).

Exposure assessment to TCE is qualitative without attempt to characterize exposure level as was done in the exposure assessment approach of Zhao et al. (2005) and Krishnadsen et al. (2007). Test stand mechanics were nonadministrative hourly positions and had the greatest potential for chemical exposures to TCE and hydrazine. Potential exposure to chemicals also existed for other subjects associated with test stand work such as instrument mechanics, inspectors, test stand engineers, and research engineers potential for chemical exposure, although Boice et al. (2006b) considered their exposure potential lower compared to that received by test stand mechanics and, thus, were not included in the cohort. Like that encountered by UCLA researchers, work history information in the personnel file was not specific to identify work location and test stand and Boice et al. (2006b) adopted ancillary information, company phone directories, as an aid to identify subjects with greater potential for TCE exposure. From these aids, investigators identified rocket stand assignment for 1,440 or 87% of the SSFL test stand mechanics. Bias is introduced through missing information on the other 211 subjects or if phone directories were not available for the full period of the study. Test stand mechanics, if exposed, had the likelihood for exposure to high TCE concentrations associated with flushing or cleaning of rocket engines; 593 of the 1,111 subjects (53%) were identified as having potential TCE exposure through rocket engine cleaning. The removal or flushing of hydrocarbon deposits in fuel jackets and in liquid oxygen dome of large engines entailed the use of 5 to 100 gallons of TCE, with TCE use starting around 1956 and ceased by the late 1960's at all test stands except one which continued until 1994. No information was provided on test stand and working conditions or the frequency of exposure-related tasks, and no atmospheric monitoring data were available on TCE. A small number of these subjects (121) also had potential exposure to hydrazines. The remaining 518 subjects in the TCE subcohort were presumed exposed to TCE as a utility solvent. Information on use of TCE as a utility solvent is lacking except that TCE as a utility solvent was discontinued in 1974 except at one test stand where it was used until 1984. These subjects have a lower likelihood of exposure compared to subjects with TCE exposure from cleaning rocket engines.

Several study design and analysis aspects limit this study for assessing risks associated with TCE exposure. Overall, exposures were likely substantially misclassified and their frequency likely low, particularly for subjects identified with TCE use as a utility solvent who comprise roughly 50% of the TCE subcohort. Analyses examining number of years employed at SSFL or worked as test stand mechanic as a surrogate for cumulative exposure has a large potential for misclassification bias due to the lack of air monitoring data and inability to account to temporal changes in TCE usage. Moreover, the exposure metric used in some dose-response

analyses is weighted by the number of workers without rationale provided and would introduce bias if the workforce changed over the period covered by this study. Some information suggests that this was likely: (1) the number of cohort subjects entering the cohort decreased over the time period of this study, as much as a 20% decrease between 1960s and 1970s, and (2) ancillary information (http://www.thewednesdayreport.com/twr/twr48v7.htm, accessed March 11, 2008; DOE Closure Project, http://www.etec.energy.gov/Reading-Room/DeSoto.html, accessed March 11, 2008). Study investigators did not carry out exposure assessment for referents and no information is provided on potential TCE exposure. If referents had more than background exposure, likely for other hourly subjects with direct association with test stand work but with a job title other than test stand mechanic, the bias introduced leads to an underestimation of risk. TCE use at SSFL was widespread and rocket engine cleaning occurred at other locations besides at test sites (Morgenstern et al., 1999), locations from which the referent population arose.

Boice JD, Marano DE, Cohen SS, Mumma MT, Blott WJ, Brill AB, Fryzek JP, Henderson BE, McLaughlin JK. (2006b). Mortality among Rocketdyne workers who tested rocket engines, 1948–1999. J Occup Environ Med 48:1070–1092.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	From abstract "objective of this study was to evaluate potential health risks associated with testing rocket engines."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	54,384 Rocketdyne workers of which 41,351 were employed on or after 1-1-1948 and for at least 6 months at SSFL or nearby facilities. Of the 41,351 subjects, 1,651 were identified as having a job title of test stand mechanic and exposure assignments could be made for 1,440 of these subjects. Site-specific mortality rates of U.S. population and of all-other Rocketdyne employees. Potential TCE exposures of all other subjects (referents) not documented but investigators assumed referents are unexposed to TCE.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality from 1948 to 12-31-1999.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Coding to ICD in use at time of death.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Qualitative exposure assessment, any TCE exposure. No quantitative information on TCE intensity by job title or to individual subjects or referents. Missing exposure potential to 12% of test stand mechanics; potential exposure hydrazine and/or TCE assigned to 1,440 of 1,651 test stand mechanics. Of 1,440 test stand mechanics, 1,111[a] identified with potential TCE exposure, 518 of the 1,111 identified as having presumed high intensity exposure from the cleaning of rocket engines. The remaining 593 subjects with potential exposure to TCE through use as "utility solvent," a job task with low likelihood or potential for TCE exposure.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	0.4% for test stand mechanic cohort (1,651 subjects).
>50% cohort with full latency	35 yrs average follow-up; 88% of 1,651 test stand mechanics >20-yr follow-up.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	TCE exposed subcohort—391 total deaths, 121 cancer deaths.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	SMR analysis restricted to male hourly test stand mechanics using U.S. population rates as referent—no adjustment of potential confounders other than age and calendar-year. Cox proportional hazard models examining TCE exposure adjusted for birth year, year of hire and potential hydrazine exposure. Race was not included in Cox proportional hazard analysis.
Statistical methods	SMR analysis and Cox proportional hazard.
Exposure-response analysis presented in published paper	Duration of exposure (employment): 2-sided tests for linear trend.
Documentation of results	All analyses are not presented in published paper. Follow-up correspondence of C Scott, U.S. EPA, to J. Boice, of 12-31-06 and 02-28-07 remain unanswered as of November 15, 2007.

[a]Zhao et al. (2005), whose study period and base population overlaps that of Boice et al. (2006b), identified a larger number of subjects with potential TCE exposures; 2,689 subjects with TCE score >3, a group having medium to high cumulative TCE exposure.

B.3.1.1.1.2. UCLA studies of Rocketdyne workers.

B.3.1.1.1.2.1. Krishnadasan et al. (2007).

B.3.1.1.1.2.1.1. Author's abstract.

Background To date, little is known about the potential contributions of occupational exposure to chemicals to the etiology of prostate cancer. Previous studies examining associations suffered from limitations including the reliance on mortality data and inadequate exposure assessment. **Methods** We conducted a nested case-control study of 362 cases and 1,805 matched controls to examine the association between occupational chemical exposures and prostate cancer incidence. Workers were employed between 1950 and 1992 at a nuclear energy and rocket engine-testing facility in Southern California. We obtained cancer incidence data from the California Cancer Registry and seven other state cancer registries. Data from company records were used to construct a job exposure matrix (JEM) for occupational exposures to hydrazine, trichloroethylene (TCE), polycyclic aromatic hydrocarbons (PAHs), benzene, and mineral oil. Associations between chemical exposures and prostate cancer incidence were assessed in conditional logistic regression models. **Results** With adjustment for occupational confounders, including socioeconomic status, occupational physical activity, and exposure to the other chemicals evaluated, the odds ratio for low/moderate TCE exposure was 1.3; 95%CI=0.8 to 2.1, and for high TCE exposure was 2.1; 95%CI=1.2 to 3.9. Furthermore, we noted a positive trend between increasing levels of TCE exposure and prostate cancer (p-value for trend=0.02). **Conclusion** Our results suggest that high levels of TCE exposure are associated with prostate cancer among workers in our study population.

B.3.1.1.1.2.2. Zhao et al. (2005).

B.3.1.1.1.2.2.1. Author's abstract.

Background A retrospective cohort study of workers employed at a California aerospace company between 1950 and 1993 was conducted; it examined cancer mortality from exposures to the rocket fuel hydrazine. **Methods** In this study, we employed a job exposure matrix (JEM) to assess exposures to other known or suspected carcinogens—including trichloroethylene (TCE), polycyclic aromatic hydrocarbons (PAHs), mineral oils, and benzene—on cancer mortality (1960–2001) and incidence (1988–2000) in 6,107 male workers. We derived rate-(hazard-) ratios estimates from Cox proportional hazard models with time-dependent exposures. **Results** High levels of TCE exposure were positively associated with cancer incidence of the bladder (rate ratio (RR): 1.98, 95% confidence interval (CI) 0.93–4.22) and kidney (4.90; 1.23–19.6). High levels of exposure to mineral oils increased mortality and incidence of lung cancer (1.56; 1.02–2.39 and 1.99; 1.03–3.85), and incidence of melanoma (3.32; 1.20–9.24). Mineral oil exposures also contributed to incidence and mortality of esophageal and stomach cancers and of non-Hodgkin lymphoma and leukemia when adjusting for other chemical exposures. Lagging exposure measures by 20 years changed effect estimates only minimally. No associations were observed for benzene or PAH exposures in this cohort. **Conclusions** Our findings suggest that

these aerospace workers who were highly exposed to mineral oils experienced an increased risk of developing and/or dying from cancers of the lung, melanoma, and possibly from cancers of the esophagus and stomach and non-Hodgkin lymphoma and leukemia. These results and the increases we observed for TCE and kidney cancers are consistent with findings of previous studies.

B.3.1.1.1.2.3. Study description and comment.

The source population for Krishnadasen et al. (2007) and Zhao et al. (2005) is the UCLA chemical cohort of 6,044 male workers with ≥2 years of employment Rocketdyne between 1950 and 1993, who engaged in rocket testing at SSFL before 1980 and who have never been monitored for radiation. Zhao et al. (2005) examined cancer mortality between 1960 and 2001, an additional 7 years from earlier analyses of the chemical subcohort (Morgenstern et al., 1999; Ritz et al., 1999), and cancer incidence (5,049 subjects) between 1988 and 2000, matching cohort subjects to names in California's Cancer Registry and eight other state cancer registries. Deaths before 1998 are coded using ICD, 9th revision, and ICD-10 after this date; ICD-0 was used to code cancer incidence with leukemia, lymphoma, and other lymphopoietic tumors grouped on the basis of morphology codes. A total of 600 cancer deaths and 691 incident cancers were identified during the study period.

Krishnadasen et al. (2007) adopted a nested case-control design to examine occupational exposure to several chemicals and prostate cancer incidence in a cohort, which included the SSFL chemically-exposed subjects and an additional 4,607 workers in the larger cohort who were enrolled in the company's radiation monitoring program. A total of 362 incident prostate cancers were identified between 1988 and 12-31-1999. Controls were randomly selected from the original cohorts using risk-set sampling and a 5:1 matching ratio on age at start of employment, age at diagnosis, and cohort.

Both studies are based on the same exposure assessment approach. Walk-through visits, interviews with managers and workers, job descriptions manual, and historical facility reports supported the development of a JEM with jobs ranked on a scale of 0 (no exposure) to 3 (highly exposure) on presumptive exposure reflecting relative intensity of that exposure over three temporal periods: 1950–1960, 1970s, 1980–1990. Of the 6,044 subjects, 2,689 had TCE exposure scores of >3 and 2,643 with an exposure score ≥3 for hydrazine. Workers with job titles indicating technical or mechanical work on rocket engines were presumed to have high hydrazine rocket fuel exposure and high TCE exposure, which was used in cleaning rocket engines and parts. Although fewer subjects had exposure to benzene (819 subjects) or mineral oil (1,499 subjects), a high percentage of these subjects were also exposed to TCE. TCE use was widespread at the facility and other mechanics, maintenance and utility workers, and machinists were presumed as having exposure. No details were provided for job titles other than rocket test stand mechanics for assigning TCE exposure intensity and historical trends in TCE usage. Air monitoring data were absent for any chemicals prior to 1985 and investigators could not link

study subjects to specific work locations and rocket-engine test stands. As a result, exposures were probably substantially misclassified, particularly those with low to moderate TCE exposure. Cumulative intensity score was the sum of the job-and time-specific intensity score and years in job. Exposure classification was assigned blinded to survival status and cause of death.

Proportional hazards modeling in calendar time with both fixed and time-dependant predictors was used by Zhao et al. (2005) to estimate exposure effects on site-specific cancer incidence and mortality for a combined exposure group of medium and high exposure intensity with workers with no to low exposure intensity as referents. Variables in the proportional hazard model included time since first employment, SES, age at diagnosis or death, and exposure to other chemical agents including benzene, polycyclic aromatic hydrocarbons (PAHs) mineral oil, and hydrazine. Krishnadasen et al. (2007) fit conditional logistic regression models to their data adjusting of cohort, age at diagnosis, occupation physical activity, SES and all other chemical exposure levels. Both publications include exposure-response analysis and present *p*-values for linear trend. Race was not controlled in either study given the lack of recording on personnel records. Smoking histories was available for only a small percentage of the cohort; for those subjects reporting smoking information, mean cumulative TCE score did not differ between smokers and nonsmokers.

This study develops semiquantitative exposure levels and is strength of the exposure assessment. However, potential for exposure misclassification exists and would be of a nondifferential direction. Rocket engine test stand mechanics had likely exposure to TCE, kerosene, and hydrazine fuels; no information is available as to exposure concentrations. Statistical analyses in both Zhao et al. (2005) and Krishnadansan et al. (2007) present risk estimates for TCE that were adjusted for these other chemical exposures. Other strengths of this study include a long follow-up period for mortality, greater than an average time of 29 years of which 16 at SSFL, use of internal referents and the examination of cancer incidence, although under ascertainment of cases is likely given only eight state cancer registries were used to identify cases and incidence ascertained after 1981, 40 years after the cohort's initial definition date.

Krishnadasan A, Kennedy N, Zhao Y, Morgenstern H, Ritz B. (2007). Nested case-control study of occupational chemical exposures and prostate cancer in aerospace and radiation workers. Am J Ind Med 50:383–390.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Nested case-control study of the UCLA chemical and radiation cohorts (Morgenstern et al., 1999, 1997) to assess occupational exposures including TCE and prostate cancer.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	4,607 radiation cohort + 6,107 Santa Susana chemical cohort (Zhao et al., 2005; Ritz et al., 1999), excluded 1,410 deaths before 1988 (date of cancer incidence follow-up). Incident prostate cancer cases identified from eight State cancer registries (California, Nevada, Arizona, Texas, Washington Florida, Arkansas, and Oregon). Controls were randomly selected from the original cohorts using risk-set sampling. 362 cases and 1,805 controls (100% participation rate).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Prostate cancer incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	TCE exposure assigned to cases and controls based on longest job held at company as identified from personnel records. Cumulative exposure—ranked exposure intensity score for TCE by three time periods—using method of Zhao et al. (2005). Blinded ranking of exposure status.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Employment records were used to assign exposure. 734 subjects (249 cases and 485 controls, or 33% of all cases and controls) were interviewed via telephone or sent a mailed questionnaire to obtain medical history, education and personal information on physical activity level and smoking history.
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	No proxy interviews.

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	Any TCE exposure: 135 cases (37%) and 668 controls (37%). High cumulative TCE exposure: 45 cases (12%) and 124 controls (7%).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Cohort, age at diagnosis, occupational physical activity, SES, other chemical exposures (benzene, PAHs, mineral oil, hydrazine). No adjustment for race due to lacking information; affect of race on OR examined using information from survey of workers still alive in 1999. Few African American workers (n = 7), TCE levels did not vary greatly with race.
Statistical methods	Crude and adjusted conditional logistic regression.
Exposure-response analysis presented in published paper	*p*-value for trend with exposure lag (0 yrs, 20 yr).
Documentation of results	Adequate.

Zhao Y, Krishnadasan A, Kennedy N, Morgenstern H, Ritz B. (2005). Estimated effects of solvents and mineral oils on cancer incidence and Mortality in a cohort of aerospace workers. Am J Ind Med 48:249–258.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	From introduction "one aim of this new investigation was to determine whether these aerospace workers also developed cancers from exposures to other chemicals including trichloroethylene (TCE), polycyclic aromatic hydrocarbons (PAHs), mineral oils, and benzene."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	6,107 male workers employed for ≥2 years and before 1980 at SSFL. Internal referents (no or low TCE exposure).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence between 1988 and 2000. Mortality between 1950 and 2001.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-0 for cancer incidence. Leukemia, lymphomas, and other lymphopoietic malignancies grouped on the basis of morphology codes. Mortality: ICD-9, before 1998, and ICD-10 thereafter. Incidence: ICD-Oncology Lymphoma and leukemia grouping includes lymphosarcoma and reticulosarcoma, Hodgkin lymphoma, other malignant neoplasm of the lymphoid and histiocytic tissue, multiple myeloma and immunoproliferative neoplasms, and all leukemias except chronic lymphoid leukemia. The following incident tumors were also included: Hodgkin lymphoma, leukemia, polycythemia vera, chronic myeloproliferative disease, myelosclerosis, eosinophilic conditions, platelet diseases, and red blood cell diseases.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Cumulative exposure—ranked exposure intensity score for TCE by three time periods Blinded ranking of exposure status.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	99% follow-up for mortality (6,044 of 6,107 subjects).
>50% cohort with full latency	Average latency = 29 yrs (Ritz et al., 1999).
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	600 cancer deaths, 621 cancer cases.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Time since first employment, SES, age (at incidence or mortality), exposure to other carcinogens, including hydrazine. No adjustment for race. Indirectly assessment of smoking through examination of smoking distribution by chemical exposure. Mean TCE cumulative exposure scores of smokers and nonsmokers is not statistically significant different.
Statistical methods	Cox proportional hazards modeling in calendar time with both fixed and time-dependent predictors. Exposure lagged 10 and 20 yrs.
Exposure-response analysis presented in published paper	Test for monotonic trend of cumulative exposure, two-sided *p*-value for trend.
Documentation of results	Liver cancer results are not reported in published paper.

B.3.1.1.1.3. Comment on the SSFL studies

Rocketdyne workers at SSFL are subject of two separate and independent studies. Both research groups draw subjects from the same underlying source population, Rocketdyne workers including those at SSFL; however, the methods adopted to identify study subjects and to define TCE exposure differ with each study. A subset of SSFL workers is common to both studies; however, no information exist in final published reports (IEI, 2005; Morgenstern et al., 1999, 1997) to indicate the percentage overlap between cohorts or between observed number of site-specific events.

Notable differences in both study design and analysis including cohort identification, endpoint, exposure assessment approaches, and statistical methods exist between Zhao et al. (2005) and Krishnadasan et al. (2007), whose source population is the UCLA cohort, and Boice et al. (2006b) whose source population is the IEI cohort. A perspective of each study's characteristics may be obtained from Table B-6.

Table B-6. Characteristics of epidemiologic investigations of Rocketdyne workers

Study	Boice et al. (2006b)	Zhao et al. (2005)
Source population	41,351 administrative/scientific and nonadministrative male and female employees between 1949 and 1999 at Rocketdyne SSFL and two nearby facilities	~55,000 subjects of SSFL and two nearby facilities employed between 1950 and 1993
TCE subcohort	1,111 male test stand mechanics with potential TCE exposure	6,107 males working at SSFL before 1980 and identified as test stand personnel, of whom 2,689 males had exposure scores greater than no- to low-TCE exposure potential
Pay-type (hourly)	100% of TCE subcohort	11.3%
Job title with potential TCE exposure	Test stand mechanics identified with greatest potential for TCE exposure Other job titles with direct association with test stand work—instrument mechanics, inspectors, test stand engineers, and research engineers—identified with lower exposure potential to TCE and included in referent population	High potential exposure group included job titles as propulsion/test mechanics or technicians; Medium potential exposure group included propulsion/test inspector, test or research engineer, and instrumentation mechanic; Low-exposure potential included employees who, according to job title may have been present during engine test firings but without direct contact
Exposure metric	Qualitative, yes/no, and employment duration	Cumulative exposure score = $\sum$ (exposure score (0–3) × number of years in job)
Endpoint	Mortality as of 1999	Mortality as of 2001 and Incidence as of 2000
Statistical analysis	SMR Proportional hazards modeling with covariates for birth year, hire year, and potential exposure to hydrazine.	Proportional hazards modeling with covariates for time since first employment, SES, age at event, and exposure to all other carcinogens, including hydrazine
Observed number of deaths:		
Total cancer	121	600
Lung	51	No/low, 99
		Medium, 62
		High, 33
Kidney	7	No/low, 7
		Medium, 7
		High, 3
Bladder	5	No/low, 8
		Medium, 6
		High, 3
NHL/Leukemia	6	No/low, 27
		Medium, 27
		High, 6

A number of strengths and limitations underlie these studies. First, the Zhao et al. (2005) and Krishnadasan et al. (2007) analyses is of a larger population and of more cancer cases or deaths; 600 cancer deaths and 691 cancer cases in Zhao et al. (2005) compared to 121 cancer deaths in the TCE subcohort of Boice et al. (2006b), and for prostatic cancer among all Rocketdyne workers, 362 incident prostatic cancer cases in Krishnandasan et al. (2007) compared to 193 deaths in Boice et al. (2006b). Second, exposed populations appear appropriately selected in the three studies although questions exist regarding the referent population in Boice et al. (2006b) whose referent population included subjects with some direct association with test stand work but whose job title was other than test stand mechanic. As a result, it appears that these studies identify TCE exposure potential different for possibly similar job titles. For example, jobs as instrument mechanics, inspectors, test stand engineers, and research engineers are identified with medium potential exposure in Zhao et al. (2005). Boice et al. (2006b) on the other hand included these subjects in the referent population and assumed they had background exposure. TCE use at SSFL was also widespread and rocket engine cleaning occurred at other locations besides at test sites (Morgenstern et al., 1999), locations from which the referent population in Boice et al. (2006b) arose. If referents in Boice et al. (2006b) had more than background exposure, the bias introduced leads to an underestimation of risk. Third, Zhao et al. (2005) and Krishnadasan et al. (2007) studies include an examination of incidence, and are likely to have a smaller bias associated with disease misclassification than Boice et al. (2006b) who examines only mortality. Fourth, use of cumulative exposure score although still subject to biases is preferred to qualitative approach for exposure assessment. Last, all three studies adjusted for potentially confounding factors such as smoking, SES, and other carcinogenic exposures using different approaches either in the design of the study, such as Boice et al. (2006b) limitation to only hourly workers, or in the statistical analysis such as Zhao et al. (2005) and Krishnadansen et al. (2007). For this reason, the large difference in hourly workers between the UCLA cohort and Boice et al. (2006b) is not likely to greatly impact observations.

B.3.1.1.2. Blair et al. (1998), Radican et al. (2008).

B.3.1.1.2.1. Radican et al. (2008)) abstract.

> OBJECTIVE: To extend follow-up of 14,455 workers from 1990 to 2000, and evaluate mortality risk from exposure to trichloroethylene (TCE) and other chemicals. METHODS: Multivariable Cox models were used to estimate relative risk (RR) for exposed vs. unexposed workers based on previously developed exposure surrogates. RESULTS: Among TCE-exposed workers, there was no statistically significant increased risk of all-cause mortality (RR = 1.04) or death from all cancers (RR = 1.03). Exposure-response gradients for TCE were relatively flat and did not materially change since 1990. Statistically significant excesses were found for several chemical exposure subgroups and causes and

were generally consistent with the previous follow-up. CONCLUSIONS: Patterns of mortality have not changed substantially since 1990. Although positive associations with several cancers were observed, and are consistent with the published literature, interpretation is limited due to the small numbers of events for specific exposures.

B.3.1.1.2.2. Blair et al. (1998) abstract.

OBJECTIVES: To extend the follow up of a cohort of 14,457 aircraft maintenance workers to the end of 1990 to evaluate cancer risks from potential exposure to trichloroethylene and other chemicals. **METHODS:** The cohort comprised civilians employed for at least one year between 1952 and 1956, of whom 5727 had died by 31 December 1990. Analyses compared the mortality of the cohort with the general population of Utah and the mortality and cancer incidence of exposed workers with those unexposed to chemicals, while adjusting for age, sex, and calendar time. **RESULTS:** In the combined follow up period (1952–90), mortality from all causes and all cancer was close to expected (standardized mortality ratios (SMRs) 97 and 96, respectively). Significant excesses occurred for ischemic heart disease (SMR 108), asthma (SMR 160), and cancer of the bone (SMR 227), whereas significant deficits occurred for cerebrovascular disease (SMR 88), accidents (SMR 70), and cancer of the central nervous system (SMR 64). Workers exposed to trichloroethylene showed non-significant excesses for non-Hodgkin's lymphoma (relative risk (RR) 2.0), and cancers of the oesophagus (RR 5.6), colon (RR 1.4), primary liver (RR 1.7), breast (RR 1.8), cervix (RR 1.8), kidney (RR 1.6), and bone (RR 2.1). None of these cancers showed an exposure-response gradient and RRs among workers exposed to other chemicals but not trichloroethylene often had RRs as large as workers exposed to trichloroethylene. Workers exposed to solvents other than trichloroethylene had slightly increased mortality from asthma, non-Hodgkin's lymphoma, multiple myeloma, and breast cancer. **CONCLUSION:** These findings do not strongly support a causal link with trichloroethylene because the associations were not significant, not clearly dose-related, and inconsistent between men and women. Because findings from experimental investigations and other epidemiological studies on solvents other than trichloroethylene provide some biological plausibility, the suggested links between these chemicals and non-Hodgkin's lymphoma, multiple myeloma, and breast cancer found here deserve further attention. Although this extended follow up cannot rule out a connection between exposures to solvents and some diseases, it seems clear that these workers have not experienced a major increase in cancer mortality or cancer incidence.

B.3.1.1.2.3. Study description and comment.

This historical cohort study of 14,457 (9,400 male and 3,138 female) civilian personnel employed at least 1 year between 1942 and 1956 at Hill Air Force Base in Utah examines mortality to the end of 1982 (Spirtas et al., 1991) to the end of 1990 (Blair et al., 1998), or to the end of 2000 (Radican et al., 2008). About half of the cohort was identified with exposure to

TCE (6,153 white men and 1,051 white women). One-fourth of subjects were born before 1909 with an attained age of 43 years at cohort's identification date of 1952 and whose first exposure could have been as early as 1939, a cohort considered as a "survivor cohort."

As of December 2008, the end of follow-up in Radican et al. (2008), 8,580 deaths (3,628 in TCE subcohort) were identified, an increase of 2,853 deaths with the additional 8 years follow-up period compared to Blair et al. (1998) (5,727 total deaths, 2,813 among TCE subcohort subjects), with a larger proportion deaths among non-TCE exposed subjects (58%) as of December 2008 compared to the December 2000 (51%). Approximately 50% of TCE-exposed subjects and 60% of all cohort subjects had died, with mean age of 75 years for TCE-exposed subjects still alive and ≥45 years since the cohort's definition (1953 to 1955), a time period longer than that typically considered for an induction or latent window for detecting an adverse outcome like cancer. Blair et al. (1998) additionally examined cancer incidence among white TCE-exposed workers alive on 1-1-1973, a period of 31 years after the cohort's inception date, to the end of 1990. Incident cancer cases are likely under ascertained for this reason.

Statistical analyses in Spirtas et al. (1991) and Blair et al. (1998) focus on site-specific mortality for white subjects or subjects with unknown race who were assumed to as white since 97% of all subjects with known race were white. SMRs are presented with expected numbers of deaths based upon age-, race-, and year-specific mortality rates of the Utah population (Blair et al., 1998; Spirtas et al., 1991) or rate ratios for mortality or cancer incidence for the TCE subcohort from Poisson regression models, adjusting for date of birth, calendar year of death, and sex where appropriate, and an internal standard of mortality rates of the cohort's nonchemical exposed subjects (internal referents) (Blair et al., 1998). Blair et al. (1998), in addition to their presentation in the published papers of risk estimates associated with TCE exposure, also, presented risk estimates for subjects with an aggregated category of "any solvent exposure" (ever exposed) and for exposure to 14 solvents. To compare with risk ratios from Poisson regression models of Blair et al. (1998), Radican et al. (2008) adopted Cox proportional hazard models to reanalyze mortality observations of follow-up through 1990. For most site-specific cancers, Radican et al. (2008) did not observe large differences between the Cox hazard ratio and Poisson rate ratio of Blair et al. (1998), although difference between risk estimates from Cox proportional hazard and Poisson regression of ≥20% was observed for kidney cancer (increased risk estimate) and primary liver cancer (decreased risk estimate). Radican et al. (2008), furthermore, noted hazard ratios for all subjects were similar to results for white subjects only; therefore, their analyses of follow-up through 2000 included all subjects.

The original exposure assessment of Stewart et al. (1991) who conducted a detailed exposure assessment of TCE exposures at Hill Air Force Base was used by Radican et al. (2008), Blair et al. (1998), and Spirtas et al. (1991). Their study was limited linking subjects with exposures principally because solvent exposures were associated with work in "shops," but work

records listed only broad job titles and administrative units. As a result, exposures were probably substantially misclassified, particularly in "mixed solvent group." TCE was used principally for degreasing and hand cleaning in work areas during 1955–1968. TCE was the predominant solvent used in the few available vapor degreasers located in the electroplating (main hanger), propeller, and engine repair shops before the mid-1950 and, afterwards, as a cold state solvent, replacing Stoddard solvent. Solvents, notably TCE after 1955, were used primarily by aircraft mechanics with short but high exposures and sheet metal workers for spot clean aircraft surfaces. The investigators determined that 32% had "frequent" exposures to peak concentrations (one or two daily peaks of about 15 minutes to TCE at 200–600 ppm) during vapor degreasing. Work areas were located in very large buildings with few internal partitions, which aided dispersion of TCE. While TCE exposures were less controlled in the 1950s, by the end of 1960s, TCE exposure had been reduced significantly. Only a small number of subjects with "high" exposure had long-duration exposures, no more than 16%. Few workers were exposed only to TCE; most had mixed exposures to other chlorinated and nonchlorinated solvents. Person-years of exposure were computed from date of first exposure, which could have been as early as 1939, to the end of 1982.

Overall, Blair et al. (1998) and Radican et al. (2008) are studies with approximately half of the larger cohort identified as having some potential for TCE exposure (the TCE subcohort) and calculation of cancer risk estimates for TCE exposure, either risk ratios in Blair et al. (1998) or hazard ratios in Radican et al. (2008), using workers in the cohort without any chemical exposures as referent population, superior to SMRs of Spirtas et al. (1991) who first reported on mortality and TCE exposure. Use of an internal referent population of workers from the same company or plant, but lacking the exposure of interest, is considered to reduce bias associated with the healthy worker effect. For follow-up in Radican et al. (2008) who examined mortality 45 years after first exposure and likely at the tail of or beyond a window for cancer induction time, any influence on exposure on disease development or detection times would be diminished or less evident if exposures like TCE shortened induction time, e.g., if exposure shortened the natural course of disease development, which would become evident in an unexposed subjects with longer follow-up periods. The induction time of 35 years in Blair et al. (1998) may also fall outside a cancer induction window; however, it is more consistent with cancer induction times observed with other chemical carcinogens such as aromatic amines (Weistenhofer et al., 2008) and vinyl chloride (Du and Wang, 1998). A strong exposure assessment was performed, but precision in the exposure assignment was limited by vague personnel data. The cohort had a modest number of highly exposed (about 100 ppm) subjects, but overall most were exposed to low concentrations (about 10 ppm) of TCE.

Radican L, Blair A, Stewart P, Wartenberg D. (2008). Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: extended follow-up. J Occup Environ Med 50:1306–1319.

Blair A, Hartge P, Stewart PA, McAdams M, Lubin J. (1998). Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow-up. Occup Environ Med 55:161–171.

Spirtas R, Stewart PA, Lee JS, Marano DE, Forbes CD, Grauman DJ, Pettigrew HM, Blair A, Hoover RN, Cohen JL. (1991). Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. Br J Ind Med 48:515–530.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Abstract: "...to evaluate cancer risks from potential exposure to trichloroethylene and other chemicals."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	All civilians employed at Hill Air Force Base for ≥1 yr between 1-1-1952 and 12-31-1956; cohort of 14,457 workers identified form earnings records. TCE subcohort—7,204 white males and females (50%). External referents, all civilian cohort—Utah population rates, 1953–1990. Internal referents, TCE subcohort analysis of mortality (Blair et al., 1998); Radican et al. (2008) and incidence (Blair et al., 1998)—workers without chemical exposures.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality, all civilian cohort and TCE subcohort. Incidence, TCE subcohort.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Underlying and contributing causes of deaths as coded to ICDA 8.

CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Detailed records on setting and job activities, worker interviews; work done in large open shops; shops not recorded in personnel records, link of job with IH data was weak. Limited exposure IH measurements for TCE between 1960 and 1990. Plant JEM, rank order assignments by history; determined exposure duration during vapor degreasing tasks about 2,000 ppm-hr and hard degreasing about 20 ppm-hr. **Median exposure were about 10 ppm for rag and bucket (cold degreasing process); 100–200 ppm for vapor degreasing (Stewart et al., 1991). Cherrie et al. (2001) estimated long-term exposure as ~50 ppm with short-term excursion up to ~600 ppm. NRC (2006) concluded the cohort had a modest number of highly exposed (about 100 ppm) subjects, but overall most were exposed to low TCE concentrations (about 10 ppm).**
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	97% of cohort traced successfully to 12-31-1982.
>50% cohort with full latency	Yes, all subjects followed minimum of 35 yrs (Blair et al., 1998) or 45 yrs (Radican et al., 2008).
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	TCE subcohort—2,813 deaths (39%), 528 cancer deaths, and 549 incident cancers (1973-1990) (Blair et al., 1998); 3,628 deaths (50%). 729 cancer deaths (Radican et al., 2008).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	SMR analysis evaluates age, sex, and calendar year (Spirtas et al., 1991). Date of hire, calendar year of death, and sex in Poisson regression analysis (Blair et al., 1998). Age, gender, and race (to compare with RR of Blair et al. (1998), or age and gender for follow-up to 2000 in Cox proportional hazard analysis (Radican et al., 2008).

Statistical methods	External analysis is restricted to Caucasian subjects—Life table analysis for mortality (Spirtas et al., 1991). Internal analysis restricted to Caucasian subjects or subject of unknown race assumed to be Caucasian and followed to 1990—Poisson regression (Blair et al., 1998) or Cox Proportional Hazard (Radican et al., 2008). Internal analysis—all subjects followed to 2000 (Radican et al., 2008).
Exposure-response analysis presented in published paper	Risk ratios from Poisson regression model and hazard ratios from Cox Proportional Hazard model for exposure rankings but no formal statistical trend test presented in papers.
Documentation of results	Adequate.

B.3.1.1.3. Boice et al. (1999).

B.3.1.1.3.1. Author's abstract.

OBJECTIVES: To evaluate the risk of cancer and other diseases among workers engaged in aircraft manufacturing and potentially exposed to compounds containing chromate, trichloroethylene (TCE), perchloroethylene (PCE), and mixed solvents. **METHODS:** A retrospective cohort mortality study was conducted of workers employed for at least 1 year at a large aircraft manufacturing facility in California on or after 1 January 1960. The mortality experience of these workers was determined by examination of national, state, and company records to the end of 1996. Standardized mortality ratios (SMRs) were evaluated comparing the observed numbers of deaths among workers with those expected in the general population adjusting for age, sex, race, and calendar year. The SMRs for 40 causes of death categories were computed for the total cohort and for subgroups defined by sex, race, and position in the factory, work duration, year of first employment, latency, and broad occupational groups. Factory job titles were classified as to likely use of chemicals, and internal Poisson regression analyses were used to compute mortality risk ratios for categories of years of exposure to chromate, TCE, PCE, and mixed solvents, with unexposed factory workers serving as referents. **RESULTS:** The study cohort comprised 77,965 workers who accrued nearly 1.9 million person-years of follow up (mean 24.2 years). Mortality follow-up, estimated as 99% complete, showed that 20,236 workers had died by 31 December 1996, with cause of death obtained for 98%. Workers experienced low overall mortality (all causes of death SMR 0.83) and low cancer mortality (SMR 0.90). No significant increases in risk were found for any of the 40 specific causes of death categories, whereas for several causes the numbers of deaths were significantly below expectation. Analyses by occupational group and specific job titles showed no remarkable mortality patterns. Factory workers estimated to have been routinely exposed to chromate were not at increased risk of total cancer (SMR 0.93) or of lung cancer (SMR 1.02). Workers routinely exposed to TCE, PCE, or a mixture of solvents also were not at increased risk of total cancer (SMRs 0.86, 1.07, and 0.89, respectively), and the numbers of deaths for specific cancer sites were close to expected values. Slight to moderately increased rates of non-Hodgkin's lymphoma were found among workers exposed to TCE or PCE, but none was significant. A significant increase in testicular cancer was found among those with exposure to mixed solvents, but the excess was based on only six deaths and could not be linked to any particular solvent or job activity. Internal cohort analyses showed no significant trends of increased risk for any cancer with increasing years of exposure to chromate or solvents.

The results from this large scale cohort study of workers followed up for over 3 decades provide no clear evidence that occupational exposures at the aircraft manufacturing factory resulted in increases in the risk of death from cancer or other diseases. Our findings support previous studies of aircraft workers in which cancer risks were generally at or below expected levels.

B.3.1.1.3.2. Study description and comment.

This study was conducted on an aircraft manufacturing worker cohort employed at Lockheed-Martin in Burbank, California with exposure assessment described by Marano et al. (2000). This large cohort study of 77,965 subject workers with at least 1 year employment on or after 1-1-1960, examined causes of mortality in the entire cohort, but also by broad job titles and for selected chemical exposures including TCE. Mortality was assessed as of 12-31-1996, with subjects lacking death certificates presumed alive at end of follow-up. Exposure assessment developed using a method of exposure assignment by job categories based on job histories (Kardex cards) and the judgment of long-term employees. Job histories were not available for every worker, and, if missing, auxiliary sources of job information were used to broadly classify workers into various job categories. Only subjects with job histories as recorded on Kardex cards are included in exposure duration analyses. TCE was used for vapor degreasing on routine basis prior to 1966 and, given the cohort beginning date of 1960, only a small percentage of the total cohort was identified as having potential TCE exposure. The investigators determined that 5,443 factory workers had potential TCE exposure. Of these subjects, 3% (2,267/77,965 subjects) had "routine" defined as use of TCE as part of daily job activities and an additional 3,176 subjects (4%) had potential "intermittent" based upon job title and judgment of nonroutine or nondaily TCE usage and were included in the mortality analysis. No information was provided on building and working conditions or the frequency of exposure-related tasks, and no atmospheric monitoring data were available on TCE, although some limited data were available after 1970 on other solvents such as perchloroethylene, which replaced TCE in 1966 in vapor degreasing, methylene chloride, and 1,1,1-trichloroethane. Without more information, it is not possible to determine the quality of some of the TCE assignments. This study had limited ability to detect exposure-related effects given its use of duration of exposure, a poor exposure metric given subjects may have differing exposure intensity with similar exposure duration (NRC, 2006). Lacking monitoring information, analyses examining the number of years of routine and intermittent TCE exposure are likely biased due to exposure misclassification related to inability to account for changes in process and chemical usage patterns over time. Stewart et al. (1991) show atmospheric TCE concentrations decreased over time. Similarly, an observation of inverse relationship between some site-specific causes of death and duration of exposure may be due to selection bias or to misallocation of person-years of follow-up (NYSDOH, 2006).

Boice JD, Marano DE, Fryzek JP, Sadler CJ, McLaughlin JK. (1999). Mortality among aircraft manufacturing workers. Occup Environ Med 56:581–597.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	From abstract: "To evaluate the risk of cancer and other diseases among workers engaged in aircraft manufacturing and potentially exposed to compounds containing chromate, trichloroethylene (TCE), perchloroethylene, and mixed solvents."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	All workers employed on or after 1-1-1960 for at least 1 yr at Lockheed Martin aircraft manufacturing factories in California. Control population: U.S. mortality rates or factory workers no exposed to any solvent (internal referents).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD code in use at the time of death.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Qualitative. Few exposure measurements existed prior to the late 1970s, a period after TCE had been discontinued at Lockheed-Martin aircraft manufacturing factories. Subjects are categorized as potentially TCE exposed received on a routine basis (2,075 subjects), daily job activity, or routine and intermittent basis (3,016 subjects), nonroutine or nondaily TCE usage, based on information on Service Record and Permanent Employment Record (Kardex) and other sources of job history information for subjects lacking Kardex cards.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	This study does not adopt methods to verify vital status of employees. All workers for which death certificate were not found are assumed to be alive until end of follow-up.
>50% cohort with full latency	Average follow-up of TCE cohort was 29 yrs.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	1,100 total deaths and 277 cancer deaths in TCE subcohort.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	SMR analysis—age, sex, and calendar-time. Poisson regression using internal referents—birth date, date first employed, date of finishing employment, race, and sex.
Statistical methods	SMR for routine TCE exposure subcohort. Poisson regression for routine and intermittent TCE exposure subcohort.
Exposure-response analysis presented in published paper	Duration of exposure for subjects with Kardex cards only— 2-sides test for linear trend.
Documentation of results	Adequate.

B.3.1.1.4. Morgan et al. (1998).

B.3.1.1.4.1. Author's abstract.

> We measured mortality rates in a cohort of 20,508 aerospace workers who were followed up over the period 1950-1993. A total of 4,733 workers had occupational exposure to trichloroethylene. In addition, trichloroethylene was present in some of the washing and drinking water used at the work site. We developed a job-exposure matrix to classify all jobs by trichloroethylene exposure levels into four categories ranging from "none" to "high" exposure. We calculated standardized mortality ratios for the entire cohort and the trichloroethylene exposed subcohort. In the standardized mortality ratio analyses, we observed a consistent elevation for nonmalignant respiratory disease, which we attribute primarily to the higher background rates of respiratory disease in this region. We also compared trichloroethylene-exposed workers with workers in the "low" and "none" exposure categories. Mortality rate ratios for nonmalignant respiratory disease were near or less than 1.00 for trichloroethylene exposure groups. We observed elevated rare ratios for ovarian cancer among those with peak exposure at medium and high levels] relative risk (RR) = 2.74; 95% confidence interval (CI) = 0.84-8.99] and among women with high cumulative exposure (RR = 7.09; 95% CI = 2.14-23.54). Among those with peak exposures at medium and high levels, we observed slightly elevated rate ratios for cancers of the kidney (RR = 1.89; 95% CI = 0.85-4.23), bladder (RR = 1.41; 95% CI = 0.52-3.81), and prostate (RR = 1.47; 95% CI = 0.85-2.55). Our findings do not indicate an association between trichloroethylene exposure and respiratory cancer, liver cancer, leukemia or lymphoma, or all cancers combined.

Erratum:

> One of the authors of the article entitled Mortality of aerospace workers exposed to trichloroethylene, by Robert W. Morgan, Michael A. Kelsh, Ke Zhao, and Shirley Heringer, published in Epidemiology (1998);9:424-431, informed us of some errors in one of the tables. In Table 5, the authors had inadvertently included both genders in counting person-years, rather than presenting gender-specific risk ratios for prostate and ovarian cancer. In addition, one subject, in the high trichloroethylene (TCE) exposure category, had been incorrectly classified with a diagnosis of ovarian cancer, instead of other female genital cancer. The authors report that correction of these errors did not change the overall conclusions of the study. The correct estimates of effect for prostate and ovarian cancer are presented in the Table below.

B.3.1.1.4.2. Study description and comment.

This study of a cohort of 20,508 aircraft manufacturing workers employed for at least 6 months between 1950 and 1985 at Hughes Aircraft in Arizona was followed through 1993 for mortality. Cause-specific SMRs are resented for the entire cohort and the TCE-subcohort using U.S. mortality rates from 1950 to 1992 as referents. Additionally, internal cohort analyses fitting Cox proportional hazards models are presented comparing risks for those with TCE exposure to

never-exposed subjects. Morgan et al. (2000, 1998) do not identify job titles of individuals in the never-exposed group; however, it is assumed these individuals were likely white-collar workers, administrative staff, or other blue-collar worker with chemical or solvents exposures other than TCE.

The company conducted a limited semiquantitative assessment of TCE exposure based on the judgment of long-term employees. Most TCE exposure occurred in vapor degreasing units between 1952 and 1977. No details were provided on the protocol for processing the jobs in the work histories into job classifications; no examples were provided. Additionally, no information is provided other chemical exposures that may also have been used in the different jobs. Of the 20,508 subjects, 4,733 were identified with TCE exposure. Exposure categories were assigned to job classifications: high = worked on degreasers (industrial hygiene reported exposures were >50 ppm); medium = worked near degreasers; and low = work location was away from degreasers but "occasional contact with (trichloroethylene)." There was also a "no exposure" category. No data were provided on the frequency of exposure-related tasks. Without more information, it is not possible to determine the quality of some of these assignments. Only the high category is an unambiguous setting. Depending on how the degreasers were operated, operator exposure to TCE might have been substantially >50 ppm. Furthermore, TCE intensity likely changed over time with changes in degreaser operations and exposure assignment based on job title only is able to correctly place subjects with a similar job title but held at different time periods. Furthermore, there are too many possible situations in which an exposure category of medium or low might be assigned to determine whether the ranking is useful. Therefore, the medium and low rankings are likely to be highly misclassified. Deficiencies in job rankings are further magnified in the cumulative exposure groupings. Internal analyses examine TCE exposed, defined as low and high cumulative exposure, compared to never-TCE exposed subjects. Low cumulative exposure group includes any workers with the equivalent of up to 5 years of exposure at jobs at low exposure or 1.4 years of medium exposure; all other workers were placed in the high cumulative exposure grouping. Ambiguity in low and medium job rankings and the lack of exposure data to define "medium" and "low" precludes meaningful analysis of cumulative exposure, specifically, and exposure-response, generally.

The development of exposure assignments in this study was insufficient to define exposures of the cohort and bias related to exposure misclassification is likely great. The inability to account for changes in TCE use and exposure potential over time introduces bias and may dampen observed risks. This study had limited ability to detect exposure-related effects and, overall, limited ability to provide insight on TCE exposure and cancer outcomes.

Morgan RW, Kelsh MA, Zhao K, Heringer S. (1998). Mortality of aerospace workers exposure to trichloroethylene. Epidemiol 9:424–431.

Morgan RW, Kelsh MA, Zhao K, Heringer S. (2000). Mortality of aerospace workers exposed to trichloroethylene. Erratum. Epidemiology 9:424–431.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	"measured mortality rates in a cohort of aerospace workers, comparing TCE workers with workers in low and none exposure categories."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	20,508 male and female workers are identified using company records and who were employed at plant for at least 6 months between 1-1-1950 and 12-31-1985. TCE subcohort—4,733 (23%) male and female subjects. External referents—U.S. population rates, 1950–1992. Internal referents—Analysis of peak exposure, low or no TCE exposure; analysis of cumulative exposure, never exposed to TCE. Internal referents are likely white-collar workers, administrative staff, and blue-collar workers with chemical exposure other than TCE. White-collar and administrative staff subjects are not representative of blue-collar workers due to SES and sex differences. Also, the never-TCE exposed blue-collar workers may potentially have other chlorinated solvents exposures, exposures that may be associated with a similar array of targets as TCE. These individuals may not be representative of a nonchemical exposed population as that used in Blair et al. (1998).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality
Changes in diagnostic coding systems for lymphoma, particularly NHL	No, ICD in use at time of death (ICD 7, 8, 9).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Semiquantitative. Limited IH measurements before 1975. Jobs ranked into high, medium, or low intensity exposure categories; categories are undefined as to TCE intensity. **Jobs with high intensity exposure rating involved work on degreaser machines with TCE exposure equivalent to 50 ppm**; assigned exposure score of 9. Job with medium rating were near (distance undefined in published paper) degreasing area and a score of 4. Jobs with low rating were away (undefined distance) from degreasing area and assigned score of 1. Cumulative exposure score = ∑ (duration exposure × score). Peak exposure defined by job with highest ranking score.

CATEGORY D: FOLLOW-UP (Cohort)	
More than 10% loss to follow-up	No, 27 subjects were excluded from analysis due to missing information.
>50% cohort with full latency	Average 22 yrs of follow-up for TCE subcohort.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	TCE subcohort—917 total deaths (19%) of subcohort, 270 cancer deaths.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, race, sex, and calendar year in SMR analysis. Internal analysis- age (for bladder, prostate, ovarian cancers), and age and sex (liver, kidney cancers).
Statistical methods	Life table analysis (SMR). Cox proportional hazards modeling (unexposed subjects as internal referents)—peak and two-levels of cumulative exposure (Morgan et al., 1998; EHS, 1997); any TCE exposure (EHS, 1997).
Exposure-response analysis presented in published paper	Qualitative presentation, only; no formal statistical test for linear trend.
Documentation of results	Adequate.

B.3.1.1.5. Costa et al. (1989).

B.3.1.1.5.1. Author's abstract.

> Mortality in a cohort of 8626 workers employed between 1954 and 1981 in an aircraft manufacturing factory in northern Italy was studied. Total follow up was 132,042 person-years, with 76% accumulated in the age range 15 to 54. Median duration of follow up from the date of first employment was 16 years. Vital status was ascertained for 98.5% of the cohort. Standardized mortality ratios were calculated based on Italian national mortality rates. Altogether 685 deaths occurred (SMR = 85). There was a significant excess of mortality for melanoma (6 cases, SMR = 561). Six deaths certified as due to pleural tumors occurred. No significant excess of mortality was found in specific jobs or work areas.

B.3.1.1.5.2. Study description and comment.

This study assesses mortality in a small cohort of 8,626 aircraft manufacturing workers employed between 1954 and the end of follow-up in June, 1981. A period of minimum employment duration before accumulating person-years was not a prerequisite for cohort definition. The cohort included employees identified as blue collar workers, technical staff, administrative clerks, and white-collar workers. Blue-collar workers comprised 7,105 of the 8,626 cohort subjects. Mortality was examined for all workers and included job title of blue collar workers, technical staff members, administrative clerks, and white-collar workers, not otherwise specified. No exposure assessment was used and the published paper does not identify chemical exposures. In fact, Costa et al. (1989) do not even mention TCE in the paper.

Overall, the lack of exposure assessment, the inability to identify TCE as an exposure to this cohort, and the inclusion of subjects who likely do not have potential TCE exposure are reasons why this study is not useful for determining whether TCE may cause increased risk of disease.

Costas G, Merletti F, Segnan N. (1989). A mortality study in a north Italian aircraft factory. Br J Ind Med 46:738–743.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	The 1st paragraph of the paper identified this study was carried out to investigate an apparently high number of malignant tumors among employees that were brought to the attention of the local health authority by staff representative. This study was not designed to examine TCE exposure and cancer outcomes.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Cohort is defined as all workers every employed between 1-1-1954 and 6-30-1981 (end of follow-up) at a north Italian aircraft manufacturing factory. Cohort include 8.626 subjects: 950 women (636 clerks, 314 blue-collar workers/technical staff) and 7,676 men (5,625 blue collar workers, 965 technical staff, 571 administrative clerks, and 515 white collar workers). External referent—Age, year (5-yr periods over 1955–1981)-sex and cause-specific death rates of Italian population.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Causes and underlying causes of death coded to ICD rule in effect at the time of death and grouped into categories consistent with ICD 8th revision.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Exposure is defined as employment in the factory. TCE is not mentioned in published paper and no exposure assessment was carried out by study investigators.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	Vital status ascertained for 98% of cohort; 2% could not be traced (1% unknown and 1% had emigrated).
>50% cohort with full latency	Average mean follow-up: males, 17 yrs; females, 13 yrs.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	642 total deaths, 168 cancer deaths.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, and calendar year.
Statistical methods	SMR.
Exposure-response analysis presented in published paper	No.
Documentation of results	Adequate.

B.3.1.1.6. Garabrant et al. (1988).

B.3.1.1.6.1. Author's abstract.

A retrospective cohort mortality study was conducted among men and women employed for four or more years, between 1958 and 1982, at an aircraft manufacturing company in San Diego County. Specific causes of death under investigation included cancer of the brain and nervous system, malignant melanoma, and cancer of the testicle, which previous reports have suggested to be associated with work in aircraft manufacturing. Follow-up of the cohort of 14,067 subjects for a mean duration of 15.8 yr from the date of first employment resulted in successful tracing of 95% of the cohort and found 1,804 deaths through 1982. Standardized mortality ratios (SMRs) were calculated based on U. S. national mortality rates and separately based on San Diego County mortality rates. Mortality due to all causes was significantly low (SMR = 75), as was mortality due to all cancer (SMR = 84). There was no significant excess of cancer of the brain, malignant melanoma, cancer of the testicle, any other cancer site, or any other category of death. Additional analyses of cancer sites for which at least ten deaths were found and for which the SMR was at least 110 showed no increase in risk with increasing duration of work or in any specific calendar period. Although this study found no significant excesses in cause-specific mortality, excess risks cannot be ruled out for those diseases that have latency periods in excess of 20 to 30 yr, or for exposures that might be restricted to a small proportion of the cohort.

B.3.1.1.6.2. Study description and comment.

This study reported on the overall mortality of a cohort of workers in the aircraft manufacturing industry in southern California who had worked 1 day at the facility and had at least 4 years duration of employment. Fifty-four percent of cohort entered cohort at beginning date (1-1-1958). This is a survivor cohort. This study lacks exposure assessment for study subjects. The only exposure metric was years of work. Examination of jobs held by 70 study subjects, no details provided in paper on subject selection criteria, identified 37% as having possible TCE exposure, but no information was presented on how they were exposed, frequency or duration of exposure, or job titles associated with exposure. No information is provided on possible TCE exposure to the remaining ~14,000 subjects in this cohort. The exposure assignment in this study was insufficient to define exposures of the cohort and the frequency of exposures was likely low. Given the enormous misclassification on exposure, the effect of exposure would have to be very large to be detected as an overall risk for the population. Null findings are to be expected due to bias likely associated with a survivor cohort and to exposure misclassification. Therefore, this study provides little information on whether TCE is related to disease risk.

Garabrant DH, Held J, Langholz B, Bernstein L. (1988). Mortality of Aircraft Manufacturing Workers in Southern California. Am J Ind Med 13:683–693.

Langholz B, Goldstein L. (1996). Risk Set Sampling in Epidemiologic Cohort Studies. Stat Sci 11:35–53.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	"Our objects were to evaluate the oval mortality among the [aircraft manufacturing] workers and to test the hypotheses that brain tumors, malignant melanoma, and testicular neoplasms are associated with work in this industry." [Introduction] This study was not designed to evaluate any specific exposure, but rather employment in aircraft manufacturing industry.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	14,067 males and females working at least 4 yrs with a large aircraft manufacturing company and who had worked for at least 1 d at a factory in San Diego County, California. Person-year accrued from the anniversary date of an individual's 4th yr of service or from 1-1-1958 to end of follow-up 12-31-1982. External referents—age-, race-, sex-, calendar year-, and cause-specific mortality rates of U.S. population.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD revision in effect at the date of death. Lymphomas in four groupings: lymphosarcoma and reticulosarcoma, HD, leukemia and aleukemia, and other.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD revision in effect at the date of death. Lymphomas in four groupings: lymphosarcoma and reticulosarcoma, HD, leukemia and aleukemia, and other.
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Exposure assessment is lacking for all subjects except 70 deaths (14 esophageal and 56 others) who were included in a nested case-control study. Of the 362 jobs held by these 70 subjects, 37% were identified as having potential for TCE exposure.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	4.7% with unknown vital status.
>50% cohort with full latency	Average 16-yr follow-up.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	1,804 deaths (12.8% of cohort), 453 cancer deaths.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, race, sex, and calendar year.
Statistical methods	SMR.
Exposure-response analysis presented in published paper	No.
Documentation of results	SMR analysis, adequate; published paper lacks documentation of nested case-control study of esophageal cancer.

B.3.1.2. Cancer Incidence Studies Using Biological Monitoring Databases

Finland and Denmark historically have maintained national databases of biological monitoring data obtained from workers in industries where toxic exposures are a concern. Legislation required that employers provide workers exposed to toxic hazards with regular health examinations, which must include biological monitoring to assess the uptake of toxic chemicals, including TCE. In Sweden, the only local producer of TCE operated a free exposure-surveillance program for its customers, measuring U-TCA. These programs used the linear relationship found for average inhaled TCE vs. U-TCA: TCE (mg/m^3) = 1.96; U-TCA (mg/L) = 0.7 for exposures <375 mg/m^3 (69.8 ppm) (Ikeda et al., 1972). This relationship shows considerable variability among individuals, which reflects variation in urinary output and activity of metabolic enzymes. Therefore, the estimated inhalation exposures are only approximate for individuals but can provide reasonable estimates of group exposures. There is evidence of nonlinear formation of U-TCA above about 400 mg/m^3 or 75 ppm of TCE. The half-life of U-TCA is about 100 hours. Therefore, the U-TCA value represents roughly the weekly average of exposure from all sources, including skin absorption. The Ikeda et al. (1972) relationship can be used to convert urinary values into approximate airborne concentration, which can lead to misclassification if tetrachloroethylene and 1,1,1-trichloroethane are also being used because they also produce U-TCA. In most cases, the Ikeda et al. relationship (1972) provides a rough upper boundary of exposure to TCE.

B.3.1.2.1. Hansen et al. (2001).

B.3.1.2.1.1. Author's abstract.

> Human evidence regarding the carcinogenicity of the animal carcinogen trichloroethylene (TCE) is limited. We evaluated cancer occurrence among 803 Danish workers exposed to TCE, using historical files of individual air and urinary measurements of TCE-exposure. The standardized incidence ratio (SIR) for cancer overall was close to unity for both men and women who were exposed to TCE. Men had significantly elevated SIRs for non-Hodgkin's lymphoma (SIR = 3.5; n = 8) and cancer of the esophagus (SIR = 4.2; n = 6). Among women, the SIR for cervical cancer was significantly increased (SIR = 3.8; n = 4). No clear dose-response relationship appeared for any of these cancers. We found no increased risk for kidney cancer. In summary, we found no overall increase in cancer risk among TCE-exposed workers in Denmark. For those cancer sites where excesses were noted, the small numbers of observed cases and the lack of dose-related effects hinder etiological conclusions.

B.3.1.2.1.2. Study description and comment.

This Danish study evaluated cancer incidence in a small cohort of individuals (n = 803) who had been monitored for TCE exposures in a national surveillance program between 1947 and 1989 for U-TCA or TCE in breath since 1974. In all, 2,397 samples were analyzed for U-

TCA of workers at 275 companies and 472 breathing zone samples of TCE from workers at 81 companies. Individual workers could not be identified for roughly one-third of the U-TCA measurements and 50% of breathing zone measurements; many of the individuals most likely had died prior to 1968, the start of the Central Population Registry from which workers were identified and follow-up for cancer incidence. A cohort of 658 males and 145 females were identified from the remaining 1,519 U-TCA and 245 air-TCE measurements. Only two of 803 cohort subjects had both urine and air measurements. Follow-up for cancer incidence ended as of 12-31-1996.

The retirement and measurement records contained general information about the type of employer and the subject's job. The subjects in this study came predominantly from the iron and metal industry with jobs such as metal-product cleaner. Each subject had 1–27 measurements of U-TCA measurements, an average of 2.2 per subject, going back to 1947. Using the linear relationship from Ikeda et al. (1972), the historic median exposures estimated from the U-TCA concentrations were low: 9 ppm for 1947–1964, 5 ppm for 1965–1973, 4 ppm for 1974–1979, and 0.7 ppm for 1980–1989. However, the distributions were highly skewed. Additionally, 5% of the cohort had urine or air samples below the limit of detection. Overall, median exposure in this cohort was 4 ppm and suggests that, in general, workers in a wide variety of industry and job groups and identified as "exposed" in this study had low TCE intensity exposures. Overall, the cohort in this study is small, drawn from a wide variety of industries, predominantly degreasing and metal cleaning, and had generally low exposures (most <20 ppm). The study has a lower power to examine TCE exposure and cancer for these reasons.

Hansen J, Raaschou-Nielsen O, Christensen JM, Johansen I, McLaughlin JK, Lipworth L, Blot WJ, Olsen JH. (2001). Cancer incidence among Danish workers exposed to trichloroethylene. J Occup Environ Med 43:133–139.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	From introduction—A study of incidence was carried out to address shortcomings in earlier TCE studies related to the lack of direct exposure information and to assessment of mortality as opposed to incidence.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	803 subjects identified from biological monitoring of urine TCA from 1947 to 1989 (1,519 measurements) or breathing zone TCE since 1974 (245 measurements) and who were alive as of 1968, followed to 1996. External referents—cancer incidence rates of Danish population (age-, sex-, calendar years-, and site-specific).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD, 7th revision.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Biological marker of TCE in urine or in breath used to assign TCE exposure to cohort subject. Historic median exposures estimated from the U-TCA were low: 9 ppm for 1947 to 1964, 5 ppm for 1965 to 1973, 4 ppm for 1974 to 1979, and 0.7 ppm for 1980 to 1989. **Overall, median TCE exposure to cohort was 4 ppm (arithmetic mean, 12 ppm).**
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	No.
>50% cohort with full latency	Unable to determine given insufficient information in paper; however, text notes follow-up for most subjects achieved a full latency.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	128 incident cancers among 804 cohort subjects (15%).

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, and calendar year.
Statistical methods	SIR, Life table analysis.
Exposure-response analysis presented in published paper	Yes, as dichotomous variable for mean exposure (<4 ppm, 4+ ppm) and for cumulative exposure.
Documentation of results	Adequate.

B.3.1.2.2. Anttila et al. (1995).

B.3.1.2.2.1. Author's abstract.

Epidemiologic studies and long-term carcinogenicity studies in experimental animals suggest that some halogenated hydrocarbons are carcinogenic. To investigate whether exposure to trichloroethylene, tetrachloroethylene, or 1,1,1-trichloroethane increases carcinogenic risk, a cohort of 2050 male and 1924 female workers monitored for occupational exposure to these agents was followed up for cancer incidence in 1967 to 1992. The overall cancer incidence within the cohort was similar to that of the Finnish population. There was an excess of cancers of the cervix uteri and lymphohematopoietic tissues, however. Excess of pancreatic cancer and non-Hodgkin lymphoma was seen after 10 years from the first personal measurement. Among those exposed to trichloroethylene, the overall cancer incidence was increased for a follow-up period of more than 20 years. There was an excess of cancers of the stomach, liver, prostate, and lymphohematopoietic tissues combined. Workers exposed to 1,1,1-trichloroethane had increased risk of multiple myeloma and cancer of the nervous system. The study provides support to the hypothesis that trichloroethylene and other halogenated hydrocarbons are carcinogenic for the liver and lymphohematopoietic tissues, especially for non-Hodgkin lymphoma. The study also documents excess of cancers of the stomach, pancreas, cervix uteri, prostate, and the nervous system among workers exposed to solvents.

B.3.1.2.2.2. Study description and comment.

This Finnish study evaluated cancer risk in a small cohort of individuals (2,050 males and 1,924 females) who had been monitored between 1965 and 1982 for exposures to TCE by measuring their U-TCA. The main source of exposure was identified as degreasing or cleaning metal surfaces. Some workplaces identified rubber work, gluing, and dry-cleaning. There was an average of 2.7 measurements per person. Using the Ikeda et al. (1972) conversion relationship, the exposure for TCE was approximately 7 ppm in 1965, which declined to approximately 2 ppm in 1982; the 75th percentiles for these dates were 14 and 7 ppm, respectively. The maximum values for males were approximately 380 ppm during 1965 to 1974 and approximately 96 ppm during 1974 to 1982. Females showed a similar pattern over time but had somewhat higher exposures than males before the 1970s. Median TCE exposure for females of 4 ppm compared to 3 ppm for males; maximum values were similar for both sexes. Duration of exposure was counted from the first measurement of U-TCA, which might underestimate the length of exposure. Without job histories, the length of exposure is uncertain. Another concern is the sampling strategy; it was not reported how the workers were chosen for monitoring. Therefore, it is not clear what biases might be present, especially the possibility of under-sampling highly exposed workers.

Overall, this TCE exposed cohort drawn from a wide variety of industries was twice the size of other Nordic biomonitoring studies (Hansen et al., 2001; Axelson et al., 1994) with urine

TCA measurements from a more recent period, 1965–1982, compared to other Nordic studies of Danish cohorts, 1947–1980s, or Swedish cohorts, 1955–1975 (Raaschou-Nielsen et al., 2002; Hansen et al., 2001; Axelson et al., 1994). Exposures to TCE were generally low, <14 ppm for the 75th percentile of all measurements, and median TCE exposures decreasing from 7 to 2 ppm over the 17-year period. The medians are similar to estimated exposures to Danish workers with biological markers of U-TCA (Hansen et al., 2001; Raaschou-Nielsen et al., 2001). The duration of exposure was uncertain.

Anttila A, Pukkala E, Sallmen M, Hernberg S, Hemminki K. (1995). Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med 37:797–806.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Yes, study aim was to assess cancer incidence among workers biologically monitored for exposure to TCE, PERC, and 1,1,1-trichloroethane.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	3, 976 subjects identified from biological monitoring of urine TCA between 1965 to 1982; PERC in blood, 1974 to 1983; and, 1,1,1-trichloroethane in blood, 1975 to 1983 (a total of 10.743 measurements). 109 of cohort subjects with TCE poisoning report between 1965 and 1976. Follow-up for mortality between 1965 and 1991 and for cancer between 1967 and 1992. TCE subcohort—3,089 (1,698 males, 1,391 females). External referents—age-, sex-, calendar year-, and site-specific cancer incidence rates of the Finnish population.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality and cancer incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD, 7th revision.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Biological marker of TCE in urine used to assign TCE exposure for TCE subcohort. There were on average 2.5 U-TCA measurements per individual. 6% of cohort had measurements for two or all three solvents. The overall medians of U-TCA for females and males were 8.3 and 6.3 mg/L, respectively, and before 1970, 10–13 mg/L for females and 13–15 mg/L for males. **Using Ikeda et al. (1972) relationship for U-TCA and TCE concentration, median TCE exposures over the period of study were roughly <4–9 ppm (median, 4 ppm; arithmetic mean, 6 ppm).**
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	No.
>50% cohort with full latency	Yes, 18-yr mean follow-up period.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	208 cancers among 3,089 TCE-exposed subjects (7%).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, and calendar year.
Statistical methods	SMR and SIR, Life table analysis.
Exposure-response analysis presented in published paper	Yes, U-TCA as dichotomous variable (<6 ppm, 6+ ppm).
Documentation of results	Adequate for SIR analysis; details on SMR analysis of TCE subcohort are few.

B.3.1.2.3. Axelson et al. (1994).

B.3.1.2.3.1. Author's abstract.

There is limited evidence for mutagenicity and carcinogenicity of trichloroethylene (TRI) in experimental test systems. Whether TRI is a human carcinogen is unclear, however. This paper presents an update and extension of a previously reported cohort of workers exposed to TRI, in total 1670 persons. Among men (n = 1421), the overall standardized mortality ratio (SMR) and cancer morbidity ratio (SIR) were close to the expected, with SMR, 0.97; 95% confidence interval (CI), 0.86 to 1.10; and SIR, 0.96; 95% CI, 0.80 to 1.16, respectively. The cancer mortality was significantly lower than expected (SMR, 0.65; 95% CI, 0.47 to 0.89), whereas an increased mortality from circulatory disorders (cardiovascular, cerebrovascular) was of borderline significance (SMR, 1.17; 95% CI, 1.00 to 1.37). No significant increase of cancer of any specific site was observed, except for a doubled incidence of nonmelanocytic skin cancer without correlation with the exposure categories. In the small female subcohort (n = 249), a nonsignificant increase of cancer and circulatory deaths was observed (SMR, 1.53 and 2.02, respectively). For both genders, however, excess risks were largely confined to groups of workers with lower exposure levels or short duration of exposure or both. It is concluded that this study provides no evidence that TRI is a human carcinogen, i.e., when the exposure is as low as for this study population.

B.3.1.2.3.2. Study description and comment.

This Swedish study evaluated cancer risk in a small cohort of individuals (1,421 males and 249 females), who were monitored for U-TCA as part of a surveillance system by the TCE producer during 1955 to 1975. Both mortality between 1955 and 1986 and cancer morbidity between 1958 and 1987 are assessed in males only due to the small number of female subjects. Eighty-one percent of the male subjects had low exposures (<50 mg/L), corresponding to an airborne concentration of TCE of approximately 20 ppm. There was uncertainty about the beginning and end of exposure. Exposure was assumed to begin with the first urine sample and to end in 1979 (the reason for this date is unclear). Because the investigators did not have job histories, there is considerable uncertainty about the duration of exposure. No information is, additionally, presented to evaluate if a large proportion of the cohort had a full latency period for cancer development. Most subjects appear to have had short durations of exposure, but these might have been underestimated. Another concern is the sampling strategy. It was not reported how the workers were chosen for monitoring. Therefore, it is not clear what biases could be present in the data, especially the possibility of under sampling highly exposed workers.

Overall, this study had a small cohort drawn from a wide variety of industries, predominantly from industries involving degreasing and metal cleaning. Exposure to TCE was generally low (most <20 ppm). The duration of exposure was uncertain and bias related to under sampling of higher exposed workers is possible but cannot be evaluated.

Axelson O, Selden A, Andersson K, Hogstedt C. (1994). Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. J Occup Environ 36:556–562.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Yes- "This paper present an update and extension of a previously reported cohort of workers exposure to TCE."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	1,670 subjects (1,421 males, 249 females) with records of biological monitoring of urine TCA from 1955 and 1975. Analysis restricted to 1,421 males. External referents—age-, sex-, calendar year-, and site-specific mortality or cancer incidence rates of Swedish population.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence from 1958 to 1987 and all-cause mortality from 1955 to 1986.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD, 7th revision. ICD, 8th revision from 1975 onward for all lympho-hematopoietic system cancers.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Biological marker of TCE in urine used to assign TCE exposure to cohort subject. No extrapolation of U-TCA data to air-TCE concentration. **Roughly ¾ of cohort had U-TCA concentrations equivalent to <20 ppm TCE.**
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	No
>50% cohort with full latency	Insufficient to estimate for full cohort; however, 42% of person years in subjects with 2+ exposure years also had 10+ yrs of latency.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	229 deaths (16% of male subjects). 107 incident cancer cases.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age and calendar year.
Statistical methods	SMR—age, sex, and calendar-year. SIR—analyses restricted to males—age and calendar-year.
Exposure-response analysis presented in published paper	Yes, by three categories of U-TCA concentration.
Documentation of results	Adequate.

B.3.1.3. Studies in the Taoyuan Region of Taiwan

B.3.1.3.1. Sung et al. (2008; 2007).

B.3.1.3.1.1. Sung et al.(2008) abstract.

There is limited evidence on the hypothesis that maternal occupational exposure near conception increases the risk of cancer in offspring. This study is to investigate whether women employed in an electronics factory increases childhood cancer among first live born singletons. We linked the databases of Birth Registration and Labor Insurance, and National Cancer Registry, which identified 40,647 female workers ever employed in this factory who gave 40,647 first live born singletons, and 47 of them developed cancers during 1979-2001. Mothers employed in this factory during their periconceptional periods (3 months before and after conception) were considered as exposed and compared with those not employed during the same periods. Poisson regression model was constructed to adjust for potential confounding by maternal age, education, sex, and year of birth. Based on 11 exposed cases, the rate ratio of all malignant neoplasms was increased to 2.26 [95% confidence interval (CI), 1.12-4.54] among children whose mothers worked in this factory during periconceptional periods. The RRs were associated with 6 years or less (RR=3.05; 95% CI, 1.20-7.74) and 7-9 years (RR=2.49; 95% CI, 1.26-4.94) of education compared with 10 years or more. An increased association was also found between childhood leukemia and exposed pregnancies (RR=3.83; 95% CI, 1.17-12.55). Our study suggests that maternal occupation with potential exposure to organic solvents during periconception might increase risks of childhood cancers, especially for leukemia.

B.3.1.3.1.2. Sung et al. (2007) abstract.

Background In 1994, a hazardous waste site, polluted by the dumping of solvents from a former electronics factory, was discovered in Taoyuan, Taiwan. This subsequently emerged as a serious case of contamination through chlorinated hydrocarbons with suspected occupational cancer. The objective of this study was to determine if there was any increased risk of breast cancer among female workers in a 23-year follow-up period. **Methods** A total of 63,982 female workers were retrospectively recruited from the database of the Bureau of Labor Insurance (BLI) covering the period 1973-1997; the data were then linked with data, up to 2001, from the National Cancer Registry at the Taiwanese Department of Health, from which standardized incidence ratios (SIRs) for different types of cancer were calculated as compared to the general population. **Results** There were a total of 286 cases of breast cancer, and after adjustment for calendar year and age, the SIR was close to 1. When stratified by the year 1974 (the year in which the regulations on solvent use were promulgated), the SIR of the cohort of workers who were first employed prior to 1974 increased to 1.38 (95% confidence interval, 1.11-1.70). No such trend was discernible for workers employed after 1974. When 10 years of employment was considered, there was a further increase in the SIR for breast cancer, to 1.62. Those workers with breast cancer who were first employed prior to 1974 were employed at a younger age and for a longer period. Previous qualitative studies of interviews with the

workers, corroborated by inspection records, showed a short-term high exposure to chlorinated alkanes and alkenes, particularly trichloroethylene before 1974. There were no similar findings on other types of cancer. **Conclusions** Female workers with exposure to trichloroethylene and/or mixture of solvents, first employed prior to 1974, may have an excess risk of breast cancer.

B.3.1.3.1.3. Study description and comment.

Sung et al. (2007) examined breast cancer incidence among females in a cohort of electronic workers with employment at one factory in Taoyuan, Taiwan between 1973 and 1992, date of factory closure, and followed to 2001. Some female subjects in Sung et al. (2007) overlap those in Chang et al. (2005; 2003) who included workers from the same factory whose employment dates were between 1978 and 1997, the closing date of the study a date of vital status ascertainment. A total of 64,000 females were identified with 63,982 in the analysis after the exclusion of 15 women with <1 full day of employment and three women with cancer diagnoses prior to the time of first employment; approximately 6,000 fewer female subjects compared to Chang et al. (2005) (70,735 females). Cancer incidence between 1979 and 2001 as identified using the National Cancer Registry which contained 80% of all cancer cases in Taiwan is examined using life table methods with exposure lag periods of 5–15 years, depending on the cancer site, and cancer rates from the larger Taiwanese population as referent.

Company employment records were lacking and the cohort was constructed using the Bureau of Labor Insurance database that contained computer records since 1978 and paper records for the period 1973–1978. Duration of employment was calculated from the beginning of coverage of labor insurance and is likely an underestimate. Labor insurance hospitalization data and a United Labor Association list of names were used to verify cohort completeness. While these sources may have been sufficient to identified current employees, their ability to identify former employees may be limited, particularly from the hospitalization data if the subject's current employer was listed.

This study assumes all employees in the factory were exposed to chlorinated organic solvent vapors and the primary exposure index was duration of employment at the plant. Most subjects had employment durations of <1 year (65%). Durations of exposure were likely underestimated as dates of commencement and termination of insurance coverage were incomplete, 7.5 and 6%, respectively. There is little to no information on chemical usage and exposure assignment to individual cohort subjects. As reported in Chang et al. (2005; 2003), records of the Department of Labor Inspection ad Bureau of International Trade, in addition, to recall of former industrial hygienists were used to identify chemicals used after 1975 in the plants. No information is available prior to this date.

Sung et al. (2008) presents an analysis of childhood cancer incidence (1979–2001) among first liveborn singleton births (1978 and 2001) of female subjects employed at the plant during a period 3 months before and after beginning of pregnancy, an estimate derived by Sung

et al. (2008) from the date of birth and estimated length of gestation plus 14 days. Sung et al. (2007) used Poisson regression methods and cancer incidence among first liveborn births of all other women in Taiwan in the same time to calculate RRs associated with leukemia risk among exposed offspring. Poisson models were adjusted for maternal age, maternal educational level, child's sex, and year of birth. A total of 8,506 first born singleton births among 63,982 female subjects were identified from the Taiwan Birth Registry database, and 11 cancers, including 6 leukemia cases and no brain/CNS cases identified from the National Cancer Registry database.

Overall, these studies do not provide substantial weight for determining whether TCE may cause increased risk of disease. The lack of TCE-assessment to individual cohort subjects; grouping cohort subjects with different exposure potential, both to different solvents and different intensities; and deficiencies in the record system used to construct the cohort introduce uncertainty.

Sung T-I, Chen P-C, Lee L J-H, Lin Y-P, Hsieh G-Y, Wang J-D. (2007). Increased standardized incidence ratio of breast cancer in female electronics workers. BMC Public Health 7:102. http://www.biomedcentral.com/content/pdf/1471-2458-7-102.pdf**.**

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	From abstract "This study is to investigate whether women employed in an electronics factory increases childhood cancer among first live born singletons." This study was not able to evaluate TCE exposures uniquely.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	63,982 females, some who were also subjects were also in cohort of Chang et al. (2005; 2003) with 70,735 females. Cohort initially established using labor insurance records (computer records after 1978 and paper records from 1973 and 1978) in the absence of company records. Cohort definition dates are not clearly identified. Cohort identified from records covering period 1973 and 1997 with vital status ascertained as of 2001. Factory closed in 1992. External referents: age-, calendar-, and sex-specific incidence rates of the Taiwanese general population.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence as ascertained from National (Taiwan) Cancer Registry (80% of all cancers reported to Registry).
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-Oncology, a supplement to ICD-9.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	All employees assumed to be potentially exposed to chlorinated organic solvent vapors; study does not assign potential chemical exposures to individual subjects. No information on specific chemical exposures or intensity. Limited identification of solvents used in manufacturing process from the period after 1975 inferred from records of Department of Labor Inspection, Bureau of International Trade, and former industrial hygienists recall. No information on solvent usage was available before 1975. Exposure index defined as duration of exposure which was likely underestimated. 21% of cohort with ≥10 yrs duration of employment and 53% with <1 yr duration.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	No information on loss to follow-up. Subject was assumed disease free at end of follow-up if lacking cancer diagnosis as recorded in the National Cancer Registry.
>50% cohort with full latency	No, 57% of cohort employed after November 21, 1978.

CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	1,311 cancer cases.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age-, calendar-, and sex-specific incidence rates.
Statistical methods	SIR, analyses include a lag period of 5, 10, or 15 yrs since first employment (as indicated by labor insurance record).
Exposure-response analysis presented in published paper	Cancer incidence examined by duration of employment; however, employment durations were likely underestimates as dates of commencement and termination dates on of insurance coverage date were incomplete and misclassification bias is likely present.
Documentation of results	Inadequate—analyses that do not include a lag are not presented nor discussed in published paper or in supplemental documentation.

Sung T-I, Wang J-D, Chen P-C. (2008). Increased risk of cancer in the offspring of female electronics workers. Reprod Toxicol 25:115–119.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	From abstract "The study was designed to examine whether breast cancer risk in females was increased, as had been observed in Chang et al. (2005; 2003) in a cohort with earlier employment dates." This study was not able to evaluate TCE exposure.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	11 cancers among 8,506 first born singleton births between 1978 and 2001 in 63,982 female subjects of Sung et al. (2007). Cancers identified from National Cancer Registry and births identified from Taiwan Birth Registration database. External referents: cancer incidence among all other first birth singleton births among Taiwanese females over the same time period.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence as ascertained from National (Taiwan) Cancer Registry (80% of all cancers reported to Registry).
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-Oncology, a supplement to ICD-9, specific leukemia subtypes not identified in paper.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	All births were among subjects with employment at factory during a period 3 months before and after beginning of pregnancy. All mothers were assumed potentially exposed to chlorinated organic solvent vapors; specific solvents are not identified nor assigned to individual subjects. Limited identification of solvents used in manufacturing process from the period after 1975 inferred from records of Department of Labor Inspection, Bureau of International Trade, and former industrial hygienists recall. No information on solvent usage was available before 1975.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	No information on loss to follow-up for females in Sung et al. (2007).
>50% cohort with full latency	66% of births would have been 16 yrs of age as of 2001, the date cancer incidence ascertainment ended.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	11 cancer cases among 8,506 first born singleton births.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Maternal age, maternal educational level, child's sex, and child's year of birth.
Statistical methods	Poisson regression using childhood cancer incidence among all other first live born children in Taiwan during same time period.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.1.3.2. Chang et al. (2005; 2003).

B.3.1.3.2.1. Chang et al. (2005) abstract.

A retrospective cohort morbidity study based on standardized incidence ratios (SIRs) was conducted to investigate the possible association between exposure to chlorinated organic solvents and various types of cancers in an electronic factory. The cohort of the exposure group was retrieved from the Bureau of Labor Insurance (BLI) computer database records dating for 1978 through December 31, 1997. Person-year accumulation began on the date of entry to the cohort, or January 1, 1979 (whichever came later), and ended on the closing date of the study (December 31, 1997), if alive without contracting any type of cancers, or the date of death, or the date of the cancer diagnosis. Vital status and cases of cancer of study subjects were determined from January 1, 1979 to December 31, 1997 by linking cohort data with the National Cancer Registry Database. The cancer incidence of the general population was used for comparison. After adjustment for age and calendar year, only SIR for breast cancer in the exposed female employees were significantly elevated when compared with the Taiwanese general population, based on the entire cohort without exclusion. The SIR of female breast cancer also showed a significant trend of period effect, but no significant dose-response relationship on duration of employment. Although the total cancer as well as the cancer for the trachea, bronchus[,] and lung for the entire female cohort was not significantly elevated, trend analysis by calendar-year interval suggested an upward trend. However, when duration of employment or latency was taken into consideration, no significantly elevated SIR was found for any type of cancer in either male or female exposed workers. In particular, the risk of female breast cancer was not indicated to be increased. No significant dose-response relationship on duration of employment and secular trend was found for the above-mentioned cancers. This study provides no evidence that exposure to chlorinated organic solvents at the electronics factory was associated with elevated human cancers.

B.3.1.3.2.2. Chang et al. (2003) abstract.

PURPOSE: A retrospective cohort mortality study based on standardized mortality ratios (SMRs) was conducted to investigate the possible association between exposure to chlorinated organic solvents and various types of cancer deaths. **METHODS**: Vital status and causes of death of study subjects were determined from January 1, 1985 to December 31, 1997, by linking cohort data with the National Mortality Database. Person-year accumulation began on the date of entry to the cohort, or January 1, 1985 (whichever came later), and ended on the closing date of the study (December 31, 1997), if alive; or the date of death. **RESULTS**: This retrospective cohort study examined cancer mortality among 86,868 workers at an electronics factory in the northern Taiwan. Using various durations of employment and latency and adjusting for age and calendar year, no significantly elevated SMR was found for any cancer in either male or female exposed workers when compared with the general Taiwanese population. In particular, the risk of female breast cancer was not found to be increased.

Although ovarian cancer suggested an upward trend when analyzed by length of employment, ovarian cancer risk for the entire female cohort was not elevated. **CONCLUSIONS**: It is concluded that this study provided no evidence that exposure to chlorinated organic solvents was associated with human cancer risk.

B.3.1.3.2.3. Study description and comment.

Both Chang et al. (2003) and Chang et al. (2005) studied a cohort of 86,868 subjects employed at an electronics factory between 1985 and 1997, and both administrative and nonadministrative (blue-collar) workers were included in the cohort. Cancer incidence between 1979 and 1997 was presented by Chang et al. (2005) and cancer mortality from 1985 to 1997 in Chang et al. (2003). The cohort was predominantly composed of females. The factory operated between 1968 and 1992, and the inclusion in the cohort of subjects after factory closure is questionable. Incidence was ascertained from the Taiwan National Cancer Registry, which contains 80% of all cancer cases in Taiwan (Parkin et al., 2002). The factory could be divided into three plants by manufacturing process: manufacture of television remote controls, manufacture of solid state and integrated circuit products, and manufacture of printed circuit boards. Furthermore, a factory waste disposal site was found to have contaminated the underground water supply of area communities with organic solvents; however, Chang et al. (2005) does not provide information on possible exposure to factory employees through ingestion. The analysis of communities adjacent to the factory is described in Lee et al. (2003).

Company employment records were lacking and the cohort was constructed using the Bureau of Labor Insurance database that contained computer records since 1978. Labor insurance hospitalization data and a United Labor Association list of names were used to verify cohort completeness. While these sources may have been sufficient to identified current employees, their ability to identify former employees may be limited, particularly from the hospitalization data if the subject's currently employer was listed.

All employees in the factory were assumed with potential exposure to chlorinated organic solvent vapors with duration of employment at the factory as the exposure surrogate. Subjects had varying exposure potentials and employment durations of <1 year (65% of cohort in Chang et al. (2005)). Durations of exposure were likely underestimated as dates of commencement and termination of insurance coverage were incomplete, 7.5 and 6%, respectively. Three plants comprised the factory and with different production processes. A wide variety of organic solvents were used in each process including dichloromethane, toluene, and methyl ethyl alcohol, used at all three plants, and perchloroethylene, propanol, and DCE, which were used at one of the three plants (Chang et al., (2005). Records of the Department of Labor Inspection and Bureau of International Trade, in addition, to recall of former industrial hygienists were used to identify chemicals used after 1975 in the plants. No information is available prior to this date. These sources documented the lack of TCE use between 1975 and 1991 and perchloroethylene was after 1981. No information was available on TCE and perchloroethylene usage during other

periods. Given the period of documented lack of TCE usage is before the cohort start date of 1978 and factory closure, there is great uncertainty of TCE exposure to cohort subjects.

Overall, both studies are not useful for determining whether TCE may cause increased risk of disease. The lack of TCE-assessment to individual cohort subjects and uncertainty of TCE usage in the factory; potential bias likely introduced through missing employment dates; and, examination of incidence using broad organ-level categories (i.e., lymphatic and hematopoietic tissue cancer together) decrease the sensitivity of this study for examining TCE and cancer. Furthermore, few cancers are expected, 1% of the cohort expected with cancer, and results in low statistical power from the cohort's young average age of 39 years.

Chang Y-M, Tai C-F, Yang S-C, Lin R, Sung F-C, Shin T-S, Liou S-H. (2005). Cancer Incidence among Workers Potentially Exposed to Chlorinated Solvents in An Electronics Factory. J Occup Health 47:171–180.

Chang Y-M, Tai C-F, Yang S-C, Chan C-J, S Shin T-S, Lin RS, Liou S-H. (2003). A cohort mortality study of workers exposed to chlorinated organic solvents in Taiwan. Ann Epidemiol 13:652–660.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	The study was not designed to uniquely evaluate TCE exposure but rather chlorinated solvents exposures. From abstract: "... to investigate the possible association between chlorinated organic solvents and various types of cancer in an electronics factory." This study is quite limited to meet stated hypothesis by the inclusion of all factory employees in the cohort and lack of exposure assessment on individual study subjects to TCE, specifically, and to chlorinated solvents, generally.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	n = 86,868 in cohort. Cohort initially established using labor insurance records in the absence of company records. Cohort definition dates are not clearly identified. Cohort identified from labor insurance records covering period 1978 and 1997; yet, plant closed in 1992. All subjects followed through 1997. Paper states cohort was completely identified; however, former workers who were eligible for cohort membership may not have been identified if validation sources did not identify former employer. Duration of employment reconstructed from insurance records: ~40% of subjects had employment durations <3 months, 9% employed >5 yrs, 0.7% employed >10 yrs. External referents: Age-, calendar-, and sex-specific incidence rates of the Taiwanese general population.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence as ascertained from National (Taiwan) Cancer Registry (80% of all cancers reported to Registry) (Chang et al., 2005). Mortality. ICD revision is not identified other than that used in 1981 (Chang et al., 2003).
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-Oncology, a supplement to ICD-9 (Chang et al., 2005). ICD, 9th revision was in effect in 1981, but paper does not identify to which ICD revision used to assign cause of death (Chang et al., 2003).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	All employees assumed to be potentially exposed to chlorinated organic solvent vapors. No information on specific chemical exposures or intensity. Limited identification of solvents used in manufacturing process from the period after 1975 inferred from records of Department of Labor Inspection, Bureau of International Trade, and former industrial hygienists recall. No information on solvent usage was available before 1975.

CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	No information on loss to follow-up. Subject was assumed disease free at end of follow-up if lacking cancer diagnosis as recorded in the National Cancer Registry.
>50% cohort with full latency	Average 16-yr follow-up (incidence) and 12 yrs (mortality).
Other	Subject's age determined by subtracting year of birth from 1997; however, insurance records did not contain DOB for 6% of subjects. Furthermore, commencement and termination dates were incomplete on insurance records, 7 and 6%, respectively.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	1,031 cancer cases. 1,357 total deaths (1.6% of cohort), 316 cancer deaths.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age-, calendar-, and sex-specific incidence rates (Chang et al., 2005) or age-, calendar-, and sex-specific mortality rates (Chang et al., 2003).
Statistical methods	SIR (Chang et al., 2005) and SMR (Chang et al., 2003).
Exposure-response analysis presented in published paper	Cancer incidence and mortality examined by duration of employment; however, employment durations were likely underestimates as dates of commencement and termination dates on of insurance coverage date were incomplete and calculated from date on insurance records. Misclassification bias is likely present.
Documentation of results	Adequate.

B.3.1.4. Studies of Other Cohorts

B.3.1.4.1. Clapp and Hoffman (2008).

B.3.1.4.1.1. Author's abstract.

BACKGROUND: In response to concerns expressed by workers at a public meeting, we analyzed the mortality experience of workers who were employed at the IBM plant in Endicott, New York and died between 1969 and 2001. An epidemiologic feasibility assessment indicated potential worker exposure to several known and suspected carcinogens at this plant. METHODS: We used the mortality and work history files produced under a court order and used in a previous mortality analysis. Using publicly available data for the state of New York as a standard of comparison, we conducted proportional cancer mortality (PCMR) analysis. RESULTS: The results showed significantly increased mortality due to melanoma (PCMR = 367; 95% CI: 119, 856) and lymphoma (PCMR = 220; 95% CI: 101, 419) in males and modestly increased mortality due to kidney cancer (PCMR = 165; 95% CI: 45, 421) and brain cancer (PCMR = 190; 95% CI: 52, 485) in males and breast cancer (PCMR = 126; 95% CI: 34, 321) in females. CONCLUSION: These results are similar to results from a previous IBM mortality study and support the need for a full cohort mortality analysis such as the one being planned by the National Institute for Occupational Safety and Health.

B.3.1.4.1.2. Study description and comment.

This proportional cancer mortality ratio study of deaths between 1969 and 2001 among employees at an IBM facility in Endicott, New York, who were included on the IBM Corporate Mortality File compared the observed number of site-specific cancer deaths are compared to the expected proportion, adjusted for age, using 10-year rather than 5-year grouping, and sex, of site-specific cancer deaths among New York residents during 1979 to 1998. Of the 360 deaths identified of Endicott employees, 115 deaths were due to cancer, 11 of these with unidentified site of cancer. Resultant PMRs estimates do not appear adjusted for race nor does the paper identify whether referent rates excluded deaths among New York City residents or are for New York deaths. The IBM Corporate Mortality File contained names of employees who had worker >5 years, who were actively employed or receiving retirement or disability benefits at time of death, or whose family had filed a claim with IBM for death benefits and Endicott plant employees were identified using worker employment data from the IBM Corporate Employee Resource Information System. Study investigators had previously obtained the IBM Corporate Mortality file through a court order and litigation.

The Endicott plant began operations in 1991 and manufactured a variety of products including calculating machines, typewriters, guns, printers, automated machines, and chip packaging. The most recent activities were the production of printed circuit boards. It was estimated from a National Institute of Occupational Safety and Health (NIOSH) feasibility study that a larger percentage of the plant's employee were potentially exposure to multiple chemicals,

including asbestos, benzene, cadmium, nickel compounds, vinyl chloride, tetrachloroethylene, TCE, PCBs, and o-toluidine. Chlorinated solvents were used at the plant until the 1980s. The study does not assign exposure potential to individual study subjects.

This study provides little information on cancer risk and TCE exposure given its lack of worker exposure history information and absence of exposure assignment to individual subjects. Other limitations in this study which reduces interpretation of the observations included incomplete identification of deaths, the analysis limited to only vested employees or to those receiving company death benefits, incomplete identification of all employees at the plant, the inherent limitation of the PMR method and instability of the effect measure particularly in light of bias resulting of excesses or deficits in deaths, and observed differences in demographic (race) between subjects and the referent (New York) population.

Clapp RW, Hoffman K. (2008). Cancer mortality in IBM Endicott plant workers, 1969–2001: an update on a NY production plant. Environ health 7:13.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	From abstract "…In response to concerns expressed by workers at a public meeting, we analyzed the mortality experience of workers who were employed at the IBM plant in Endicott, New York and died between 1969 and 2001."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Deaths among IBM workers identified in IBM Corporate Mortality File; workers with ≥5 yrs employment, who were actively employed or receiving retirement or disability benefits at time of death, or whose family had filed a claim with IBM for death benefits. Expected number of site-specific cancer deaths calculated from proportion of cancer deaths among New York residents. Paper does not identify if referent included all New York residents or those living upstate.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD 9.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	This study lacks exposure information. TCE and other chemicals were used at the factory and inclusion on the employee list served as a surrogate for TCE exposure of unspecified intensity and duration.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	Not able to evaluate given inability to identify complete cohort.
>50% cohort with full latency	Not able to evaluate given lack of work history records.
Other	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	360 deaths, 115 due to cancer, between 1969 and 2001.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age and gender. No information was available on race and PMRs are unadjusted for race.
Statistical methods	PMR.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.1.4.2. ATSDR (2004a).

B.3.1.4.2.1. Author's abstract.

The View-Master stereoscopic slide viewer has been a popular children's toy since the 1950s. For nearly half a century, the sole U.S. manufacturing site for the View-Master product was a factory located on Hall Boulevard in Beaverton, Oregon. Throughout this period, an on-site supply well provided water for industrial purposes and for human consumption. In March 1998, chemical analysis of the View-Master factory supply well revealed the presence of the degreasing solvent trichloroethylene (TCE) at concentrations as high as 1,670 micrograms per liter (⌠g/L)—the U.S. Environmental Protection Agency maximum contaminant level is 5 ⌠g/L. Soon after the contamination was discovered, the View-Master supply well was shut down. Up to 25,000 people worked at the plant and may have been exposed to the TCE contamination. In September of 2001, the Oregon Department of Human Services (ODHS) entered into a cooperative agreement with the Agency for Toxic Substances and Disease Registry (ATSDR) to determine both the need for and the feasibility of an epidemiological study of the View-Master site. In this report, ODHS compiles the findings of the feasibility investigation of worker exposure to TCE at the View-Master factory.

On the basis of the levels of TCE found in the supply well, the past use of the well as a source of drinking water, and the potential for adverse health effects resulting from past exposure to TCE, ODHS determined that the site posed a public health hazard to people who worked at or visited the plant prior to the discovery of the contamination. Because the use of the View-Master supply well was discontinued when the contamination was discovered in March 1998, the View-Master supply well does not pose a current public health hazard. No other drinking water wells tap into the contaminated aquifer, and the long-term remediation efforts appear to be containing the contamination.

ATSDR and ODHS obtained a list of 13,700 former plant workers from the Mattel Corporation. In collaboration with ATSDR, ODHS conducted a preliminary analysis of mortality and identified excesses in the proportions of deaths due to kidney cancer and pancreatic cancer among the factory's former employees. Although this analysis was limited by the lack of information about the entire worker population and individual exposures to TCE, the preliminary findings underscore the need to fully investigate the impact of TCE exposure on the population of former View-Master workers.

The findings of this feasibility investigation are:

- TCE appears to have been the primary contaminant of the drinking water at the plant;
- Contamination was likely present for a long period of time (estimated to have been present in the groundwater since the mid-1960s);
- A large number were likely exposed to the contamination:
- The primary route of exposure (for the last 18 years the factory operated) was through contaminated drinking water;

- Levels of TCE contamination were 300 time the maximum contaminant levels; and
- A significant portion of the former workers of their next of kin can indeed be located and invited to participate in a public health evaluation of their exposures.

Therefore, ODHS recommends further investigation to include the following:

1. A fate and transport assessment to better establish when TCE reached the supply well, and to provide a historical understanding of the concentration of TCE in the well, and
2. Epidemiological studies among former workers to determine their exposure and whether they have experienced adverse health and reproductive outcomes associated with TCE exposure at the plant, to determine the mortality experience of the population, and to document the cancer incidence in this population.

B.3.1.4.2.2. Study description and comment.

This PMR study of deaths between 1995 and 2001 among 13,697 former employees at a View-Master toy factory in Beaverton, Oregon contains no exposure information on individual study subjects. The PMR analysis was conducted as a feasibility study for further epidemiologic investigations of these subjects by Oregon Department of Health on behalf of ATSDR, and findings have not been published in the peer-reviewed literature. A former plant owner provided a listing of former employees; however, employees were not identified using IRS records and the roster was known to be incomplete. Additionally, work history records were not available and not information was available on employment length or job title. The goal of the feasibility analysis was to evaluate ability to identify completeness of death identification using several sources.

Monitoring of a water supply well in March 1998 showed detectable concentrations of TCE, and this study assumes all subjects had exposure to TCE in drinking water. TCE had been used in large quantities for metal degreasing at the factory between 1952 and 1980; this activity mostly occurred in the paint shop located in one building. At the time metal degreasing ceased, company records suggested historical use of TCE was up to 200 gallons per month. Historical practices resulted in releases of hazardous substances at the factory site and former employees reported waste TCE from the degreased was transported to other sites on the premises, and discharged to the ground (ATSDR, 2004a). Additionally, chemical spills allegedly occurred in the paint shop and one report in 1964 of an inspection of the degreaser indicated atmospheric TCE concentrations above occupational limits. TCE was detected at concentrations between 1,220 and 1,670 µg/L in four water samples and the Oregon Department of Environmental Quality estimated the well had been contaminated for over 20 years. Other VOCs besides TCE

detected in the supply well water in March 1998 included cis-1,2-DCE at levels up to 33 µg/L and perchloroethylene at concentrations up to 56 µg/L. The 160-foot-deep supply well was on the property since original construction in 1950 and it supplied water for drinking, sanitation, fire fighting, and industrial use. Connection to municipal water supply occurred in 1956; however, although municipal water was directed to some parts of the plant, the supply well continued to serve the facility's needs, including most of the drinking and sanitary water (ATSDR, 2003b).

This study provides little information on cancer risk and TCE exposure given the absence of monitoring data beyond a single time period, absence of estimated TCE concentrations in drinking water, and exposure pathways other than ingestion. Other limitation in this study which reduces interpretation of the observations included incomplete identification of employees with the result of missing deaths likely, the inherent limitation of the PMR method and instability of the effect measure particularly in light of bias resulting of excesses or deficits in deaths, and observed differences in demographic (age and male/female ratio) between subjects and the referent (Oregon) population.

ATSDR (Agency for Toxic Substances and Disease Registry). (2004a). Feasibility investigation of worker exposure to trichloroethylene at the View-Master Factory in Beaverton, Oregon. Final Report. Submitted by Environmental and Occupational Epidemiology, Oregon Department of Human Services. December 2004.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	The goal of this feasibility investigation for a cohort epidemiologic study of former employees at a plant manufacturing stereoscopic slide viewers examined the ability to identify former employees and ascertain vital status.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Name of ~13,000 former employee names were provided to ATSDR by the former plant owner. The current list of employees was known to be incomplete. The proportion of site-specific mortality among workers between 1989 and 2001 was compared to the proportion expected using all death in Oregon for a similar time period.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD 9 and ICD 10.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	This study lacks actual exposure information; work history records were not available. TCE was used at the factory and inclusion on the employee list served as a surrogate for TCE exposure of unspecified intensity and duration.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	Not able to evaluate given inability to identify complete cohort.
>50% cohort with full latency	Not able to evaluate given lack of work history records.
Other	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	616 deaths between 1989 and 2001.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age and gender. No information was available on race and PMRs are unadjusted for race.
Statistical methods	PMR.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.1.4.3. Raaschou-Nielsen et al. (2003).

B.3.1.4.3.1. Author's abstract.

Trichloroethylene is an animal carcinogen with limited evidence of carcinogenicity in humans. Cancer incidence between 1968 and 1997 was evaluated in a cohort of 40,049 blue-collar workers in 347 Danish companies with documented trichloroethylene use. Standardized incidence ratios for total cancer were 1.1 (95% confidence interval (CI): 1.04, 1.12) in men and 1.2 (95% CI: 1.14, 1.33) in women. For non-Hodgkin's lymphoma and renal cell carcinoma, the overall standardized incidence ratios were 1.2 (95% CI: 1.0, 1.5) and 1.2 (95% CI: 0.9, 1.5), respectively; standardized incidence ratios increased with duration of employment, and elevated standardized incidence ratios were limited to workers first employed before 1980 for non-Hodgkin's lymphoma and before 1970 for renal cell carcinoma. The standardized incidence ratio for esophageal adenocarcinoma was 1.8 (95% CI: 1.2, 2.7); the standardized incidence ratio was higher in companies with the highest probability of trichloroethylene exposure. In a subcohort of 14,360 presumably highly exposed workers, the standardized incidence ratios for non-Hodgkin's lymphoma, renal cell carcinoma, and esophageal adenocarcinoma were 1.5 (95% CI: 1.2, 2.0), 1.4 (95% CI: 1.0, 1.8), and 1.7 (95% CI: 0.9, 2.9), respectively. The present results and those of previous studies suggest that occupational exposure to trichloroethylene at past higher levels may be associated with elevated risk for non-Hodgkin's lymphoma. Associations between trichloroethylene exposure and other cancers are less consistent.

B.3.1.4.3.2. Study description and comment.

Raaschous-Nielsen et al. (2003) examined cancer incidence among a cohort of workers drawn from 347 companies with documented TCE. Almost half of these companies were in the iron and metal industry. The cohort was identified using the Danish Supplementary Pension Fund, which includes type of industry of a company and a history of employees, for the years 1964 to 1997. Altogether, 152,726 workers were identified of whom 39,074 were white-collar and assumed not to have TCE exposure, 56,970 workers were of unknown status, and 56,578 blue-collar workers, of which 40,049 had been employed at the company for >3 months and are the basis of the analysis. The cohort was relatively young, 56% were 38 to 57 years old at end of follow-up, and 29% of subjects were older than 57 years of age. Cancer rates typically increase with increasing ages; thus, the lower age of this cohort likely limits the ability of this study to fully examine TCE and cancer, particularly cancers that may be associated with aging. Observed number of site-specific incident cancers are obtained from 4-1-1968 to the end of 1997 and compared to expected numbers of site-specific cancers based on incidence rates of the Danish population.

A separate exposure assessment was conducted using regulatory agency data from 1947 to 1989 (Raaschou-Nielsen et al., 2002). This assessment identified three factors as increasing potential for TCE exposure, duration of employment, year of first employment, and number of

employees, to increase the likelihood of cohort subjects as TCE exposed. The percentage of exposed workers was found to decrease as company size increased: 81% for <50 workers, 51% for 50–100 workers, 19% for 100–200 workers, and 10% for >200 workers. About 40% of the workers in the cohort were exposed (working in a room where TCE was used). Smaller companies had higher exposures. Median exposures to TCE were 40–60 ppm for the years before 1970, 10–20 ppm for 1970–1979, and approximately 4 ppm for 1980–1989. Additionally, an assessment of TCA concentrations in urine of Danish workers suggested a similar trend over time; mean concentrations of 58 mg/L for the period between 1960 and 1964 and 14 mg/L in sample taken between 1980 and 1985 (Raaschou-Nielsen et al., 2001).

Only a small fraction of the cohort was exposed to TCE. The highest exposures occurred before 1970 at period in which 21.2% of blue-collar workers had begun employment in a TCE-using company. The iron and metal industry doing degreasing and cleaning with TCE had the highest exposures, with a median concentration of 60 ppm and a range up to about 600 ppm. Overall, strengths of this study include its large numbers of subjects; however, the younger age of the cohort and the small fraction expected with TCE exposure limit the ability of the study to provide information on cancer risk and TCE exposure. For these reasons, positive associations observed in this study are noteworthy.

Raaschou-Nielsen O, Hansen J, McLaughlin JK, Kolstad H, Christensen JM, Tarone RE, Olsen JH. (2003). Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. Am J Epidemiol 158:1182–1192.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This study was designed to evaluate associations observed in Hansen et al. (2001) with TCE exposure and NHL, esophageal adenocarcinoma, cervical cancer, and liver-biliary tract cancer.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Cohort of 40,049 blue-collar workers employed in 1968 or after with >3 months employment duration identified by linking 347 companies, who were considered as having a high likelihood for TCE exposure, with the Danish Supplementary Pension Fund to identify employees and with Danish Central Population Registry. External referents are age-, sex-, calendar year-, and site-specific cancer incidence rates of the Danish population.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence between 4-1-1968 and 12-31-1997 as identified from records of Danish Cancer Registry.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD, 7th revision.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Qualitative exposure assessment. A previous industrial hygiene survey of Danish companies identified several characteristics increase likelihood of TCE exposure-duration of employment, year of 1st employment, and number of employees in company (Raaschou-Nielsen et al., 2002). Exposure index defined as duration of employment. **Median exposures to TCE were 40–60 ppm for the years before 1970, 10–20 ppm for 1970–1979, and approximately 4 ppm for 1980–1989. Additionally, an assessment of TCA concentrations in urine of Danish workers suggested a similar trend over time; mean concentrations of 58 mg/L for the period between 1960 and 1964 and 14 mg/L in sample taken between 1980 and 1985 (Raaschou-Nielsen et al., 2001).**
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	Danish Cancer Registry is considered to have a high degree of reporting and accurate cancer diagnoses.
>50% cohort with full latency	Yes, average follow-up was 18 yrs.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	

CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	3.244 cancers (8% of cohort had developed a cancer over the period from 1968 to 1997). Although of a large number of subjects, this cohort is of a young age, 29% of cohort was >57 yrs of age at end of follow-up.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, and calendar year.
Statistical methods	SIR using life-table analysis.
Exposure-response analysis presented in published paper	Yes, duration of employment.
Documentation of results	Adequate.

B.3.1.4.4. Ritz (1999a).

B.3.1.4.4.1. Author's abstract.

> Data provided by the Comprehensive Epidemiology Data Resource allowed us to study patterns of cancer mortality as experience by 3814 uranium-processing workers employed at the Fernald Feed Materials Production Center in Fernald, Ohio. Using risk-set analyses for cohorts, we estimated the effects of exposure to trichloroethylene, cutting fluids, and kerosene on cancer mortality. Our results suggest that workers who were exposed to trichloroethylene experienced an increase in mortality from cancers of the liver. Cutting-fluid exposure was found to be strongly associated with laryngeal cancers and, furthermore, with brain, hemato- and lymphopoietic system, bladder, and kidney cancer mortality. Kerosene exposure increased the rate of death from several digestive-tract cancers (esophageal, stomach, pancreatic, colon, and rectal cancers) and from prostate cancer. Effect estimates for these cancers increased with duration and level of exposure and were stronger when exposure was lagged.

B.3.1.4.4.2. Study description and comment.

This study of 3,814 white male uranium processing workers employed for at least 3 months between 1-1-1951 and 12-31-1972 at the Fernald Feed Materials Production Center in Fernald, Ohio, was of deaths as of 1-1-1990. Subjects were part of a larger cohort study of Fernald workers with potential uranium and products of uranium decay exposures that observed associations with lung cancer and lymphatic/hematopoietic cancer (Ritz, 1999b). Average length of follow-up time was 31.5 years. During this period, 1,045 deaths were observed with expected numbers of deaths based upon age- and calendar-specific U.S. white male mortality rates and age- and calendar-specific white male mortality rates from the NIOSH Computerized Occupational Referent Population System (CORPS) (Zahm, 1992). Internal analyses based upon risk-set sampling and Cox proportional hazards modeling compared workers with differing exposure intensity rankings (light and moderate) and a category for no- TCE exposure/<2 year duration TCE exposure.

Fernald produced uranium metal products for defense programs (Hornung et al., 2008). Subjects had potential exposures to uranium, mainly as insoluble compounds and varying from depleted to slight enriched, small amounts of thorium, an alpha particle emitter, respiratory irritants such as tributyl phosphate, ammonium hydroxide, sulfuric acid, and hydrogen fluoride, TCE, and cutting fluids (Ritz, 1999a, b). Exposure assessment for analysis of chemical exposures utilized a JEM to assign intensity of TCE, cutting fluids, and kerosene to individual jobs from the period 1952–1977. Industrial hygienists, a plant foreman, and an engineer during the late 1970s and early 1980s determined the likelihood of exposure to TCE, cutting fluids, and kerosene for each job title and plant area. Based on work records, the workforce appeared stable and 54% were employed ≥5 years and had held only one job title during employment. Both intensity or exposure level and duration of exposure in years were used to rank subjects into four

categories of no exposure (level 0), light exposure (level 1), moderate exposure (level 2), and heavy exposure (level 3). Seventy eight percent of the cohort was identified with some potential for TCE exposure, 2,792 subjects were identified with low TCE exposure (94%), 179 with moderate exposure (6%), and no subjects were identified with heavy TCE exposure. TCE exposure was highly correlated with other chemical exposures and with alpha radiation (Hornung et al., 2008; Ritz, 1999a, b). Fernald subjects had higher exposures to radiation compared to those of radiation-exposed Rocketdyne workers (Ritz et al., 2000; Ritz, 1999b; Ritz et al., 1999). Atmospheric monitoring information is lacking on TCE exposure conditions as is information on changes in TCE usage over time. The cohort was identified from company rosters and personnel records and it is not known whether these were sources for a subject's job title information. Analysis of TCE exposure carried out using conditional logistic regression adjusting for pay status, time since first hired, external and internal radiation dose, and previous chemical exposure. Relative risks for TCE exposure are also presented with a lag time period of 15 years.

Overall, strengths of this study are the long follow-up time and a large percentage of the cohort who had died by the end of follow-up. TCE exposure intensity is low in this cohort, 94% of TCE exposed subjects were identified with "light" exposure intensity, and all subjects had potential for radiation exposure, which was highly correlated with chemical exposures. No information is presented on the definition of "light" exposure and monitoring data are lacking. Only 179 subjects were identified with TCE exposure above "light" and the number of cancer deaths not presented. The published paper reported limited information on site-specific cancer and TCE exposure; risk estimates are reported for lymphatic and hematopoietic cancers, esophageal and stomach cancer, liver cancer, prostate cancer and brain cancer. Risk estimates for bladder and kidney cancer and TCE exposure are found in NRC (2006). Few deaths were observed with moderate TCE exposure and exposure durations of >2 years: one death due to lymphatic and hematopoietic cancer, no deaths due to kidney or bladder cancer (as noted in NRC (2006)), and two liver cancer deaths among these subjects. Low statistical power reflecting few cases with moderate TCE exposure and multicollinearity of chemical and radiation exposures greatly limits the support that this study provides in an overall weight-of-evidence analysis.

Ritz B. (1999a). Cancer mortality among workers exposed to chemicals during uranium processing. J Occup Environ Med 41:556–566.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	The hypothesis in this study was to examine the influence of chemical exposures in the work environment of the Fernald Feed Materials Production Center (FFMPC) in Fernald, Ohio, on cancer mortality with a focus on the effects of TCE, cutting fluids, and a combination of kerosene exposure with carbon (graphite) and other solvents.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	3,814 white male subjects identified from company rosters and personnel records, hired between 1951 and 1972 and who were employed continuously for 3 months and monitored for radiation. 2,971 subjects identified as exposed to TCE at "light" and "moderate" exposures. Subjects were identified in a previous study of cancer mortality and radiation exposure and most subjects had radiation exposures above 10+ mSV (Ritz, 1999b). External analysis: U.S. white male mortality rates and NIOSH-Computerized Occupational Referent Population System mortality rates. Internal analysis: cohort subjects according to level and duration of chemical exposure.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality. Vital status searched through Social Security Administration records, before 1979, and National Death Index for the period 1979–1989.
Changes in diagnostic coding systems for lymphoma, particularly NHL	External analysis: ICDA, 8th revision. Internal analysis: aggregation of several subsite causes of deaths into larger categories based on ICD, 9th revision.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Semiquantitative approach and development of JEM. JEM developed by expert assessment by plant employees to classify jobs into four levels of chemical exposures for the period 1952 to 1977. Intensity using the four-level scale and duration of exposure to TCE, cutting fluids and kerosene were assigned to individual cohort subjects using JEM. 73% of cohort identified as TCE exposed (2,971 male with TCE exposure in cohort of 3,814 subjects). Only 4% of TCE-exposed subjects with exposure identified as "moderate" and no subjects with "high" exposure. High correlation between TCE and other chemical exposure and radiation exposure.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	All workers without death certificate assumed alive at end of follow-up.
>50% cohort with full latency	Average follow-up time, 31.5 yrs.
Other	

CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	1,045 deaths (27% of cohort), 328 due to cancer. No information on number of all-cancer deaths among TCE exposed subjects, although reported numbers for specific sites reported by Ritz (1999a) or NRC (2006): >2-yr exposure duration, hemato- and lymphopoietic cancer (n = 18 with light exposure, 1 with moderate exposure), esophageal and stomach cancer (n = 15 with light exposure, 0 with moderate exposure), liver cancers (n = 3 with light exposure, 1 with moderate exposure), kidney and bladder cancers, (n = 7 with light exposure, 0 with moderate exposure) prostate cancers (n = 10 with light exposure, 1 with moderate exposure), and brain cancers (n = 6 with light exposure, 1 with moderate exposure).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	External analysis: age- and calendar-specific mortality rates for white males. Internal analysis: pay status, time since first hired, and cumulative time-dependent external- and internal-radiation doses (continuous); indirect assessment of smoking through examination of smoking distribution by chemical exposure.
Statistical methods	SMR (external analysis) and RR (internal analysis).
Exposure-response analysis presented in published paper	Yes, RR presented for exposure to TCE (level 1 and level 2, separately) by duration of exposure.
Documentation of results	Adequate.

B.3.1.4.5. Henschler et al. (1995).

B.3.1.4.5.1. Author's abstract.

> A retrospective cohort study was carried out in a cardboard factory in Germany to investigate the association between exposure to trichloroethene (TRI) and renal cell cancer. The study group consisted of 169 men who had been exposed to TRI for at least 1 year between 1956 and 1975. The average observation period was 34 years. By the closing day of the study (December 31, 1992) 50 members of the cohort had died, 16 from malignant neoplasms. In 2 out of these 16 cases, kidney cancer was the cause of death, which leads to a standard mortality ratio of 3.28 compared with the local population. Five workers had been diagnosed with kidney cancer: four with renal cell cancers and one with an urothelial cancer of the renal pelvis. The standardized incidence ratio compared with the data of the Danish cancer registry was 7.97 (95% CI: 2.59-18.59). After the end of the observation period, two additional kidney tumors (one renal cell and one urothelial cancer) were diagnosed in the study group. The control group consisted of 190 unexposed workers in the same plant. By the closing day of the study 52 members of this cohort had died, 16 from malignant neoplasms, but none from kidney cancer. No case of kidney cancer was diagnosed in the control group. The direct comparison of the incidence on renal cell cancer shows a statistically significant increased risk in the cohort of exposed workers. Hence, in all types of analysis the incidence of kidney cancer is statistically elevated among workers exposed to TRI. Our data suggest that exposure to high concentrations of TRI over prolonged periods of time may cause renal tumors in humans. A causal relationship is supported by the identity of tumors produced in rats and a valid mechanistic explanation on the molecular level.

B.3.1.4.5.2. Study description and comment.

This was a cohort study of workers in a cardboard factory in the area of Arnsberg, Germany. TCE was used in this area until 1975 for degreasing and solvent needs. Plant records indicated that 2,800–23,000 L/year was used. Small amounts of tetrachloroethylene and 1,1,1-trichloroethane were used occasionally, but in much smaller quantities than TCE. TCE was used in three main areas: cardboard machine, locksmith's area, and electrical workshop. Cleaning the felts and sieves and cleaning machine parts of grease were done regularly every 2 weeks, in a job that required 4–5 hours, plus whatever additional cleaning was needed. TCE was available in open barrels and rags soaked in it were used for cleaning. The machines ran hot (80–120°C) and the cardboard machine rooms were poorly ventilated and warm (about 50°C), which would strongly enhance evaporation. This would lead to very high concentrations of airborne TCE. Cherrie et al. (2001) estimated that the machine cleaning exposures to TCE were >2,000 ppm. Workers reported frequent strong odors and a sweet taste in their mouths. The odor threshold for TCE is listed as 100 ppm (ATSDR, 1997c). Workers often left the work area for short breaks "to get fresh air and to recover from drowsiness and headaches." Based on reports of anesthetic effects, it is likely that concentrations of TCE exceeded 200 ppm (Stopps and McLaughlin,

1967). Those reports, the work setting description, and the large volume of TCE used are all consistent with very high concentrations of airborne TCE. The workers in the locksmith's area and the electrical workshop also had continuous exposures to TCE associated with degreasing activities; parts were cleaned in cold dip baths and left on tables to dry. TCE was regularly used to clean floors, work clothes, and hands of grease, in addition to the intense exposures during specific cleaning exercises, which would produce a background concentration of TCE in the facility. Cherrie et al. (2001) estimated the long-term exposure to TCE was approximately 100 ppm.

The subjects in this study clearly had substantial peak exposures to TCE that exceeded 2,000 ppm and probably sustained long-term exposures >100 ppm, which are not confounded by concurrent exposures to other chlorinated organic solvents.

Henschler D, Vamvakas S, Lammert M, Dekant W, Kraus B, Thomas B, Ulm K. (1995). Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. Arch Toxicol 69:291–299.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	From abstract "…retrospective cohort study was carried out in a cardboard factory I Germany to investigate the association between exposure to trichloroethene and renal cell cancer."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Employee records were used to identify 183 males employed in a cardboard factory for at least 1 yr between 1956 and 1975 and with presumed TCE exposure and a control group of 190 male workers at same factory during the same period of time but in jobs not involving possible TCE exposure. Mortality rates from German population residing near factory used as referent in mortality analysis. Renal cancer incidence rates from Danish Cancer Registry used to calculate expected number of incident cancer. The age-standardized rate in the late 1990s among men in Denmark was 10.6 per 100,000 and in Germany, it was 1.2 per 100,000 (Ferlay et al., 2004). If these differences in rates apply when the study was carried out, this would imply that the expect number of deaths would have been inflated by about 14% (and the rate ratio underestimated by that amount).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality and renal cell cancer incidence.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-9 for deaths. Hospital pathology records were used to verify diagnosis of RCC.
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Walkthrough survey and interviews with long-term employees were used to identify work areas and jobs with potential TCE exposure. The workers in the locksmith's area and the electrical workshop also had continuous exposures to TCE associated with degreasing activities; parts were cleaned in cold dip baths and left on tables to dry. **Cherrie et al. (2001) estimated that the machine cleaning exposures to TCE were >2,000 ppm with average long-term exposure as 10–225 ppm. Estimated average chronic exposure to TCE was ~100 ppm to subjects using TCE in cold degreasing processes.**
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	14 exposed subjects (8%) were excluded from life-table analysis and no information is presented in paper on loss-to-follow-up among control subjects.
>50% cohort with full latency	Median follow-up period was over 30 yrs for both exposed and control subjects.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	

Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	50 total deaths (30%) and 15 cancer death among exposed subjects. 52 deaths (27%) and 15 cancer deaths among control subjects.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age and calendar-year.
Statistical methods	SMR and SIR. Analysis excludes person-years of subjects excluded from exposed population with the number of person-years underestimated and an underestimate of the expected numbers of deaths and incident renal carcinoma cases.
Exposure-response analysis presented in published paper	No.
Documentation of results	Adequate.

B.3.1.4.6. Greenland et al. (1994).

B.3.1.4.6.1. Author's abstract.

To address earlier reports of excess cancer mortality associated with employment at a large transformer manufacturing plant each plant operation was rated for seven exposures: Pyranol (a mixture of polychlorinated biphenyls and trichlorobenzene), trichloroethylene, benzene, mixed solvents, asbestos, synthetic resins, and machining fluids. Site-specific cancer deaths among active or retired employees were cases; controls were selected from deaths (primarily cardiovascular deaths) presumed to be unassociated with any of the study exposures. Using job records, we then computed person-years of exposure for each subject. All subjects were white males. The only unequivocal association was that of resin systems with lung cancer (odds ratio = 2.2 at 16.6 years of exposure, P = 0.0001, in a multiple logistic regression including asbestos, age, year of death, and year of hire). Certain other odds ratios appeared larger, but no other association was so robust and remained as distinct after considering the multiplicity of comparisons. Study power was very limited for most associations, and several biases may have affected our results. Nevertheless, further investigation of synthetic resin systems of the type used in the study plant appears warranted.

B.3.1.4.6.2. Study description and comment.

This nested case-control study at General Electric's Pittsfield, Massachusetts, plant was of deaths reported to the GE pension fund among employees vested in the pension fund. The cohort from which cases and controls were identified was defined as plant employees who worked at the facility before 1984; whose date of deaths was between 1969, the date pension records became available, and 1984; and existence of a job history record. The size of the underlying employee cohort was unknown because work history records did not exist for a large fraction of former employees, especially in the earlier years of deaths. All deaths were identified from records maintained by GE's pension office; other record sources such as the Social Security Administration and National Death Index were not utilized. Requirements for eligibility or "vestment" for a pension varied over time, but for most of the study period, required 10–15 years employment with the company. The analysis was restricted to white males because of few deaths among females and nonwhite males. A total of 1,911 deaths were identified from pension records and cases and controls, with 90 deaths excluded as possible cases and controls due to several reasons. Cases were identified as site-specific deaths and controls were selected from the remaining noncancer deaths due to circulatory disease, respiratory disease, injury, and other causes. No information was available on the number of controls selected per case. Controls were not matched to cases, were slightly older than cases, and were from earlier birth cohorts, which have a lower job history availability or greater frequency of missing exposure ratings in work history records (Salvan, 1990). Statistical analysis of the data included covariates for age and year of death.

The company's job history record served as the source for exposure rating. The JEM linked possible exposures to over 1,000 job title from 50 separate departments and 100 buildings. A categorical ranking was developed for exposure to seven exposures (Pyranol, TCE, benzene, other solvents, asbestos, resin systems, machining fluids) from 1901 to 1984 based upon on-site interviews with 18 long-term employees and knowledge of one of the study investigators who was an industrial hygienist. Two categories were used for potential TCE exposure: Level 1, duration of indirect exposure (TCE in workplace but does not work directly with TCE) and Level 2, duration of direct work with TCE, with the continuous exposure scores rescaled to the 97th percentile of controls (Salvan, 1990). Statistical analyses in Greenland et al. (1994) collapsed these two categories into a dichotomous ranking of no exposure or any exposure. In many instances, exposure levels were inaccurately estimated and some exposures were highly correlated (Salvan, 1990). Although of low correlation, TCE exposure was statistically significantly correlated with exposure to other solvents (r = 0.11), benzene (r = 0.22) and machining fluids (r = 0.28) (Salvan, 1990). Industrial hygiene monitoring data were not available before 1978 and limited production and purchase records did not extend far back in time (Salvan, 1990). TCE was used as a degreaser since the 1930s and discontinued between 1966 and 1975, depending on department. In all, fewer than 10% of jobs were identified as have TCE exposure potential, primarily through indirect exposure and not directly working with TCE. In fact, few subjects were identified with as working directly with TCE (Salvan, 1990). It is not surprising that exposure score distributions were highly skewed towards zero (Salvan, 1990). No details were provided on the protocol for processing the jobs in the work histories into job classifications.

Job history information was missing for roughly 35% of the cases and controls, particularly from subjects with earlier years of death. The highest percentage of missing information among cases was for leukemia deaths (43% of deaths) and the lowest percentage for rectal deaths (11%). Moreover, work history records did not exist for a large fraction of former employees, especially in the earlier years of death. Bias resulting from exposure misclassification is likely high due to the lack of industrial monitoring to support rankings and the inability of the JEM to account for changes in TCE exposure concentrations over time.

This study had a number of weaknesses with the likely result of dampening observed risks. Deaths were underestimated given nonpensioned employees are not included in the analysis; possible differences in exposure potential between pensioned and nonpensioned workers may introduce bias, particularly if a subject leaves work as a consequence of a precondition related to exposure, and would dampen observed associations (Robins, 1987). Misclassification bias related to exposure is highly likely given missing job history records for over one-third of deaths, mostly among deaths from the earlier study period, a period when TCE was used. Salvan (1990) noted "exposure measurements should be regarded as heavily nondifferentially misclassified relative to the true exposure does" and exposure associations with

outcomes will be underestimated. For TCE specifically, the development of exposure assignments in this study was insensitivity to define TCE exposures of the cohort-industrial hygiene data were not available for the time period of TCE use, exposure rates applied to a job-building-operation time matrix and may not reflect individual variation, and exposure ratings obtained by employee interview are subject to subjective assessment and measurement error. NRC (2006) also noted a low likelihood of exposure potential to subjects in this nested case-control study. Last, the lymphoma category includes Hodgkin lymphoma, in addition to traditional NHL forms such as reticulosarcoma and lymphosarcoma. Overall, the sensitivity of this study for evaluating cancer and TCE exposure is quite limited. The inability of this study to detect associations for two known human carcinogens, benzene and leukemia and asbestos and lung cancer, provides ancillary support for the study's low sensitivity and statistical power.

Greenland S, Salvan A, Wegman DH, Hallock MF, Smith TH. (1994). A case-control study of cancer mortality at the transformer-assembly facility. Int Arch Occup Environ Health 66:49–54.

Greenland S. (1992). A semi-Bayes approach to the analysis of correlated multiple associations with an application to an occupational cancer-mortality study. Stat Med 11:219–230.

Salvan A. (1990). Occupational exposure and cancer mortality at an electrical manufacturing plant: A case-control study. Ph.D. Dissertation, University of California, Los Angeles.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	The study was carried out to reevaluate an earlier observation from a PMR study of GE employment and excess leukemia and colorectal cancer risks.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Selection of cases and controls is not adequate because only deaths among pensioned workers were included in the analysis. Also, the size of the underlying cohort was not known and potential for selection bias is likely given cases and controls are drawn from a select population. Cases were identified from deaths among white males employed before 1984, who had died between 1969 and 1984, and for whom a job history record was available. Controls selected from noncancer deaths due to cardiovascular disease, circulatory disease, respiratory disease, injury, or other causes. Controls are not matched to cases on covariates such as age, or date of hire. In total, 2,653 subjects were identified as meeting criteria for inclusion in subject, either as a case or as a control. Job history records were available for 1,714 (512 cases, 1,202 controls) of these subjects (65%).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD, 8th revision. Lymphomas, Codes 200–202 and includes Hodgkin lymphoma.
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Dichotomous ranking, not exposed/exposed, for indirect and direct exposure potential. Most subjects identified with indirect TCE exposure. The company's job history record served as the source for exposure rating. The JEM linked possible exposures to over 1,000 job title from 50 separate departments and 100 buildings. Potential TCE exposure assigned to 10% of all job titles. The seven exposures were highly correlated. NRC (2006) noted a low likelihood of TCE exposure potential to subjects in this nested case-control study.
CATEGORY D: FOLLOW-UP (COHORT)	

More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	Record study.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	220 of 732 cases and 1,202 or 1,921 possible controls had job history records; job history records are missing for 35% of all possible cases and controls. Any potential TCE exposure prevalence among cases: Laryngeal, pharyngeal cancer, 38% Liver and biliary passages, 22% Pancreas, 45% Lung, 33% Bladder, 30% Kidney, 33% Lymphoma, 27% Leukemias, 36% Brain, 31% Control exposure prevalence, 34%.
Control for potential confounders in statistical analysis	Age and year of death. Other unidentified covariates are included if risk estimate is altered by >20%.
Statistical methods	Logistic regression with: (1) dichotomous exposure (Greenland et al., 1994); (2) epoch analysis (Salvan, 1990); and (3) empirical Bayes models (Greenland, 1992).
Exposure-response analysis presented in published paper	No.
Documentation of results	Adequate.

B.3.1.4.7. Sinks et al. (1992).

B.3.1.4.7.1. Author's abstract.

A physician's alert prompted us to investigate workers' can cancer risk at a paperboard printing manufacturer. We conducted a retrospective cohort mortality study of all 2,050 persons who had worked at the facility for more than 1 day, calculated standardized incidence ratios (SIRs) for bladder and renal cell cancer, and conducted a nested case-control study for renal cell cancer. Standardized mortality ratios (SMRs) from all causes [SMR = 1.0, 95% confidence interval (CI) = 0.9 – 1.2] and all cancers (SMR = 0.6, 95% CI = 0.3 – 1.0) were not greater than expected. One bladder cancer and one renal cell cancer were included in the mortality analysis. Six incident renal cell cancers were observed, however, compared with less than two renal cell cancers expected (SIR = 3.7, 95% CI = 1.4 – 8.1). Based on a nested case-control analysis, the risk of renal cell carcinoma was associated with overall length of employment but was not limited to any single department or work process. Although pigments containing congeners of dichlorobenzidine and o-toluidine had been used at the plant, environmental sampling could not confirm any current exposure. Several limitations and a potential selection bias limit the inferences that can be drawn.

B.3.1.4.7.2. Study description and comment.

Sinks et al. (1992) is the published report of analyses examining morbidity and mortality among employees at a James River Corporation plant in Newnan, Georgia. This plant manufactured paperboard (cardboard) packaging. The study was carried out as a NIOSH, Health Hazard Evaluation to investigate a possible cluster of urinary tract cancers and work in the plant's Finishing Department (NIOSH, 1992)\. A cohort of 2,050 white and nonwhite, male and female, subjects were identified from company personnel and death records, considered complete since 1-1-1957, and were follows for site-specific mortality and cancer morbidity to 6-30-1988. Records of an additionally 36 subjects were missing hire dates or birth dates, indicated employment duration of <1 day, and or employment outside the study period and these subjects were excluded from the analysis. This study suffers from missing information. A large percentage of personnel records did not identify a subject's race and these subjects were considered as white in statistical analyses. Additionally, vital status was unknown for approximately 10% of the cohort. Life-table analyses are based upon U.S. population age-, race-, sex-, calendar- and cause-specific mortality rates. Expected numbers of incident bladder and kidney cancers for white males were derived using white male age-specific bladder and renal cell incidence rates from the Atlanta-SEER registry for the years 1973–1977.

A nested case-control analysis of the incident renal carcinoma cases was also undertaken. This analysis is based on 6 RCC cases and 48 controls (1:8 matching) who were selected by risk set sampling of all employees born within 5 years of the case, the same sex as the case, and having attained the age at which the case was diagnosed or died if date of diagnosis was not known. A diagnosis of renal carcinoma was confirmed for four of the six cases through

pathologic examination. Both the nested case-control analysis and the life-table analyses of morbidity included a renal carcinoma case from the original cluster.

Exposures are poorly defined in this study assessing renal cancer among paper board printing workers. TCE was mentioned in material-safety data sheets for one or more materials used by the process but no information was provided regarding TCE usage and use by job title. It was not possible to assess the degree of contact with TCE or the printing inks which were identified as containing benzidine. Furthermore, the lack of monitoring data precludes evaluation of possible exposure intensity. This study is limited for assessing risks associated with exposures to TCE due to the large percentage of missing information and due to its exposure assessment approach.

Sinks T, Lushniak B, Haussler BJ, Sniezek J, Deng J-F, Roper P, Dill P, Coates R. (1992). Renal cell cancer among paperboard printing workers. Epidemiol 3:483–489.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	The purpose of the cohort and nested case-control investigations was to determine whether an excess of bladder or renal cell cancer had occurred among workers in a paperboard packaging plant and, if so, to determine whether it was associated with any specific exposure or work-related process.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Cohort analysis: 2,050 males and females employed at the plant between 1-1-1957 and 6-30-1988. External referents for mortality analysis were age-, sex-, race-, and calendar- cause specific mortality rates of the U.S. population. External referents for morbidity analysis were age-specific bladder and renal-cell cancer rate for white males from the Atlanta-SEER registry for the years 1973–1977. Nested case-control analysis: Cases were all subjects with renal cell cancer; eight non-RCC controls chosen from a risk set of all employees matched to case on date of birth (within 5 yrs), sex and attained age of cancer diagnosis or death, if diagnosis date unknown.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD revision in effect at the time of death; incident cases of RCC diagnoses confirmed with pathology reports for four of six cases.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Exposure in cohort analysis defined broadly at level of the plant and, in case-control study, department worked as identified on company's personnel.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	Yes, 10% of cohort with unknown vital status (n = 204). P-Y for these workers were censored at the date of last follow-up.
>50% cohort with full latency	18-yr average follow-up.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Department assignment based on company personnel records.
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	141 total deaths (7% of cohort had died by end of follow-up), 16 cancer deaths.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Mortality analysis: Age, race, sex, and calendar year. Morbidity analysis limited to white males: age. Nested case-control analysis: Risk set sampling matching controls to cases on date of birth (within 5 yrs), sex, and attained age at diagnosis.
Statistical methods	SIR. Conditional logistic regression used for nested case-control analysis.
Exposure-response analysis presented in published paper	No.
Documentation of results	Adequate.

B.3.1.4.8. Blair et al. (1989).

B.3.1.4.8.1. Author's abstract.

> Work history records and fitness reports were obtained for 1767 marine inspectors of the U.S. Coast Guard between 1942 and 1970 and for a comparison group of 1914 officers who had never been marine inspectors. Potential exposure to chemicals was assessed by one of the authors (RP), who is knowledgeable about marine inspection duties. Marine inspectors and noninspectors had a deficit in overall mortality compared to that expected from the general U.S. population (standardized mortality ratios [SMRs = 79 and 63, respectively]). Deficits occurred for most major causes of death, including infectious and parasitic diseases, digestive and urinary systems, and accidents. Marine inspectors had excesses of cirrhosis of the liver (SMR = 136) and motor vehicle accidents (SMR = 107, and cancers of the lymphatic and hematopoietic system (SMR = 157, whereas noninspectors had deficits for these causes of death. Comparison of mortality rates directly adjusted to the age distribution of the inspectors and noninspectors combined also demonstrated that mortality for these causes of death was greater among inspectors than noninspectors (directly adjusted ratio ratios of 190, 145, and 198) for cirrhosis of the liver, motor vehicle accidents, and lymphatic and hematopoietic system cancer, respectively. The SMRs rose with increasing probability of exposure to chemicals for motor vehicle accidents, cirrhosis of the liver, liver cancer, and leukemia, which suggests that contact with chemicals during inspection of merchant vessels may be involved in the development of these diseases among marine inspectors.

B.3.1.4.8.2. Study description and comment.

This cohort of 1,767 U.S. Coast Guard male officers and enlisted personnel performing marine inspection duties between 1942 and 1970 and 1,914 noninspectors matched to inspectors for registry, rank, and year that rank was achieved examined mortality as of January 1, 1980. Standardized mortality ratios compared the observed number of site-specific deaths among marine inspectors (n = 483, 27%) to that expected of the total U.S. white male population and to standardized mortality ratios of noninspectors (n = 369, 19%). The cohort was predominantly white (91%), race was unknown for the remaining 8% of subjects, considered in the statistical analysis as white, with a large percentage (69%) of the marine inspectors having >20-year employment duration. The minimum latent period was 10 years, calculated from the end date of cohort identification to the date of vital status ascertainment.

This study lacks exposure information on potential exposures of marine inspectors, who enter cargo tanks, void spaces, cofferdams, and pump rooms during inspections. TCE is identified in the paper as a possible exposure along with nine other agents. One authors acquainted with Coast Guard processes estimated the level of exposure to general chemical exposures during a marine inspection. A four-point rating scales was developed: nonexposed, person generally held administrative position; low exposed, assigned to staff with duties that occasionally required vessel inspections; moderate exposed, assigned to inspection duties that

did not regularly include hull structures, and regular inspection of hull structures in geographic areas where chemicals were not major items of cargo; and high exposed, assigned to subjects who performed hull inspections at ports were vessels transported chemicals. A cumulative exposure score was calculated by summing the product of the four-point rating scale and the duration in each job.

Overall, the exposure assessment in this study is insufficient for examining TCE exposure and cancer mortality. Furthermore, the few site-specific deaths among marine inspectors greatly limits statistical power.

Blair A, Haas T, Prosser R, Morrissette M, Blackman, Grauman D, van Dusen P, Morgan F. (1989). Mortality among United States Coast Guard marine Inspectors. Arch Environ Health 44:150–156.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	The purpose of the cohort study was to examine mortality patterns among Coast Guard marine inspectors. This study was not designed to examine specific exposures, including TCE.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	1,767 U.S. Coast Guard male officers and enlisted personnel performing marine inspections between 1942 and 1970 and 1,914 noninspectors matched to inspectors on registry, rank, and year that rank was achieved. External referents: age-specific mortality rates of the U.S. white male population and noninspectors.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICDA, 8th revision.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	TCE identified in paper as 1 of 10 potential exposures; however, no exposure assessment to TCE to individual subjects. Exposure in cohort analysis defined broadly at level of the plant and, in case-control study, department worked as identified on company's personnel. A cumulative exposure surrogate developed from duration in each job and a four-point rating scale: nonexposed, person generally held administrative position; low exposed, assigned to staff with duties that occasionally required vessel inspections; moderate exposed, assigned to inspection duties that did not regularly include hull structures, and regular inspection of hull structures in geographic areas where chemicals were not major items of cargo; and high exposed, assigned to subjects who performed hull inspections at ports were vessels transported chemicals.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	No
>50% cohort with full latency	Not reported; minimum latent period was 10 yrs.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	483 deaths among marine inspectors (27% of cohort), 103 cancer deaths.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Mortality analysis: Age, race, sex, and calendar year. Directly adjusted rate ratios compared cause-specific SMR of marine inspectors to that of noninspectors.
Statistical methods	SMR and RR.
Exposure-response analysis presented in published paper	Yes, using a ranked cumulative exposure surrogate.
Documentation of results	Adequate.

B.3.1.4.9. Shannon et al. (1988).

B.3.1.4.9.1. Author's abstract.

A historical prospective study of cancer in lamp manufacturing workers in one plant was conducted. All men and women who worked for a total of at least 6 months and were employed at some time between 1960 and 1975 were included. Work histories were abstracted and subjects were divided according to whether they had worked in the coiling and wire drawing area (CWD). Cancer morbidity from 1964 to 1982 was ascertained via the provincial registry, and was compared with the site-specific incidence in Ontario, adjusting for age, sex and calendar period. Of particular interest were primary breast and gynecological cancers in women.

The cancers of a priori concern were significantly increased in women in CWD, but not elsewhere in the plant. The excess was greatest in those with more than 5 yr exposure (in CWD) and more than 15 yr since first working in CWD, with eight cases of breast and gynecological cancers observed in this category compared with 2.67 expected. Only three cancers occurred in men in CWD. Environmental measurements had not been made in the past and little information was available on substances used in the 1940s and 1950s, the period when the women with the highest excess began employment. It is known that methylene chloride and trichloroethylene have been used, but not enough is known about the dates and patterns.

B.3.1.4.9.2. Study description and comments.

This cohort of 1,770 workers (1,044 females, 826 males) employed >6 months and working between 1960 and 1975 at a General Electric plant in Ontario, Canada, in the lamp manufacturing department identified cancer incidence cases from a regional cancer registry from 1964, the first date of high quality information, to 1982. Office workers were included in the study population. The study was carried out in response to previous reports of excess breast and gynecological cancer in women employed in the CWD area. SIRs compared the observed number of site-specific incident cancers to that expected of the Ontario population and supplied by the regional cancer registry. SIR estimates were calculated for all lamp department workers, and for two subgroups defined by job title, workers in the coil and wire-drawing area (CWD), and workers in all other areas. The cohort was successfully traced, with low rates of lost to follow-up (6% among CWD workers, 7% of all other workers). A total of 98 incident cancer cases were identified (58 in females, 40 in males) and over half of the incident cancers in females (n = 31) due to breast and gynecological cancers. The number of incident cancers is likely underestimated given the 4-year period between cohort identification and the first date of high quality information in the cancer registry. Additionally, cancer cases among workers who moved from the province would not be found in the registry, leading to underascertainment of cases. This is likely a small number given follow-up tracing identified 2% of workers had left the province.

This study lacks exposure information on individual study subjects. Exposures in CWD were of concern given previous reports. The study lacks exposure monitoring data and potential exposures in CWD area were identified using purchase records. A number of chemicals were identified including methylene chloride from 1959 onward and TCE, which records suggested may have been used beforehand.

Overall, the exposure assessment in this study is insufficient for examining TCE exposure and cancer mortality. The inclusion of office workers, who likely have low potential exposure, would introduce a downward bias. Furthermore, the few site-specific deaths among CWD and all other workers greatly limits statistical power.

Shannon HS, Haines T, Bernholz C, Julian JA, Verma DK, Jamieson E, Walsh C. (1988). Cancer morbidity in lamp manufacturing workers. Am J Ind Med 14:281–290.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This study was undertaken in response to previous report of apparent excess breast and gynecological cancers in women employed in the coil and wire drawing area of a lamp manufacturing plant.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Cohort analysis: 1,770 workers (1,044 females, 826 males) in the lamp manufacturing department of a GE plant in Ontario Province, Canada. External referents: Age-, sex-, and race-specific site-specific cancer incidence rates for Ontario Province population.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Not reported.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	This study does not assign TCE exposure to individual subjects. Job title and work in the CWD area used to assign exposure potential and chemical usage in CWD identified from purchase records. Methylene chloride used from 1959 onward, with one report from 1955 indicating TCE used as degreasing solvent.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	No, follow-up was incomplete for 6% of CWD workers and 7% for all other workers.
>50% cohort with full latency	Not reported
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	98 incident cancer cases

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, race, sex, and calendar year.
Statistical methods	SIR.
Exposure-response analysis presented in published paper	No.
Documentation of results	Adequate.

B.3.1.4.10. Shindell and Ulrich (1985).

B.3.1.4.10.1. Author's abstract.

> A prospective study was conducted of 2,646 employees who worked three months or more during the period January, 1957, through July, 1983, in a manufacturing plant that used trichloroethylene as a degreasing agent throughout the study period. Ninety-eight percent of the study cohort were traced; they accounted for 16,388 person-years of employment and 38,052 person-years of follow-up. Mortality experience was found to be generally more favorable than that of the comparable segment of the U.S. population over the same period of time. For the white male cohort there were fewer deaths than expected from heart disease, cancer, and trauma (standard mortality rate for all causes = 0.79, p less than .01). Reports by current and former employees of health problems requiring medical treatment showed that there were only one third as many persons with heart disease or hypertension as were reported in a comparable reference population studied over the past five years.

B.3.1.4.10.2. Study description and comment.

This study of 2, 546 current and former office and production employees at a manufacturing plant in northern Illinois compares broad groupings of cause-specific mortality between 1957 and 1983 to expected number of deaths based on U.S. population mortality rates for the period. The published paper lacks an assessment of TCE exposure other than noting TCE was used as a degreasing agent at the plant. No information is presented on quantity used, job titles with potential exposure, or likely exposure concentrations. Not all study subjects had the same potential for exposure and the inclusion of office workers who had a very low exposure potential decreased the study's detection sensitivity. Deaths were identified from company records or from direct or indirect contact with former employees or next-of-kin for subjects not known to the company to be deceased instead of using national-based registries such as Social Security listings or National Death Index for identifying vital status. There were few deaths in this cohort, a total of 141 among male and female subjects; vital status could not be ascertained for 52 subjects. The few numbers of cancer deaths (21 total) precluded examination of cause-specific cancer mortality. Overall, this study provides no information on TCE and cancer; it lacked exposure assessment to TCE and the few cancer deaths observed greatly limited its detection sensitivity.

Shindell S, Ulrich S. (1985). A cohort study of employees of a manufacturing plant using trichloroethylene. J Occup Med 27:577–579.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This study was designed to assess mortality patterns of office and production employees at an Illinois manufacturing plant.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	2,646 males and female workers employed from 1-1-1957 to 7-31-1983. Mortality rates of U.S. population used as referent. The paper lacks information on source for identifying cohort subjects and if company records were complete.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Not identified.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	The paper does not identify TCE usage other than as a degreaser. Conditions of exposure and jobs potentially exposure are not identified in paper. This study lacks an assessment of TCE exposure.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	2%.
>50% cohort with full latency	No information provided in paper.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	This study does not use standard approaches to verify deaths and vital status. Deaths are self-reported in response to contact by employer representative. 141 deaths (6%) were reported to employer, 9 deaths lacked a death certificate.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Sex and race.
Statistical methods	SMR.
Exposure-response analysis presented in published paper	No.
Documentation of results	The paper lacks discussion of process used to contact former employees to verify vital status and methods used to identify subjects.

B.3.1.4.11. Wilcosky et al. (1984).

B.3.1.4.11.1. Author's abstract.

> Some evidence suggests that solvent exposures to rubber industry workers may be associated with excess cancer mortality, but most studies of rubber workers lack information about specific chemical exposure. In one large rubber and tire-manufacturing plant, however, historical documents allowed a classification of jobs based on potential exposures to all solvents that were authorized for use in the plant. A case-control analysis of a 6,678 member cohort compared the solvent exposure histories of a 20% age-stratified random sample of the cohort with those of cohort members who died during 1964-1973 for stomach cancer, respiratory system cancer, prostate cancer, lymphosarcoma, or lymphatic leukemia. Of these cancers, only lymphosarcoma and lymphatic leukemia showed significant positive associations with any other potential solvents exposures. Lymphatic leukemia was especially strongly related to carbon tetrachloride (OR = 1.3, p< .0001) and carbon disulfide (OR = 8.9, p = .0003). Lymphosarcoma showed similar, but weaker, association with these two solvents. Benzene, a suspected carcinogen, was not significantly associated with any of the cancers.

B.3.1.4.11.2. Study description and comment.

Exposure was assessed in this nested case-control study of four site-specific cancers among rubber workers at a plant in Akron, Ohio through use of a JEM originally used to examine benzene specifically, but had the ability to assess 24 other solvents, including TCE, or solvent classes. Exposure was inferred using information on production operations and product specifications that indicated whether solvents were authorized for use during tire production, and by process area and calendar year. A subject's work history record was linked to the JEM to assign exposure potential to TCE. Overall, a low prevalence of TCE exposure, ranging from 9 to 20% for specific cancers was observed among cases.

The JEM was developed originally to assign exposure to benzene and other aromatic solvents in a nested case-control study of lymphocytic leukemia (Arp et al., 1983). Details of exposure potential to TCE are not described by either Arp et al. (1983) or Wilcosky et al. (1984). No data were provided on the frequency of exposure-related tasks. Without more information, it is not possible to determine the quality of some of the assignments. Similarly, the lack of industrial hygiene monitoring data precluded validation of the JEM.

Cases of respiratory, stomach and prostate cancers; lymphosarcoma and reticulum cell sarcoma; and lymphatic leukemia were identified from a previous study, which had observed associations with these site-specific cancers among a cohort of rubber workers employed at a large tire manufacturing plant in Akron, Ohio. Statistical power is low in this study, particularly for evaluation of lymphatic cancer for which there were 9 cases of lymphosarcoma and 10 cases of lymphatic leukemia. Controls were chosen from a 20% age-stratified random sample of the cohort. The published paper does not identify if subjects with other diseases associated with

solvents or TCE were excluded as controls. If no exclusion criteria were adopted, a bias may have been introduced which would dampen observed associations towards the null.

The few details provided in the paper on exposure assessment and JEM developments, few details of control selection, the low prevalence of TCE exposure and the few lymphatic cancer cases greatly limit the ability of this study for assessing risks associated with exposures to TCE.

Wilcosky TC, Checkoway H, Marshall EG, Tyroler HA. (1984). Cancer mortality and solvent exposure in the rubber industry. Am Ind Hyg Assoc J 45:809–811.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This study was identified as "exploratory" to examine several site-specific cancer and specific solvents, primarily benzene.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Underlying population at risk was a cohort of 6,678 male workers employed in the rubber industry in 1964. Cases are deaths due to respiratory, stomach and prostate cancers; lymphosarcoma; and lymphatic leukemia observed in the cohort analysis—30 deaths due to stomach cancer, 333 deaths from prostate cancer, 9 deaths from lymphosarcoma, and 10 deaths from lymphatic leukemia. Controls were a 20% age-stratified random sample of the cohort (exclusion criteria not identified in paper).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICDA, 8th revision.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Procedure to assign TCE and other solvent exposures based upon JEM developed originally to assess benzene and other solvent exposures (Arp et al., 1983). The JEM was linked to a detailed work history as identified from a subject's personnel record to assign TCE exposure potential. Details of JEM for TCE not well-described in Wilcosky et al. (1984). Multiple solvent exposures likely (McMichael et al., 1976).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Record study with exposure assignment using JEM and personnel records.
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	N/A

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	TCE exposure prevalence: Stomach cancer, five exposed cases (17% exposure prevalence) Prostate cancer, three exposed cases (9% exposure prevalence) Lymphosarcoma, three exposed cases (33% exposure prevalence) Lymphatic leukemia, two exposed cases (20% exposure prevalence). No information presented in paper on exposure prevalence among control subjects.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age.
Statistical methods	Not described in published paper.
Exposure-response analysis presented in published paper	No.
Documentation of results	Methods and analyses not fully described in published paper.

B.3.2. Case-Control Studies

B.3.2.1. Bladder Cancer Case-Control Studies

B.3.2.1.1. Pesch et al. (2000a)

B.3.2.1.1.1. Author's abstract.

BACKGROUND: This multicentre population-based case-control study was conducted to estimate the urothelial cancer risk for occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons (PAH), and chlorinated hydrocarbons besides other suspected risk factors. METHODS: In a population-based multicentre study, 1035 incident urothelial cancer cases and 4298 controls matched for region, sex, and age were interviewed between 1991 and 1995 for their occupational history and lifestyle habits. Exposure to the agents under study was self-assessed as well as expert-rated with two job-exposure matrices and a job task-exposure matrix. Conditional logistic regression was used to calculate smoking adjusted odds ratios (OR) and to control for study centre and age. RESULTS: Urothelial cancer risk following exposure to aromatic amines was only slightly elevated. Among males, substantial exposures to PAH as well as to chlorinated solvents and their corresponding occupational settings were associated with significantly elevated risks after adjustment for smoking (PAH exposure, assessed with a job-exposure matrix: OR = 1.6, 95% CI: 1.1-2.3, exposure to chlorinated solvents, assessed with a job task-exposure matrix: OR = 1.8, 95% CI: 1.2-2.6). Metal degreasing showed an elevated urothelial cancer risk among males (OR = 2.3, 95% CI: 1.4-3.8). In females also, exposure to chlorinated solvents indicated a urothelial cancer risk. Because of small numbers the risk evaluation for females should be treated with caution. CONCLUSIONS: Occupational exposure to aromatic amines could not be shown to be as strong a risk factor for urothelial carcinomas as in the past. A possible explanation for this finding is the reduction in exposure over the last 50 years. Our results strengthen the evidence that PAH may have a carcinogenic potential for the urothelium. Furthermore, our results indicate a urothelial cancer risk for the use of chlorinated solvents.

B.3.2.1.1.2. Study description and comment.

This multicenter study of urothelial (bladder, ureter, and renal pelvis) and RCC in Germany included the five regions (West Berlin, Bremen, Leverkusen, Halle, Jena), identified two case series from participating hospitals, 1,035 urothelial cancer cases and 935 RCC cases with a single population control series matched to cases by region, sex, and age (1:2 matching ratio to urothelial cancer cases and 1:4 matching ratio to RCC cases). Findings in Pesch et al. (2000a) are from analyses of urothelial cancer analysis and Pesch et al. (2000b) from analyses of RCC. In all, 1,035 (704 males, 331 females) urothelial carcinoma cases were interviewed face-to-face using with a structured questionnaire in the hospital within 6 months of first diagnosis and 4,298 randomly selected population controls were interviewed at home. Logistic regression models were fit separately to for males and females conditional on age (nine 5-year groupings), study region, and smoking, to examine occupational chemical exposures and urothelial carcinoma.

Two general JEMs, British and German, were used to assign exposures based on subjects' job histories reported in an interview. This approach was the same as that described for the RCC analysis of Pesch et al. (2000b). Researchers also asked about job tasks associated with exposure, such as metal degreasing and cleaning, and use of specific agents (organic solvents chlorinated solvents, including specific questions about carbon tetrachloride, TCE, and tetrachloroethylene) to evaluate TCE potential using a JTEM. A category of "any use of a solvent" mixes the large number with infrequent slight contact with the few noted earlier who have high intensity and prolonged contact. Analyses examining TCE exposure using either the JEM of JTEM assigned a cumulative TCE exposure index of none to low, medium high and substantial, defined as the product of exposure probability x intensity x duration with the following cutpoints: none to low, $<30^{th}$ percentile of cumulative exposure scores; medium, 30^{th}–$<60^{th}$ percentile; high, 60^{th}–$<90^{th}$ percentile; and, substantial, $\geq 90^{th}$ percentile. The use of the German JEM identified approximately twice as many cases with any potential TCE exposure (44%) compared to the JTEM (22%) and, in both cases, few cases identified with substantial exposure, 7% by JEM and 5% by JTEM. Pesch et al. (2000a) noted "exposure indices derived from an expert rating of job tasks can have a higher agent-specificity than indices derived from job titles." For this reason, the JTEM approach with consideration of job tasks is considered a more robust exposure metric for examining TCE exposure and urothelial carcinoma due to likely reduced potential for exposure misclassification compared to TCE assignment using only job history and title.

While this case-control study includes a region in the North Rhine-Westphalia region where the Arnsberg area is also located, several other regions are included as well, where the source of the TCE and chlorinated solvent exposures are expected as much less well defined. Few cases were identified as having substantial exposure to TCE and, as a result, most subjects identified as exposed to TCE probably had minimal contact, averaging concentrations of about 10 ppm or less (NRC, 2006).

Pesch B, Haerting H, Ranft U, Klimpel A, Oelschlagel B, Schill W, and the MURC Study Group. 2000a. Occupational risk factors for urothelial carcinoma: agent-specific results from a case-control study in Germany. Int J Epidemiol 29:238–247.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Yes, this case-control study was conducted to estimate urothelial carcinoma risk for exposure to occupational-related agents; chlorinated solvents including TCE were identified as exposures of a priori interest.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	1,035 urothelial (bladder, ureter, renal pelvis) carcinoma cases were identified from hospitals in a five-region area in Germany between 1991 and 1995. Cases were confirmed histologically. 4,298 population controls identified from local residency registries in the five-region area were frequency matched to cases by region, sex and age comprised the control series for both the urothelial carcinoma cases and the RCC cases, published as Pesch et al. (2000a). Participation rate: cases, 84%; controls, 71%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	No information in paper.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	A trained interviewer interviewed subjects using a structured questionnaire which covered occupational history and job title for all jobs held >1 yr, medical history, and personal information. Two general JEMs, British and German, were used to assign exposures based on subjects' job histories reported in an interview. Researchers also asked about job tasks associated with exposure, such as metal degreasing and cleaning, and use of specific agents (organic solvents chlorinated solvents, including specific questions about carbon tetrachloride, TCE, and tetrachloroethylene) and chemical-specific exposure were assigned using a JTEM. Exposure index for each subject is the sum over all jobs of duration × probability × intensity. A four category grouping was used in statistical analyses defined by exposure index distribution of controls: no-low; medium, 30th percentile; high, 60th percentile; substantial, 90th percentile.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Interviewers carried out face-to-face interview with all cases and controls. All cases were interviewed in the hospital within 6 months of initial diagnosis. All controls had home interviews.
Blinded interviewers	No, by nature of interview location.

CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	No, all cases and controls were alive at time of interview.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	JEM: 460 cases with TCE exposure index of medium or higher (44% exposure prevalence among cases), 71 cases with substantial exposure (7% exposure prevalence). JTEM: 157 cases with TCE exposure index of medium or higher (22% exposure prevalence among cases), and 36 males assigned substantial exposure (5% exposure prevalence). No information is presented in paper on control exposure prevalence.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, study center, and smoking.
Statistical methods	Conditional logistic regression.
Exposure-response analysis presented in published paper	Yes.
Documentation of results	Yes.

B.3.2.1.2. Siemiatycki et al. (1994), Siemiatycki (1991).

B.3.2.1.2.1. Author's abstract.

> A population-based case-control study of the associations between various cancers and occupational exposures was carried out in Montreal, Quebec, Canada. Between 1979 and 1986, 484 persons with pathologically confirmed cases of bladder cancer and 1,879 controls with cancers at other sites were interviewed, as was a series of 533 population controls. The job histories of these subjects were evaluated by a team of chemist/hygienists for evidence of exposure to a list of 294 workplace chemicals, and information on relevant non-occupational confounders was obtained. On the basis of results of preliminary analyses and literature review, 19 occupations, 11 industries, and 23 substances were selected for in-depth multivariate analysis. Logistic regression analyses were carried out to estimate the odds ratio between each of these occupational circumstances and bladder cancer. There was weak evidence that the following substances may be risk factors for bladder cancer: natural gas combustion products, aromatic amines, cadmium compounds, photographic products, acrylic fibers, polyethylene, titanium dioxide, and chlorine. Among the substances evaluated which showed no evidence of an association were benzo(a)pyrene, leather dust, and formaldehyde. Several occupations and industries were associated with bladder cancer, including motor vehicle drivers and textile dyers.

B.3.2.1.2.2. Study description and comment.

Siemiatycki et al. (1994) and Siemiatycki (1991) reported data from a case-control study of occupational exposures and bladder cancer conducted in Montreal, Quebec (Canada) and part of a larger study of 10 other site-specific cancers and occupational exposures. The investigators identified 617 newly diagnosed cases of primary bladder cancer, confirmed on the basis of histology reports, between 1979 and 1985; 484 of these participated in the study interview (78% participation). One control group (n = 1,295) consisted of patients with other forms of cancer (excluding lung and kidney cancer) recruited through the same study procedures and time period as the bladder cancer cases. A population-based control group (n = 533, 72% response), frequency matched by age strata, was drawn using electoral lists and random digit dialing. Face-to-face interviews were carried out with 82% of all cancer cases with telephone interview (10%) or mailed questionnaire (8%) for the remaining cases. Twenty percent of all case interviews were provided by proxy respondents. The occupational assessment consisted of a detailed description of each job held during the working lifetime, including the company, products, nature of work at site, job activities, and any additional information that could furnish clues about exposure from the interviews.

A team of industrial hygienists and chemists blinded to subject's disease status translated jobs into potential exposure to 294 substances with three dimensions (degree of confidence that exposure occurred, frequency of exposure, and concentration of exposure). Each of these exposure dimensions was categorized into none, any, or substantial exposure. Siemiatycki et al.

(1994) presents observations of analyses examining job title, occupation, and some chemical-specific exposures, but not TCE. Observations on TCE are found in the original report of Siemiatycki (1991). Any exposure to TCE was 2% among cases (n = 8) but <1% for substantial TCE exposure (n = 5); "substantial" is defined as ≥10 years of exposure for the period up to 5 years before diagnosis. Logistic regression models adjusted for age, ethnicity, SES, smoking, coffee consumption, and status of respondent (Siemiatycki et al., 1994) or Mantel-Henszel χ^2 stratified on age, family income, cigarette smoking, coffee, and respondent status (Siemiatycki, 1991). Odds ratios for TCE exposure are presented in Siemiatycki (1991) with 90% CIs.

The strengths of this study were the large number of incident cases, specific information about job duties for all jobs held, and a definitive diagnosis of bladder cancer. However, the use of the general population (rather than a known cohort of exposed workers) reduced the likelihood that subjects were exposed to TCE, resulting in relatively low statistical power for the analysis. The JEM, applied to the job information, was very broad since it was used to evaluate 294 chemicals.

Siemiatycki J, Dewar R, Nadon L, Gérin M. (1994). Occupational risk factors for bladder cancer: results from a case-control study in Montreal, Quebec, Canada. Am J Epidemiol 140:1061–1080.

Siemiatycki J. (1991). Risk Factors for Cancer in the Workplace. Baca Raton: CRC Press.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This population case-control study was designed to generate hypotheses on possible association between 11 site-specific cancers and occupational title or chemical exposures.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	617 bladder cancer cases were identified among male Montreal residents between 1979 and 1985 of which 484 were interviewed. 740 eligible male controls identified from the same source population using random digit dialing or electoral lists; 533 were interviewed. A second control series consisted of all other cancer controls excluding lung and kidney cancer cases. Participation rate: cases, 78%; population controls, 72%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-O, 188 (malignant neoplasm of bladder).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Unblinded interview using questionnaire sought information on complete job history with supplemental questionnaire for jobs of a priori interest (e.g., machinists, painters). Team of chemist and industrial hygienist assigned exposure using job title with a semiquantitative scale developed for 300 exposures, including TCE. For each exposure, a three-level ranking was used for concentration (low or background, medium, high) and frequency (percent of working time: low, 1–5%; medium, >5–30%; and high, >30%).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	82% of all cancer cases interviewed face-to-face by a trained interviewer, 10% telephone interview, and 8% mailed questionnaire. Cases interviews were conducted either at home or in the hospital; all population control interviews were conducted at home.
Blinded interviewers	Interviews were unblinded but exposure coding was carried out blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Yes, 20% of all cancer cases had proxy respondents.
CATEGORY G: SAMPLE SIZE	

Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	484 cases (78% response), 533 population controls (72%). Exposure prevalence: Any TCE exposure, 2% cases; Substantial TCE exposure (exposure for ≥10 yrs and up to 5 yrs before disease onset), <1% cases.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, income, index for cigarette smoking, coffee, and respondent status (Siemiatycki, 1991). Age, ethnicity, SES, smoking, coffee consumption, and status of respondent (Siemiatycki et al., 1994).
Statistical methods	Mantel-Haenszel (Siemiatycki, 1991). Logistic regression (Siemiatycki et al., 1994).
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.2. CNS Cancers Case-Control Studies

B.3.2.2.1. De Roos et al. (2001).

B.3.2.2.1.1. Author's abstract.

To evaluate the effects of parental occupational chemical exposures on incidence of neuroblastoma in offspring, the authors conducted a multicenter case-control study, using detailed exposure information that allowed examination of specific chemicals. Cases were 538 children aged 19 years who were newly diagnosed with confirmed neuroblastoma in 1992–1994 and were registered at any of 139 participating hospitals in the United States and Canada. One age-matched control for each of 504 cases was selected through random digit dialing. Self-reported exposures were reviewed by an industrial hygienist, and improbable exposures were reclassified. Effect estimates were calculated using unconditional logistic regression, adjusting for child's age and maternal demographic factors. Maternal exposures to most chemicals were not associated with neuroblastoma. Paternal exposures to hydrocarbons such as diesel fuel (odds ratio (OR) = 1.5; 95% confidence interval (CI): 0.8, 2.6), lacquer thinner (OR = 3.5; 95% CI: 1.6, 7.8), and turpentine (OR = 10.4; 95% CI: 2.4, 44.8) were associated with an increased incidence of neuroblastoma, as were exposures to wood dust (OR = 1.5; 95% CI: 0.8, 2.8) and solders (OR = 2.6; 95% CI: 0.9, 7.1). The detailed exposure information available in this study has provided additional clues about the role of parental occupation as a risk factor for neuroblastoma.

B.3.2.2.1.2. Study description and comment.

De Roos et al. (2001), a large multicenter case-control study of neuroblastoma in offspring and part of the pediatric collaborative clinical trial groups, the Children's Cancer Group and the pediatric Oncology Group, examined parental and maternal chemical exposures, focusing on solvent exposures, expanding the exposure assessment approach of Olshan et al. (1999) who examined parental occupational title among cases and controls. Neuroblastoma in patients under the age of 19 years was identified at 1 of 139 participating hospitals in the United States and Canada from 1992 to 1996. One population control per case s was using a telephone random digit dialing procedure and matched to the case on date of birth (+6 months for cases 3 years old or younger and +1 year for cases older than 3 years of age). A total of 741 cases and 708 controls were identified with direct interviews by telephone obtained from 538 case mothers (73% participation), 405 case fathers, 504 control mothers (71% participation), and 304 control fathers. Mothers served as proxy respondents for paternal information for 67 cases (12%) and 141 controls (28%).

A strength of the study was its use of industrial hygienist review of self-reported occupational exposure to increase specificity, reduce the number of false-positive information from self-reported exposures, and to minimize exposure misclassification bias. A parent was coded as having been exposed to individual chemicals or chemical group (halogenated hydrocarbons, paints, metals, etc.) if the industrial hygiene review determined probable exposure

in any job. Individual chemicals in the halogenated hydrocarbons grouping included carbon tetrachloride, chloroform, Freon, methylene chloride, perchloroethylene and TCE. Typical of population case-control studies, reported TCE exposure was uncommon among cases and controls. Only 6 case and 8 control mothers were identified by industrial hygiene review of occupational information to have probable exposure to halogenated hydrocarbons. The few numbers prevented examination of specific chemical exposure. Of the 538 cases and 504 controls, paternal exposure to TCE was self-reported for 22 cases (5%) and 12 controls (4%) were identified with paternal TCE exposure with fewer fathers with probable TCE exposure confirmed from industrial hygiene expert review, 9 cases (2%) and 7 controls (2%).

Overall, this study has a low sensitivity and statistical power for evaluating parental TCE exposure and neuroblastoma in offspring due to the low exposure prevalence to TCE. Although study investigators took effort to reduce false positive reporting, exposure misclassification bias may still be possible from false negative reporting of occupational information. As discussed by study authors, job duty information reported by parents was best used to infer exposure to chemical categories but was not detailed sufficiently to infer specific exposures. The study's reported risk estimates for TCE exposure are imprecise and do not provide support for or against an association.

De Roos AJ, Olshan AF, Teschke K, Poole Ch, Savitz DA, Blatt J, Bondy ML, Pollock BH. (2001). Parental occupational exposure to chemicals and incidence of neuroblastoma in offspring. Am J Epidemiol 154:106–114.

Olshan AF, De Roos AJ, Teschke K, Neglin JP, Stram DO, Pollock BH, Castleberry RP. (1999). Neuroblastoma and parental occupation. Cancer Causes Control 10:539–549.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This multicenter population case-control study examined parental chemical-specific occupational exposures using detailed exposure information.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	538 cases of neuroblastoma in children <19 yrs of age and diagnosed between 1992 and 1994 at any of 139 U.S. or Canadian hospitals participating in the Children's Cancer Group and Pediatric Oncology Group studies. 504 population controls were selected through random digit dialing and matched (1:1) with cases on date of birth. Controls could not be located for 34 cases. 538 of 741 potentially eligible cases (73% participation rate). 504 of 681 potentially eligible controls (74% participation rate).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Self-reported exposure to any of 65 chemicals, compounds, or broad categories was obtained from structured questionnaire. An industrial hygienist confirmed each respondent's self-reported chemical exposure responses. Exposures were not assigned using JEM. TCE exposure examined in analysis as separate exposure and as one of several chemicals in the broader category of "halogenated hydrocarbons."
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Telephone interview with mother and father of each case and control.
Blinded interviewers	Not identified in paper.
CATEGORY F: PROXY RESPONDENTS	

>10% proxy respondents	No proxy information on maternal exposure; direct interview with mother was obtained for 537 cases and 503 controls. Analysis of paternal chemical exposures did not include information on paternal exposure from proxy interviews.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	Self-reported TCE exposure: 22 cases (5% exposure prevalence) and 12 controls (4% exposure prevalence). IH-reviewed TCE exposure: 9 cases (2% exposure prevalence) and 7 controls (2% exposure prevalence).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Analyses of maternal and paternal occupational exposure each adjusted for child's age, maternal race, maternal age, and maternal education.
Statistical methods	Separate analyses are conducted for maternal and paternal exposure using logistic regression methods.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes, results are well documented.

B.3.2.2.2. Heineman et al. (1994).

B.3.2.2.2.1. Author's abstract.

Chlorinated aliphatic hydrocarbons (CAHs) were evaluated as potential risk factors for astrocytic brain tumors. Job-exposure matrices for six individual CAHs and for the general class of organic solvents were applied to data from a case-control study of brain cancer among white men. The matrices indicated whether the CAHs were likely to have been used in each industry and occupation by decade (1920–1980), and provided estimates of probably and intensity of exposure for "exposed" industries and occupations. Cumulative exposure indices were calculated for each subject.

Associations of astrocytic brain cancer were observed with likely exposure to carbon tetrachloride, methylene chloride, tetrachloroethylene, and trichloroethylene, but were strongest for methylene chloride. Exposure to chloroform or methyl chloroform showed little indication of an association with brain cancer. Risk of astrocytic brain tumors increase with probability and average intensity of exposure, and with duration of employment in jobs considered exposed to methylene chloride, but not with a cumulative exposure score. These trends could not be explained by exposures to the other solvents.

B.3.2.2.2.2. Study description and comment.

Heineman et al. (1994) studied the association between astrocytic brain cancer (ICD-9 codes 191, 192, 225, and 239.7) and occupational exposure to chlorinated aliphatic hydrocarbons. Cases were identified using death certificates from southern Louisiana, northern New Jersey, and the Philadelphia area. This analysis was limited to white males who died between 1978 and 1981. Controls were randomly selected from the death certificates of white males who died of causes other than brain tumors, cerebrovascular disease, epilepsy, suicide, and homicide. The controls were frequency matched to cases by age, year of death, and study area.

Next-of-kin were successfully located for interview for 654 cases and 612 controls, which represents 88 and 83% of the identified cases and controls, respectively. Interviews were completed for 483 cases (74%) and 386 controls (63%). There were 300 cases of astrocytic brain cancer (including astrocytoma, glioblastoma, mixed glioma with astrocytic cells). The ascertainment of type of cancer was based on review of hospital records, which included pathology reports for 229 cases and computerized tomography reports for 71 cases. After excluding 66 controls with a possible association between occupational exposure to chlorinated aliphatic hydrocarbons and cause of death (some types of cancer, cirrhosis of the liver), the final analytic sample consisted of 300 cases and 320 controls.

In the next-of-kin interviews, the work history included information about each job held since the case (or control) was 15 years old (job title, description of tasks, name and location of company, kinds of products, employment dates, and hours worked per week). Occupation and industry were coded based on four-digit Standard Industrial Classification and Standard Occupational Classification (Department of Commerce) codes. The investigators developed

matrices linked to jobs with likely exposure to six chlorinated aliphatic hydrocarbons (carbon tetrachloride, chloroform, methyl chloroform, methylene dichloride, tetrachloroethylene, and TCE), and to organic solvents (Gómez et al., 1994). This assessment was done blinded to case-control status. Exposure was defined as the probability of exposure to a substance (the highest probability score for that substance among all jobs), duration of employment in the exposed occupation and industry, specific exposure intensity categories, average intensity score (the three-level semiquantitative exposure concentration assigned to each job multiplied by duration of employment in the job, summed across all jobs), and cumulative exposure score (weighted sum of years in all exposed jobs with weights based on the square of exposure intensity [1, 2, 3] assigned to each job). Secular trends in the use of specific chemicals were considered in the assignment of exposure potential. Exposures were lagged 10 or 20 years to account for latency. Thus, this exposure assessment procedure was quite detailed.

The strengths of this case-control study include a large sample size, detailed work histories including information not just about usual or most recent industry and occupation, but also about tasks and products for all jobs held since age 15, and comprehensive exposure assessment and analysis along several different dimensions of exposure. The major limitation was the lack of direct exposure information and potential inaccuracy of the description of work histories that was obtained from next-of-kin interviews. The authors acknowledge this limitation in the report, and in response to a letter by Norman (1968) criticizing the methodology and interpretation of the study with respect to the observed association with methylene chloride, Heineman et al. (1994) noted that while the lack of direct exposure information must be interpreted cautiously, it does not invalidate the results. Differential recall bias between cases and controls was unlikely because work histories came from next-of-kin for both groups and, the industrial hygienists made their judgments blinded to disease status. Nondifferential misclassification is possible due to underreporting of job information by next of kin and would, on average, attenuate true associations.

Heineman EF, Cocco P, Gomez MR, Dosemeci M, Stewart PA, Hayes RB, Zahm SH, Thomas TL, Blair A. (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. Am J Ind Med 26:155–169.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Yes, study further examines six specific solvents including TCE in a previous study of brain cancer which reported association with electrical equipment production and repair.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Brain cancer deaths among white males in southern Louisiana, northern New Jersey, and Philadelphia, Pennsylvania, were identified using death certificates (n = 741). Controls were randomly selected (source not identified in paper) among other cause-specific deaths among white male residents of these areas and matched to cases by age, year of death and study area (n = 741). Participation rate, 483 of 741 (65% of cases with brain cancer); 386 of 741 controls (52%). Of the 483, 300 deaths were due to astrocytic brain cancer.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD, 9th revision, Codes 191, 192, 225, 239.7.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	The job-exposure-matrix of Gomez et al. (1994) was used to assign potential exposure to six solvents including TCE.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Interview with next-of-kin but paper does not identify whether telephone or face-to-face.
Blinded interviewers	Interviewer was blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Proxy information was obtained from 100% of cases and controls.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	TCE exposure prevalence: 128 cases (43%) and 125 controls (39%).

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Stratified analysis controlled for age, year of death and study area; employment in electronics-related occupations was included in addition in logistic regression analyses.
Statistical methods	Stratified analysis using 2 × 2 tables and logistic regression.
Exposure-response analysis presented in published paper	Yes.
Documentation of results	Yes.

B.3.2.3. Colon and Rectal Cancers Case-Control Studies

B.3.2.3.1. Goldberg et al. (2001), Siemiatycki (1991).

B.3.2.3.1.1. Author's abstract.

BACKGROUND: We conducted a population-based case-control study in Montreal, Canada, to explore associations between hundreds of occupational circumstances and several cancer sites, including colon. METHODS: We interviewed 497 male patients with a pathologically confirmed diagnosis of colon cancer, 1514 controls with cancers at other sites, and 533 population-based controls. Detailed job histories and relevant potential confounding variables were obtained, and the job histories were translated by a team of chemists and industrial hygienists into a history of occupational exposures. RESULTS: We found that there was reasonable evidence of associations for men employed in nine industry groups (adjusted odds ranging from 1.1 to 1.6 per a 10-year increase in duration of employment), and in 12 job groups (OR varying from 1.1 to 1.7). In addition, we found evidence of increased risks by increasing level of exposures to 21 occupational agents, including polystyrene (OR for "substantial" exposure (OR(subst) = 10.7), polyurethanes (OR(subst) = 8.4), coke dust (OR(subst) = 5.6), mineral oils (OR(subst) = 3.3), polyacrylates (OR(subst) = 2.8), cellulose nitrate (OR(subst) = 2.6), alkyds (OR(subst) = 2.5), inorganic insulation dust (OR(subst) = 2.3), plastic dusts (OR(subst) = 2.3), asbestos (OR(subst) = 2.1), mineral wool fibers (OR(subst) = 2.1), glass fibers (OR(subst) = 2.0), iron oxides (OR(subst) = 1.9), aliphatic ketones (OR(subst) = 1.9), benzene (OR(subst) = 1.9), xylene (OR(subst) = 1.9), inorganic acid solutions (OR(subst) = 1.8), waxes, polishes (OR(subst) = 1.8), mononuclear aromatic hydrocarbons (OR(subst) = 1.6), toluene (OR(subst) = 1.6), and diesel engine emissions (OR(subst) = 1.5). Not all of these effects are independent because some exposures occurred contemporaneously with others or because they referred to a group of substances. CONCLUSIONS: We have uncovered a number of occupational associations with colon cancer. For most of these agents, there are no published data to support or refute our observations. As there are few accepted risk factors for colon cancer, we suggest that new occupational and toxicologic studies be undertaken focusing on the more prevalent substances reported herein.

B.3.2.3.1.2. Study description and comment.

Goldberg et al. (2001), and Siemiatycki (1991) reported data from a case-control study of occupational exposures and colon cancer conducted in Montreal, Quebec (Canada) and part of a larger study of 10 other site-specific cancers and occupational exposures. The investigators identified 607 newly diagnosed cases of primary colon cancer (ICD9, 153), confirmed on the basis of histology reports, between 1979 and 1985; 497 of these participated in the study interview (81.9% participation). One control group (n = 1,514) consisted of patients with other forms of cancer (excluding cancers of the lung, peritoneum, esophagus, stomach, small intestine, rectum, liver and intrahepatic bile ducts, gallbladder and extrahepatic bile ducts and pancreas) recruited through the same study procedures and time period as the colon cancer cases. A population-based control group (n = 533, 72% response), frequency matched by age strata, was

drawn using electoral lists and random digit dialing. Face-to-face interviews were carried out with 82% of all cancer cases with telephone interview (10%) or mailed questionnaire (8%) for the remaining cases. Twenty percent of all case interviews were provided by proxy respondents. The occupational assessment consisted of a detailed description of each job held during the working lifetime, including the company, products, nature of work at site, job activities, and any additional information that could furnish clues about exposure from the interviews.

A team of industrial hygienists and chemists blinded to subject's disease status translated jobs into potential exposure to 294 substances with three dimensions (degree of confidence that exposure occurred, frequency of exposure, and concentration of exposure). Each of these exposure dimensions was categorized into none, any, or substantial exposure. Goldberg et al. (2001) presents observations of analyses examining industries, occupation, and some chemical-specific exposures, but not TCE. Observations on TCE are found in the original report of Siemiatycki (1991). Any exposure to TCE was 2% among cases (n = 12) and 1% for substantial TCE exposure (n = 7); "substantial" is defined as ≥10 years of exposure for the period up to 5 years before diagnosis.

Logistic regression models adjusted for a number of nonoccupational variables including age, ethnicity, birthplace, education, income, parent's occupation, smoking, alcohol consumption, tea consumption, respondent status, heating source and cooking source in childhood home, consumption of nonpublic water supply, and BMI (Goldberg et al., 2001) or Mantel-Haenszel χ^2 stratified on age, family income, cigarette smoking, coffee, ethnic origin, and beer consumption (Siemiatycki, 1991). ORs for TCE exposure are presented in Siemiatycki (1991) with 90% CIs.

The strengths of this study were the large number of incident cases, specific information about job duties for all jobs held, and a definitive diagnosis of colon cancer. However, the use of the general population (rather than a known cohort of exposed workers) reduced the likelihood that subjects were exposed to TCE, resulting in relatively low statistical power for the analysis. The JEM, applied to the job information, was very broad since it was used to evaluate 294 chemicals.

Goldberg MS, Parent M-E, Siemiatycki J, Desy M, Nadon L, Richardson L, Lakhani R, Lateille B, Valois M-F. (2001). A case-control study of the relationship between the risk of colon cancer in men and exposure to occupational agents. Am J Ind Med 39:5310–546.

Siemiatycki J. (1991). Risk Factors for Cancer in the Workplace. Baca Raton: CRC Press.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This population case-control study was designed to generate hypotheses on possible association between 11 site-specific cancers and occupational title or chemical exposures.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	607 colon cancer cases were identified among male Montreal residents between 1979 and 1985 of which 497 were interviewed. 740 eligible male controls identified from the same source population using random digit dialing or electoral lists; 533 were interviewed. A second control series consisted of all other cancer controls excluding lung peritoneum and other digestive cancers. Participation rate: cases, 81.9%; population controls, 72%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-9, 153 (malignant neoplasm of colon).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Unblinded interview using questionnaire sought information on complete job history with supplemental questionnaire for jobs of a priori interest (e.g., machinists, painters). Team of chemist and industrial hygienist assigned exposure using job title with a semiquantitative scale developed for 294 exposures, including TCE. For each exposure, a three-level ranking was used for concentration (low or background, medium, high) and frequency (percent of working time: low, 1–5%; medium, >5–30%; and high, >30%).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	82% of all cancer cases interviewed face-to-face by a trained interviewer, 10% telephone interview, and 8% mailed questionnaire. Cases interviews were conducted either at home or in the hospital; all population control interviews were conducted at home.
Blinded interviewers	Interviews were unblinded but exposure coding was carried out blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	

>10% proxy respondents	Yes, 20% of all cancer cases had proxy respondents.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	497 cases (81.9% response), 533 population controls (72%). Exposure prevalence: Any TCE exposure, 2% cases; substantial TCE exposure (exposure for ≥10 yrs and up to 5 yrs before disease onset), 1% cases.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, ethnicity, birthplace, education, income, parent's occupation, smoking, alcohol consumption, tea consumption, respondent status, heating source and cooking source in childhood home, consumption of nonpublic water supply, and BMI (Goldberg et al., 2001). Age, family income, cigarette smoking, coffee, ethnic origin, and beer consumption (Siemiatycki, 1991).
Statistical methods	Mantel-Haenszel (Siemiatycki, 1991). Logistic regression (Goldberg et al., 2001).
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.3.2. Dumas et al.(2000), Siemiatycki (1991).

B.3.2.3.2.1. Author's abstract.

In 1979, a hypothesis-generating, population-based case-control study was undertaken in Montreal, Canada, to explore the association between occupational exposure to 294 substances, 130 occupations and industries, and various cancers. Interviews were carried out with 3,630 histologically confirmed cancer cases, of whom 257 had rectal cancer, and with 533 population controls, to obtain detailed job history and data on potential confounders. The job history of each subject was evaluated by a team of chemists and hygienists and translated into occupational exposures. Logistic regression analyses adjusted for age, education, cigarette smoking, beer consumption, body mass index, and respondent status were performed using population controls and cancer controls, e.g., 1,295 subjects with cancers at sites other than the rectum, lung, colon, rectosigmoid junction, small intestine, and peritoneum. We present here the results based on cancer controls. The following substances showed some association with rectal cancer: rubber dust, rubber pyrolysis products, cotton dust, wool fibers, rayon fibers, a group of solvents (carbon tetrachloride, methylene chloride, trichloroethylene, acetone, aliphatic ketones, aliphatic esters, toluene, styrene), polychloroprene, glass fibers, formaldehyde, extenders, and ionizing radiation. The independent effect of many of these substances could not be disentangled as many were highly correlated with each other.

B.3.2.3.2.2. Study description and comment.

Dumas et al. (2000) and Siemiatycki (1991) reported data from a case-control study of occupational exposures and rectal cancer conducted in Montreal, Quebec (Canada) and part of a larger study of 10 other site-specific cancers and occupational exposures. The investigators identified 304 newly diagnosed cases of primary rectal cancers, confirmed on the basis of histology reports, between 1979 and 1985; 257 of these participated in the study interview (84.5% response). One control group (n = 1,295) consisted of patients with other forms of cancer (excluding lung cancer and other intestinal cancers) recruited through the same study procedures and time period as the rectal cancer cases. A population-based control group (n = 533), frequency-matched by age strata, was drawn using electoral lists and random digit dialing (72% response). The occupational assessment consisted of a detailed description of each job held during the working lifetime, including the company, products, nature of work at site, job activities, and any additional information that could furnish clues about exposure from the interviews. The percentage of proxy respondents was 15.2% for cases, 19.7% for other cancer controls, and 12.6% for the population controls.

A team of industrial hygienists and chemists blinded to subject's disease status translated jobs into potential exposure to 294 substances with three dimensions (degree of confidence that exposure occurred, frequency of exposure, and concentration of exposure). Each of these exposure dimensions was categorized into none, any, or substantial exposure. Any exposure to

TCE was 5% among cases (n = 12) and 1% for substantial TCE exposure (n = 3); "substantial" is defined as ≥10 years of exposure for the period up to 5 years before diagnosis.

Logistic regression models adjusted for age, education, respondent status, cigarette smoking, beer consumption and BMI (Dumas et al., 2000) or Mantel-Haenszel χ^2 stratified on age, family income, cigarette smoking, coffee, ethnic origin, and beer consumption (Siemiatycki, 1991). Dumas et al. (2000) presents observations of analyses examining industries, occupation, and some chemical-specific exposures, including TCE. Observations on TCE from Mantel-Haenszel analyses are found in the original report of Siemiatycki (1991). ORs for TCE exposure are presented in Siemiatycki (1991) with 90% CIs and 95% CIs in Dumas et al. (2000).

The strengths of this study were the large number of incident cases, specific information about job duties for all jobs held, and a definitive diagnosis of rectal cancer. However, the use of the general population (rather than a known cohort of exposed workers) reduced the likelihood that subjects were exposed to TCE, resulting in relatively low statistical power for the analysis. The JEM, applied to the job information, was very broad since it was used to evaluate 294 chemicals.

Dumas S, Parent M-E, Siemiatycki J, Brisson J. (2000). Rectal cancer and occupational risk factors: a hypothesis-generating, exposure-based case-control study. Int J Cancer 87:874–879.

Siemitycki J. (1991). Risk Factors for Cancer in the Workplace. Boca Raton: CRC Press.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This population case-control study was designed to generate hypotheses on possible association between 11 site-specific cancers and occupational title or chemical exposures.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	304 rectal cancer cases were identified among male Montreal residents between 1979 and 1985 of which 294 were interviewed. 740 eligible male controls identified from the same source population using random digit dialing or electoral lists; 533 were interviewed. A second control series consisted of all other cancer controls excluding lung and other intestinal cancer cases. Participation rate: cases, 84.5%; population controls, 72%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-O, 154 (malignant neoplasm of rectum, rectosigmoid junction and anus).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Unblinded interview using questionnaire sought information on complete job history with supplemental questionnaire for jobs of a priori interest (e.g., machinists, painters). Team of chemist and industrial hygienist assigned exposure using job title with a semiquantitative scale developed for 294 exposures, including TCE. For each exposure, a three-level ranking was used for concentration (low or background, medium, high) and frequency (percent of working time: low, 1–5%; medium, >5–30%; and high, >30%).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	82% of all cancer cases interviewed face to face by a trained interviewer, 10% telephone interview, and 8% mailed questionnaire. Cases interviews were conducted either at home or in the hospital; all population control interviews were conducted at home.
Blinded interviewers	Interviews were unblinded but exposure coding was carried out blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Yes, 20% of all cancer cases had proxy respondents.
CATEGORY G: SAMPLE SIZE	

Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	294 cases (78% response), 533 population controls (72% response). Exposure prevalence: Any TCE exposure, 5% cases; substantial TCE exposure (exposure for ≥10 yrs and up to 5 yrs before disease onset), 1% cases.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, education, respondent status, cigarette smoking, beer consumption and BMI (Dumas et al., 2000). Age, family income, cigarette smoking, coffee, ethnic origin, and beer consumption (Siemiatycki, 1991).
Statistical methods	Mantel-Haenszel (Siemiatycki, 1991). Logistic regression (Dumas et al., 2000).
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.3.3. Fredriksson et al. (1989).

B.3.2.3.3.1. Author's abstract.

A case-control study on colon cancer was conducted encompassing 329 cases and 658 controls. Occupations and various exposures were assessed by questionnaires. A decreased risk was found in persons with physically active occupations. This effect was most pronounced in colon descendens and sigmoideum with an odds ratio (OR) of 0.49 whereas no reduced risk was found for right-sided colon cancer. Regarding specific jobs, reduced ORs were found for agricultural, forestry, and saw mill workers and increased OR for railway employees. High-grade exposure to asbestos or to organic solvents gave a two-fold increased risk. Regarding exposure to trichloroethylene in general, a slightly increased risk was found whereas such exposure among dry cleaners gave a 7-fold increase of the risk.

B.3.2.3.3.2. Study description and comment.

Fredriksson et al. (1989) reported data from a population case-control study of occupational and nonoccupational exposures and rectal cancer conducted in Ureå, Sweden. The investigators identified 329 diagnosed cases of rectal cancers (ICD 8, 153), between 1980 and 1983, confirmed on the basis of histology reports and alive at the time of data collect between 1984 and 1986; 302 (165 males and 165 females) of these participated in the study interview (92% response). A population-based control group (n = 658), matched by a 1:2 ratio to cases on age sex and county residence, was drawn using the Swedish National Population Register list; 623 (306 males and 317 females) returned mailed questionnaires and participated in the study (95% response).

The occupational assessment consisted of a detailed description of each job held during the working lifetime, including details on specific occupations and exposures. Occupation information was provided directly from each case and control given the study's eligibility requirement of being alive at the time of data collection. A team of experts independently classified three exposures of interest (asbestos, organic solvents, and impregnating agents) into two categories, low grade exposure and high grade exposure and other chemical-specific exposures, including TCE, as either "exposed" or "unexposed." Fredriksson et al. (1989) do not define these categories nor do they provide information on exposure potential, frequency of exposure, or concentration of exposure. No information is provided whether experts were blinded as to disease status.

Statistical analysis examining occupation and agent-specific exposures was carried out using Mantel-Haenszel χ^2 stratified on age, sex, and an index of physical activity. Odds ratios associated with specific chemical exposure are presented with their 95% CIs.

The strengths of this study were its specific information about job duties for all jobs held and a definitive diagnosis of rectal cancer. However, the study's assignment of exposure

potential from information using mailed questionnaires is considered inferior to information obtained directly from trained interviewers and expert assessment because of greater uncertainty and misclassification (Fritschi et al., 1996). The degree of potential exposure misclassification bias in this population case-control study of colon cancer is not known. Furthermore, exposure prevalence to TCE appears low, as judged by the wide CI around the OR. This study is considered as having decreased sensitivity for examining colon cancer and TCE given the apparent lower exposure prevalence and likely exposure misclassification bias associated with mailed questionnaire information.

Fredriksson M, Bengtsson N-O, Hardell L, Axelson O. (1989). Colon cancer, physical activity, and occupational exposure. A case-control study. Cancer 63:1838–1842.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Abstract—to evaluate occupational and nonoccupational exposures as risk factors for colon cancer.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	302 (165 males and 165 females) cases participated in study out of 329 eligible cases reported to the Swedish Cancer Registry between 1980 and 1983, among resident of Umeå, Sweden, alive at time of data collection 1984 and 1986, and with histological-confirmed diagnosis of colon cancer. 623 (306 males and 317 females) identified from Swedish Population Registry and matched for age, sex, and county of residence. Participation rate: cases, 92%; population controls, 95%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-8, 153 (malignant neoplasm of large intestine, except rectum).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Self-reported information on occupational exposure as obtained from a mailed questionnaire to study participants. Questionnaire sought information on complete working history, other exposures, and dietary habits. Procedure for assigning chemical exposures from job title information not described in paper.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Mailed questionnaire.
Blinded interviewers	No information in published paper.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	No proxy respondents, all cases and controls alive at time of data collection.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	302 cases (92% response), 623 population controls (95% response). Exposure prevalence not calculated, published paper lacks number of TCE exposed cases and controls.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Yes, age, sex, and index of physical activity.
Statistical methods	Mantel-Haenszel.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.4. Esophageal Cancer Case-Control Studies

B.3.2.4.1. Parent et al. (2000a), Siemiatycki (1991).

B.3.2.4.1.1. Parent et al. (2000b) abstract.

OBJECTIVES: To describe the relation between oesophageal cancer and many occupational circumstances with data from a population based case-control study. METHODS: Cases were 99 histologically confirmed incident cases of cancer of the oesophagus, 63 of which were squamous cell carcinomas. Various control groups were available; for the present analysis a group was used that comprised 533 population controls and 533 patients with other types of cancer. Detailed job histories were elicited from all subjects and were translated by a team of chemists and hygienists for evidence of exposure to 294 occupational agents. Based on preliminary results and a review of literature, a set of 35 occupational agents and 19 occupations and industry titles were selected for this analysis. Logistic regression analyses were adjusted for age, birthplace, education, respondent (self or proxy), smoking, alcohol, and beta-carotene intake. RESULTS: Sulphuric acid and carbon black showed the strongest evidence of an association with oesophageal cancer, particularly squamous cell carcinoma. Other substances showed excess risks, but the evidence was more equivocal-namely chrysotile asbestos, alumina, mineral spirits, toluene, synthetic adhesives, other paints and varnishes, iron compounds, and mild steel dust. There was considerable overlap in occupational exposure patterns and results for some of these substances may be mutually confounded. None of the occupations or industry titles showed a clear excess risk; the strongest hints were for warehouse workers, food services workers, and workers from the miscellaneous food industry. CONCLUSIONS: The data provide some support for an association between oesophageal cancer and a handful of occupational exposures, particularly sulphuric acid and carbon black. Many of the associations found have never been examined before and warrant further investigation.

B.3.2.4.1.2. Study description and comment.

Parent et al. (2000b) and Siemiatycki (1991) reported data from a case-control study of occupational exposures and esophageal cancer conducted in Montreal, Quebec (Canada) and part of a larger study of 10 other site-specific cancers and occupational exposures. The investigators identified 129 newly diagnosed cases of primary esophageal cancers, confirmed on the basis of histology reports, between 1979 and 1985; 99 of these participated in the study interview (76.7% response). One control group consisted of patients with other forms of cancer recruited through the same study procedures and time period as the esophageal cancer cases. A population-based control group (n = 533), frequency-matched by age strata, was drawn using electoral lists and random digit dialing (72% response). Face-to-face interviews were carried out with 82% of all cancer cases with telephone interview (10%) or mailed questionnaire (8%) for the remaining cases. Twenty percent of all case interviews were provided by proxy respondents.

The occupational assessment consisted of a detailed description of each job held during the working lifetime, including the company, products, nature of work at site, job activities, and

any additional information that could furnish clues about exposure from the interviews. A team of industrial hygienists and chemists blinded to subject's disease status translated jobs into potential exposure to 294 substances with three dimensions (degree of confidence that exposure occurred, frequency of exposure, and concentration of exposure). Each of these exposure dimensions was categorized into none, any, or substantial exposure. Any exposure to TCE was 1% among cases (n = 1) and 1% for substantial TCE exposure (n = 1); "substantial" is defined as ≥10 years of exposure for the period up to 5 years before diagnosis.

Logistic regression models adjusted for age, education, respondent status, birthplace, cigarette smoking, beer consumption spirits consumption and beta-carotene intake (Parent et al., 2000a) or Mantel-Haenszel χ^2 stratified on age, family income, cigarette smoking, coffee, and an index for alcohol consumption (Siemiatycki, 1991). Parent et al. (2000b) presents observations of analyses examining industries, occupation, and some chemical-specific exposures, including solvents, but not TCE. Observations on TCE from Mantel-Haenszel analyses are found in the original report of Siemiatycki (1991). Odds ratios for TCE exposure are presented in Siemiatycki (1991) with 90% CIs and 95% CIs in Parent et al. (2000b).

The strengths of this study were the large number of incident cases, specific information about job duties for all jobs held, and a definitive diagnosis of esophageal cancer. However, the use of the general population (rather than a known cohort of exposed workers) reduced the likelihood that subjects were exposed to TCE, resulting in relatively low statistical power for the analysis. The JEM, applied to the job information, was very broad since it was used to evaluate 294 chemicals.

Parent M-E, Siemiatycki J, Fritschi L. (2000b). Workplace exposures and oesophageal cancer. Occup Environ Med 57:325–334.

Siemitycki J. (1991). Risk Factors for Cancer in the Workplace. Boca Raton: CRC Press.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This population case-control study was designed to generate hypotheses on possible association between 11 site-specific cancers and occupational title or chemical exposures.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	129 esophageal cancer cases were identified among male Montreal residents between 1979 and 1985 of which 99 were interviewed. 740 eligible male controls identified from the same source population using random digit dialing or electoral lists; 533 were interviewed. A second control series consisted of all other cancer controls. Participation rate: cases, 76.7%; population controls, 72%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-O, 150 (malignant neoplasm of esophagus).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Unblinded interview using questionnaire sought information on complete job history with supplemental questionnaire for jobs of a priori interest (e.g., machinists, painters). Team of chemist and industrial hygienist assigned exposure using job title with a semiquantitative scale developed for 294 exposures, including TCE. For each exposure, a three-level ranking was used for concentration (low or background, medium, high) and frequency (percent of working time: low, 1–5%; medium, >5–30%; and high, >30%).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	82% of all cancer cases interviewed face-to-face by a trained interviewer, 10% telephone interview, and 8% mailed questionnaire. Cases interviews were conducted either at home or in the hospital; all population control interviews were conducted at home.
Blinded interviewers	Interviews were unblinded but exposure coding was carried out blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Yes, 20% of all cancer cases had proxy respondents.

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	99 cases (76.7% response), 533 population controls (72%). Exposure prevalence: Any TCE exposure, 1% cases; substantial TCE exposure (exposure for ≥10 yrs and up to 5 yrs before disease onset), 1% cases.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, education, respondent status, birthplace, cigarette smoking, beer consumption spirits consumption, and beta-carotene intake (Parent et al., 2000b). Age, family income, cigarette smoking, and index for alcohol consumption (Siemiatycki, 1991).
Statistical methods	Mantel-Haenszel (Siemiatycki, 1991). Logistic regression (Parent et al., 2000b).
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.5. Liver Cancer Case-Control Studies

B.3.2.5.1. Lee et al. (2003).

B.3.2.5.1.1. Author's abstract.

Aims: To investigate the association between cancer mortality risk and exposure to chlorinated hydrocarbons in groundwater of a downstream community near a contaminated site. Methods: Death certificates inclusive for the years 1966–97 were collected from two villages in the vicinity of an electronics factory operated between 1970 and 1992. These two villages were classified into the downstream (exposed) village and the upstream (unexposed) according to groundwater flow direction. Exposure classification was validated by the contaminant levels in 49 residential wells measured with gas chromatography/mass spectrometry. Mortality odds ratios (MORs) for cancer were calculated with cardiovascular-cerebrovascular diseases as the reference diseases. Multiple logistic regressions were performed to estimate the effects of exposure and period after adjustment for age. Results: Increased MORs were observed among males for all cancer, and liver cancer for the periods after 10 years of latency, namely, 1980–89, and 1990–97. Adjusted MOR for male liver cancer was 2.57 (95% confidence interval 1.21 to 5.46) with a significant linear trend for the period effect. Conclusion: The results suggest a link between exposure to chlorinated hydrocarbons and male liver cancer risk. However, the conclusion is limited by lack of individual information on groundwater exposure and potential confounding factors.

B.3.2.5.1.2. Study description and comment.

Exposure potential to chlorinated hydrocarbons was assigned in this community case-control study of liver cancer in males >30 years of age using residency as coded on death certificates obtained from local household registration offices. No information is available to assess the completeness of death reporting to the local registration office. Of the 1,333 deaths between 1966 and 1997 in two villages surrounding a hazardous waste site, an electronics factory operating between 1970 and 1992 in Taoyuan, Taiwan,[3] 266 cancer deaths were identified; 53 liver cancer deaths, 39 stomach cancer deaths, 26 colorectal deaths, and 41 lung cancer deaths. Controls were identified from 344 deaths due to cardiovascular and cerebrovascular diseases, without arrhythmia; 286 were included in the statistical analysis. Residents from a village north and northeast of the plant were considered exposed and residents living south considered unexposed to chlorinated hydrocarbons. Statistical analyses are limited to Mantel-Haenszel χ^2 approaches stratified by sex and age and, for male cases and controls, logistic regression with age as a covariate. Socioeconomic characteristics were similar between residents of the two villages (Wang, 2004). The study does not include control for potential confounding from hepatitis virus; high rates of hepatitis B and C are endemic to Taiwan and northern Taiwan, the location of this study, has a high prevalence of hepatitis C virus infection

[3]The factory's workers were subjects in the cohort studies of Chang et al. (2003, 2005) and Sung et al. (2007, 2008).

(Lee et al., 2003). Confounding would be introduced if the prevalence of hepatitis C differed between the two villages.

Exposure assessment is quite limited and misclassification bias likely high using residence address as recorded on the death certificate as a surrogate for consumption of contaminated drinking water. The paper not only lacks information on intensity and duration of hydrocarbon exposures to individual cases and controls, but no information is available on an estimate of the amount of TCE ingested. Information on residence length, population mobility, and chemical usage at the plant are lacking. Similarly, well water monitoring is sparse, based on seven chlorinated hydrocarbons monitored over a 7-month period between 1999 and 2000 in 69 groundwater samples from 44 wells to the north and northeast, or downstream from the factory, and in 5 groundwater samples from 2 wells to the south or upstream from the factory. Monitoring from other time periods is lacking with no information available to judge if current monitoring are representative of past concentrations. Median concentrations (µg/L or ppb) and ranges (µg/L or ppb) for these seven chemicals are identified in the table below. Highest concentration of contaminants was from wells closest to the factory boundary with concentrations detected at or close to maximum contaminant levels in wells located 0.5 mile (1,000 meters) away. A municipal system supplied water to upstream village residents (start date not identified); however, wells served as source for water to the north or downstream village residents. The exposure assessment does not consider potential occupational exposure.

Chemical	Downstream		Upstream	
	Median	Range	Median	Range
TCE	28	ND–1,791	0.1	0.1–0.1
Perchloroethylene	3	ND–5,228	0.05	ND–0.1
cis-1,2-DCE	3	ND–1,376	ND	ND
1,1-Dichloroethane	2	ND–228	0.05	ND–0.1
1,1-DCE	1	ND–1,240	ND	ND
Vinyl chloride	0.003	ND–72	ND	ND

ND = not detected

Lee L J-H, Chung C-W, Ma Y-C, Wang G-S, Chen P-C, Hwang Y-H, Wang J-D. (2003). Increased mortality odds ratio of male liver cancer in a community contaminated by chlorinated hydrocarbons in groundwater. Occup Environ Med 60:364–369.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Study hypothesis of investigating cancer mortality risk and exposure to chlorinated hydrocarbons in groundwater.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Deaths in 1966–1997 identified from local housing registration offices among residents in two villages were the source for case and control series. The two villages were north (contaminated community) and south (unexposed) of an electronics factory declared as a hazardous waste site. No information if all death among residents were reported to registration office. Cases: 53 liver cancer deaths in males and females, 51 included in statistical analysis (96%); stomach cancer deaths (n = 39), colon and rectum deaths (n = 26), and lung cancer deaths (n = 41). Paper does not present numbers of stomach, colo-rectal, and lung cancer deaths used in statistical analyses. Controls: 344 cardiovascular-cerebrovascular CV-CB disease deaths, 286 CV-CB deaths without arrhythmia included in statistical analysis (83%).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-9.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Exposure potential to chlorinated hydrocarbons in drinking water was inferred from residence address on deaths certificate.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	NA, Record based information.
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	NA

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	Liver cancer case exposure prevalence [downstream village resident], 53% (n = 24 males, n = 4 females). Control exposure prevalence [upstream village resident], 30% (n = 44 males, n = 41 females).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Sex and age (categorical). No control for potential confounding due to hepatitis virus (for liver cancer) or smoking (for lung cancer analyses).
Statistical methods	Mantel-Haenszel χ^2. Multiple logistic regressions (males deaths only).
Exposure-response analysis presented in published paper	No, MORs presented by time period.
Documentation of results	Inadequate, the paper does not discuss mobility patterns of residents, percentage of population who may have moved from area, or completeness of death ascertainment using certificates obtained from local housing registration offices.

MOR = mortality odds ratio

B.3.2.6. Lymphoma Case-Control Studies

B.3.2.6.1. Gold et al. (2011), Purdue et al. (2011)

B.3.2.6.1.1. Gold et al. (2011) abstract.

Objectives Few studies have examined whether exposure to chlorinated solvents is associated with multiple myeloma. We evaluated associations between multiple myeloma and occupational exposure to six chlorinated solvents: 1,1,1-trichloroethane, trichloroethylene (TCE), methylene chloride (DCM), perchloroethylene, carbon tetrachloride and chloroform. **Methods** In-person interviews obtained occupational histories and information on jobs with likely solvent exposure. We assigned exposure metrics of probability, frequency, intensity and confidence using job-exposure matrices modified by job-specific questionnaire information. We used logistic regression to estimate ORs and 95% CIs for associations between multiple myeloma and ever exposure to each, and any, chlorinated solvent and analysed whether associations varied by duration and cumulative exposure. We also considered all occupations that were given the lowest confidence scores as unexposed and repeated all analyses. **Results** Risk of multiple myeloma was elevated for subjects ever exposed to 1,1,1-trichloroethane (OR (95% CI): 1.8 (1.1 to 2.9)). Ever exposure to TCE or DCM also entailed elevated, but not statistically significant, risks of multiple myeloma; these became statistically significant when occupations with low confidence scores were considered unexposed (TCE: 1.7 (1.0 to 2.7); DCM: 2.0 (1.2 to 3.2)). Increasing cumulative exposure to perchloroethylene was also associated with increasing multiple myeloma risk. We observed non-significantly increased multiple myeloma risks with exposure to chloroform; however, few subjects were exposed. **Conclusions** Evidence from this relatively large case-control study suggests that exposures to certain chlorinated solvents may be associated with increased incidence of multiple myeloma; however, the study is limited by relatively low participation (52%) among controls.

B.3.2.6.1.2. Purdue et al. (2011) abstract.

BACKGROUND: Previous epidemiologic findings suggest an association between exposure to trichloroethylene (TCE), a chlorinated solvent primarily used for vapor degreasing of metal parts, and non-Hodgkin lymphoma (NHL). OBJECTIVES: We investigated the association between occupational TCE exposure and NHL within a population-based case-control study using detailed exposure assessment methods. METHODS: Cases (n = 1,189; 76% participation rate) and controls (n = 982; 52% participation rate) provided information on their occupational histories and, for selected occupations, on possible workplace exposure to TCE using job-specific interview modules. An industrial hygienist assessed potential TCE exposure based on this information and a review of the TCE industrial hygiene literature. We computed odds ratios (ORs) and 95% confidence intervals (CIs) relating NHL and different metrics of estimated TCE exposure, categorized using tertiles among exposed controls, with unexposed subjects as the reference group. RESULTS: We observed associations with NHL for the highest tertiles of estimated average weekly exposure (23 exposed cases; OR = 2.5; 95% CI, 1.1–6.1) and cumulative exposure (24 exposed cases; OR =

2.3; 95% CI, 1.0-5.0) to TCE. Tests for trend with these metrics surpassed or approached statistical significance (p-value for trend = 0.02 and 0.08, respectively); however, we did not observe dose–response relationships across the exposure levels. Overall, neither duration nor intensity of exposure was associated with NHL, although we observed an association with the lowest tertile of exposure duration (OR = 2.1; 95% CI, 1.0-4.7). CONCLUSIONS: Our findings offer additional support for an association between high levels of exposure to TCE and increased risk of NHL. However, we cannot rule out the possibility of confounding from other chlorinated solvents used for vapor degreasing and note that our exposure assessment methods have not been validated.

B.3.2.6.1.3. Gold et al. (2011) study description and comment.

The population case-control study of multiple myeloma in men and women who were residents of two SEER reporting sites, the Seattle-Puget Sound, Washington region and the Detroit, Michigan metropolitan area, evaluated occupational risk factors in relation to the risk of multiple myeloma (MM). Detailed exposure information obtained from job-specific questionnaires allowed evaluation of association between 1, 1, 1-trichloroethane, TCE, dichloromethane, perchloroethylene carbon tetrachloride, and chloroform. Histologically-confirmed incident cases of MM (ICD-O-2/3, Codes 9731, 9732) in men and women without a previous diagnosis of MM, NHL or HIV, between 35 and 74 years of age, and diagnosed between 2000 and 2002 were eligible as cases, with population controls having Seattle-Puget Sound, Washington or Detroit, Michigan metropolitan area addresses identified from random digit dialing if <65 years of age, or by random selection from Medicare or Medicaid files for controls 65–74 years of age. Controls for this study were the same as those participating in the population-based case-control study of NHL carried out at the same time in these SEER areas, in addition, to two other SEER areas. A greater proportion of controls than cases were from Seattle-Puget Sound area. Face-to-face interviews were completed for 181 cases (71% participation rate) and 418 (52% participation rate).

In-person interviews were conducted using a computer-assisted interview program with modules focused specifically on solvent exposures for jobs held >2 years in 20 occupations. Proxy interviews were not permitted but were allowed to aid in recalling occupational details. All jobs were coded according to the Standard Occupational Classification system. For each of the six solvents, exposure metrics of probability, frequency, intensity, and confidence were assigned by modifying JEMs based on the subjects' answers to the questionnaire's sections on work history and job module. The JEMs were developed for each decade for specific industries, occupational and tasks by an industrial hygienist after reviewing published paper and reports on chlorinated solvents (e.g., 2007 for TCE). The assignment of exposure probability defined as the theoretical percentage of workers reporting the same information that would have been likely to have had exposure to the solvent is one strength of the study. For all jobs with probability scores of at least 1 (≥1% of subjects were likely to have had exposure), frequency and intensity scores

were also assigned, with values of 1, 2, 3, or 4 for each variable. Additionally, depending on the information source for assigning the probability, frequency, and intensity score, whether from literature review or self-reported, a confidence level was assigned on a scale of 1–4. Exposure surrogates developed for each of the six solvents were ever exposed and cumulative exposure, defined as the sum over all jobs of the product of intensity, exposure duration, and frequency. Of the 180 cases, 66 (37%) were identified as having been ever exposed to TCE (confidence scores of 1 or higher) with 24 of the TCE exposed cases (13% of all cases) assigned to the highest cumulative exposure group. Moreover, roughly one-third of the TCE-exposed cases were identified as having a low confidence level score (no information was available on probability, frequency or intensity or contradictory information exists in the literature), suggesting a greater potential for exposure misclassification bias in TCE assignment.

Association between MM and individual occupational solvents exposure was assessed using unconditional logistic regression to estimate ORs and 95% CIs. Jobs with probability score of ≥2 (≥10% subjects in that job were likely to have had TCE exposure) were defined as ever exposed to TCE. A lag period of 10 years, e.g., summing TCE exposures up to a period 10 years before disease diagnosis, was also examined in analyses of cumulative exposure. All statistical models included covariates for sex, age (three categories), race (four categories), education (three categories), and SEER site. Each of the continuous exposure metrics was categorized into four groups according to quartiles of the control exposure distribution. For TCE, cumulative exposure scores were 2,218 ppm-year (median) (range, 1–50,000 ppm-year). Test of trend were conducted using a linear term for the median duration and cumulative scores among controls in each category. Gold et al. (2011) further reported findings from sensitivity analyses considering all cases and controls with confidence scores of 1 as unexposed to address potential misclassification bias resulting from the identification of unexposed individuals as exposed. In studies with low exposure prevalences like Gold et al. (2011) this misclassification bias would diminish observed associations between TCE and multiple myeloma (Stewart and Correa-Villaseor, 1991).

B.3.2.6.1.4. Purdue et al. (2011) study description and comment.

This population case-control study of NHL in four SEER reporting areas was designed to investigate the association between NHL and occupational factors and focused on TCE exposures with a detailed exposure assessment method. Histologically-confirmed incident cases of NHL in men and women between 20 and 74 years of age, diagnosed between 1998 and 2000, and without know HIV infection were identified from four SEER reporting areas—the State of Iowa, the Seattle, Washington and Detroit, Michigan metropolitan areas, and Los Angeles County, California—with populations controls having addresses in the four SEER reporting areas identified from random digit dialing for men and women <65 years of age, or by random

selection from Medicare files, for men and women 65–74 years of age. NHLs were classified using according to the ICD-O-2 (converted to ICD-O-3, Codes 967-972): B-cell lymphomas, including small B-cell lymphoma, large diffuse B-cell lymphoma, follicular, or precursor lymphoblastic leukemia, and T-cell lymphoma, including anaplastic T-cell, N/K, and lymphoblastic leukemia. Subjects with CLL were ineligible; however, 28 recruited cases of small lymphocytic lymphoma were later identified by pathology review to be cases of CLL and were retained because the two diagnoses comprise the same disease. Face-to-face interviews were completed for 1,321 NHL cases (76% participation rate) and 1,057 controls (52% participation rate). Of these, 132 cases and 75 controls that were never employed or had unknown occupation were excluded, leaving 1,189 cases and 982 controls for the analysis.

Subjects provided information on residential and occupation history from a mailed calendar, with an in-person interview and home visit using a computer-assisted interview program with modules on solvent exposure, added 1 year after the study's start date. Of the computer-assisted personal interviews, 682 cases and 640 controls included the solvent-focused modules. The occupational history gathered information on each job held by the subject for ≥1 year since the age of 16. For selected occupations, 1 of 32 job- or industry-specific modules was administered based on information collected in the occupational histories. The information collected in the modules included the average frequency of various solvent-related tasks, the average length of time it took to perform given solvent-related tasks, sensory descriptions, dermal exposure, work practices, engineering controls, and personal protective equipment use. Information was also sought from subjects who reported jobs that could involve degreasing on the usual number of hours per instance spent degreasing, the identity of the chemical used for degreasing, the percentage of time each chemical was used, whether the degreasing solvent was heated or at room temperature, and the manner in which parts were cleaned.

The 23 exposure matrices developed by the industrial hygienist using information from the literature review, including Bakke et al. (2007), the subject's occupational history, and the information collected in the job modules, an expert industrial hygienist assessed levels of probability, frequency, and intensity of TCE exposure for each job. The assignment of exposure probability defined as the theoretical percentage of workers reporting the same information that would have been likely to have had exposure to the solvent is one strength of this study. For all jobs with probability scores of at least 1 (≥1% of subjects were likely to have had exposure), frequency and intensity scores were also assigned on a scale of 1–4 for frequency and 1–5 for intensity. The intensity score also reflected dermal exposure. The job-specified estimates of frequency and intensity for each subject were integrated to develop several metrics of TCE exposure. A subject was identified as "unexposed" if all jobs had been assigned an exposure probability of 0%, "possibly exposed" if one or more jobs had been assigned an exposure probability of <50% (probability scores of 1, 2, or 3, and "probably exposed" if at least one job had been assigned an exposure probability of ≥50% (probability scores of 4 or 5). For subjects

defined as probably exposed, the following additional exposure metrics were calculated: exposure duration; cumulative exposure, defined as the sum, across all jobs with exposure probability scores of 4 or 5, of the product of intensity midpoint, the frequency midpoint, and the duration in weeks; average week exposure, defined as the cumulative exposure divided by exposure duration; and average exposure intensity defined as the duration-weighted average intensity level across all jobs with probability scores of 4 or 5. Of the 1,189 cases, 545 (46%) were assigned an exposure level of "possible" and 45 cases (4%) an exposure level of "probable." Among subjects with probable confidence TCE exposure, the median cumulative exposure score was 150 ppm-year [range, 1–≥234,000 ppm-year].

Association between NHL and TCE exposure metrics was assessed using unconditional logistic regression to estimate ORs and 95% CIs. Other than the ever/never analysis, all analyses include subjects with probable TCE exposure, those with probability scores of 4 or 5. The observed exposure prevalence among subjects assigned possible exposure, defined as holding a job with a confidence score of 1, 2, or 3, suggested poor specificity and was inconsistent with the narrow set of occupational applications for TCE from the literature review. The higher likelihood for possible exposure misclassification bias and the importance of high specificity exposure assessment, further analysis of this measure was judged as unlikely to be informative. All statistical analyses included covariates for age (three categories), sex, race (four categories), education (three categories) and SEER area. The exposure metrics were categorized using tertiles among probably exposed controls as cut-points. In addition, ORs and 95% CIs were reported for exposure defined as the difference between the second and third tertiles among exposed controls. Test of trend were performed by modeling exposure the exposure metrics as continuous variables. Last, the association between TCE exposure and specific histologically-defined NHL subtypes (diffuse large B-cell, follicular lymphoma, and small lymphocytic lymphoma/CLL, were reported using polytomous regression to explore possible heterogeneity.

Gold LS, Stewart PA, Milliken K, Purdue M, Severson R, Seixas N, Blair A, Hartge P, Davis S, Dr Roos AJ. (2011). The relationship between multiple myeloma and occupational exposure to six chlorinated solvents. Occup Environ Med 68:391-399. doi:10.1136/oem.2009.054809].

Purdue MP, Bakke B, Stewart P, De Roos AJ, Schenk M, Lynch CF, Bernstein L, Morton LM, Cerhan JR, Severson RK, Cozen W, Davis S, Rothman N, Martge P, Colt JS. (2011). A case-control study of occupational exposure to trichloroethylene and non-Hodgkin lymphoma. Environ Health Perspect 119:232–238 doi:10.1289/ehp.1002106 [Online 2 November 2010]

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Study hypotheses of investigating association between TCE exposure and NHL using detailed exposure assessment methods (Purdue et al., 2011) and evaluating associations between multiple myeloma (Gold et al., 2011) and occupational exposure to six chlorinated solvents: 1,1,1-trichloro-ethane, methylene chloride, perchloroethylene, carbon tetrachloride, and chloroform.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Cases: 1,321 (2,248 eligible) histologically-confirmed NHL cases in males and females, 20–74 yrs of age, 1998–2000, and residents of four SEER reporting areas—Iowa, Los Angeles County, California, Seattle, Washington metropolitan area and Detroit, Michigan metropolitan area (Purdue et al., 2011); 181 (255 eligible) histologically-confirmed multiple myeloma cases in males and females, 35–74 yrs of age, 2000–2002, and residents of two SEER reporting areas—Seattle-Puget Sound, Washington area and Detroit, Michigan metropolitan area (Gold et al., 2011) Controls: 1,057 (2,409 eligible) controls identified from random digit dialing (<65 yrs old) or Medicare file (65–75 yrs old) who were residents in the four SEER areas (Purdue et al., 2011); 481 (1,133 eligible) controls identified from Purdue et al. (2011) who were 35–74 yrs of age, no previous diagnosis of HIV, MM, plasmacytoma, or NHL, spoke English, and residents of Seattle-Puget Sound, Washington area and Detroit, Michigan metropolitan area (Gold et al.).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	NHL and multiple myeloma incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-0-2 [Codes 967-972, NHL; 9731-9732, MM].
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Literature review, exposure matrices occupational histories and information collected in the job module supported assignment by expert industrial hygienist of probability, frequency, and intensity of TCE for each job held ≥12 months (Purdue et al., 2011) or ≥2 yrs (Gold et al., 2011).

CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	In-person interview using questionnaire or computer-assisted personal interview (682 of 1,321 cases and 640 of 1,057 controls in Purdue et al. (2011) with modules for jobs of interest.
Blinded interviewers	Interviewer not blinded. Exposure assessment assigned blinded.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	No proxy interviews.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	1,321 cases (76% participation rate); 1,051 controls (52% participation rate) (Purdue et al., 2011). Of these, 132 cases and 75 controls that were never employed or had unknown occupation were excluded, leaving 1,189 cases and 982 controls for the analysis. 181 cases (71% participation rate); 1,113 controls (52% participation rate) (Gold et al., 2011). Exposure prevalence, ever exposed to TCE (≥50% of subjects in job probably exposed), 27 (2.8%) NHL cases; 0.7% of cases in highest cumulative exposure category and 2.3% in highest average exposure intensity category (Purdue et al., 2011); ever exposed to TCE (>10% of subjects in job with probable exposure) (Gold et al., 2011).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, SEER center, race and education (Gold et al.; Purdue et al., 2011).
Statistical methods	Unconditional logistic regression.
Exposure-response analysis presented in published paper	Test for trend performed by modeling the exposure metrics as continuous variable (Purdue et al., 2011) or using median duration and cumulative scores among controls for each exposure category.
Documentation of results	Yes, study was well documented with supplemental material on publisher's webpage (Purdue et al., 2011).

B.3.2.6.2. Cocco et al. (2010).

B.3.2.6.2.1. Author's abstract.

BACKGROUND: Several studies have suggested an association between occupational exposure to solvents and lymphoma risk. However, findings are inconsistent and the role of specific chemicals is not known. Objective To investigate the role of occupational exposure to organic solvents in the aetiology of B-cell non-Hodgkin's lymphoma (B-NHL) and its major subtypes, as well as Hodgkin's lymphoma and T-cell lymphoma. METHODS: 2348 lymphoma cases and 2462 controls participated in a case-control study in six European countries. A subset of cases were reviewed by a panel of pathologists to ensure diagnostic consistency. Exposure to solvents was assessed by industrial hygienists and occupational experts based on a detailed occupational questionnaire. RESULTS: Risk of follicular lymphoma significantly increased with three independent metrics of exposure to benzene, toluene and xylene (BTX) (combined p=4 x 10(-7)) and to styrene (p=1 x 10(-5)), and chronic lymphocytic leukaemia (CLL) risk increased with exposure to solvents overall (p=4 x 10(-6)), BTX (p=5 x 10(-5)), gasoline (p=8 x 10(-5)) and other solvents (p=2 x 10(-6)). Risk of B-NHL for ever exposure to solvents was not elevated (OR=1.1, 95% CI 1.0 to 1.3), and that for CLL and follicular lymphoma was 1.3 (95% CI 1.1 to 1.6) and 1.3 (95% CI 1.0 to 1.7), respectively. Exposure to benzene accounted, at least partially, for the association observed with CLL risk. Hodgkin's lymphoma and T-cell lymphoma did not show an association with solvent exposure. CONCLUSION: This analysis of a large European dataset confirms a role of occupational exposure to solvents in the aetiology of B-NHL, and particularly, CLL. It is suggested that benzene is most likely to be implicated, but we cannot exclude the possibility of a role for other solvents in relation to other lymphoma subtypes, such as follicular lymphoma. No association with risk of T-cell lymphoma and Hodgkin's lymphoma was shown.

B.3.2.6.3. Study description and comment.

This population case control study of NHL in the Czech Republic, France, Germany, Italy, Ireland, and Spain was designed to examine possible personal and occupational risk factors for lymphoma subtypes as defined using the WHO classification (the Epilymph study). Observations in German subjects are reported separately in Seidler et al. (2007) (see B.3.2.6.6). The publication of Cocco et al. (2010) examined solvents and adopted expert assessment to assign exposure potential to organic solvents, specifically, chlorinated aliphatic hydrocarbons, benzene, toluene, xylene, gasoline, mineral spirits, styrene, and TCE. Cases of lymphoma in adults, >17 years of age, and diagnosed in 22 centers in 1998 and 2004 with population controls selected by sampling from the general population, and matched to cases on sex, age, and residence area, in Germany and Italy, or matched hospital controls limited to diagnoses other than cancer, infectious diseases, and immunodeficient diseases in the Czech Republic, France, Ireland, and Spain. The lymphoma diagnosis was classified according to the 2001 WHO classification of lymphoma, and slides of about 20% of cases from each center were reviewed

centrally by a panel of pathologists and reclassified when necessary. Lymphoma cases included in this study were B-cell lymphomas, including B-cell subtypes, T-cell lymphomas, and Hodgkin lymphoma. Informed consent was obtained for 2,348 lymphoma cases (88%) and 2,462 controls (81% hospital controls, 52% population controls) who participated in the study. Most cases were B-cell lymphomas (n = 1,869) with fewer T-cell (n = 133) and Hodgkin (n = 339) lymphoma.

Trained interviewers administered a structured questionnaire through in-person interviews with cases and controls to collect information on sociodemographic factors, lifestyle, health history, and complete work history for all full-time jobs held for ≥1 year. Special questionnaire modules for specific occupations gathered additional details on jobs and exposure of a priori interest. Industrial hygienists in each center reviewed the general and specific questionnaires and assessed exposure to 43 agents, including organic solvents according to confidence, intensity, and frequency of exposure. The paper does not report if proxy or next-of-kin provided information if the case or control was deceased. Confidence represented the degree of certainty that the worker had been exposed to the agent and was based both on probability of exposure and on the proportion of workers exposed in a give job, <40% (possible exposure), 40–90%, (probable exposure), and >90% (certain/definite exposure). Intensity of exposure was defined as a rank-ordered variable, unexposed (0), low (1), medium (2), high (3), with agent-specific cut-off points defined based on current threshold limit values, likely half the threshold limit value (TLV) (low), 51–150% (medium), and >150% (high) (Kiran et al., 2010). Exposure frequency expressed the proportion of work time involving contact with the agent: unexposed (coded as 0), 1–5% of the work time (coded as 1), >5–30% of the work time (coded as 2), and >30% of the work time (coded as 3). Exposure potential to TCE for cases and controls was based surrogates for overall exposure and cumulative exposure score. The cumulative exposure score was the sum over a subjects work history of the product of duration and frequency/3 to the power of intensity and results in a log distribution of exposure scores. Exposure prevalence to TCE is low in this study; Cocco et al. (2010) identifies 71 cases of B-cell lymphoma (4% exposure prevalence) and 117 controls (5% exposure prevalence) with high confidence overall TCE exposure and of these exposed subjects, 29 cases (2%) and 37 (2%) with a high-confidence, high-cumulative exposure score.

Association between B-cell lymphoma and B-cell lymphoma subtypes and individual occupational solvent exposures was assessed using unconditional logistic regression, which adjusted for age, sex, education, and center. Alcohol and smoking were not included as a potential confounder as previous analysis of the Epilymph data showed no association (Besson et al., 2006). Statistical analyses are limited to subjects whose jobs TCE exposure was assessed with high degree of confidence, defined as >90%of worker exposed in a given job. Lymphoma subtypes examined included diffuse large B-cell lymphoma, follicular lymphoma, CLL, and multiple myeloma. There were few cases of T-cell lymphomas with high confidence TCE exposure; six cases with overall exposure, two of which with high confidence high cumulative

score. Two-tailed 95% CIs of the OR were calculated with the Wald statistics and trend test defining cumulative exposure score as a continuous variable using Wald's test for trend. As common to epidemiological studies, the many statistical analyses and comparisons in Cocco et al. (2010) increases the potential for false positive errors and Cocco et al. (2010) used Bonferroni correction of individual CIs and trend tests as an attempt to reduce this type of bias.

This study adopted a detailed exposure assessment, current classification system for lymphomas, and was of a large number of cases and controls, although exposure prevalence to TCE was <5%, typical of population case-control studies. This study defines the cumulative exposure score using a log scale, in addition, to using a rank-order value for intensity instead of a midpoint of an range of exposure concentrations. Other cohort and case-control studies of TCE and NHL, e.g., Purdue et al. (2011), define their cumulative exposure score as a product of intensity, frequency, and duration. Each approach will produce a slightly different rank ordering (personal communication). In the cumulative exposure formula of Cocco et al. (2010), exposure duration contributes the greatest weight in light of the formula's treatment of 1/3 the value of frequency (Cocco et al., 2010). The direction of bias in estimated trends of disease risk by cumulative exposure depends on the variation of duration, with large variation in durations between exposure exposures leading to downward bias. Cocco et al. (2010), also, reported ORs and CIs for high confidence TCE exposure, assigned to a job title when over 90% of workers were exposed. In comparison, both Purdue et al. (2011) and Gold et al. (2011) defined probable exposure if at least one job has been assigned an exposure probability of ≥50%. Any differences in reported findings between Cocco et al. (2010) and the other NHL studies of Miligi et al. (2006), Wang et al. (2009), and Purdue et al. (2011) may be due to these differences.

Cocco P, Mannetje A, Fadda D, Melis M, Becker N, Sanjosé S, Foretova L, Marekova J, Staines A, Kleefeld S, Maynadié M, Nieters A, Brennan P, Boffetta P. (2010). Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study. Occup Environ Med 67:341–347.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This study evaluated occupational exposure to organic solvents as risk factors of NHL in a population-based, case-control study of men and women in six European countries.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	2,348 hospital cases of NHL diagnosed between 1998 and 2004 among men and women, >17 yrs of age, and residents of Czech Republic, France, Germany, Ireland, Italy, and Spain; 2,462 population and hospital controls, identified from census lists in Germany and Italy or small hospitals as the cases, in all other countries, and matched to cases on age, sex, and study center.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Lymphoma incidence – B-cell lymphoma (CLL, follicular, and diffuse large B-cell), T-cell lymphoma, Hodgkin lymphoma, and multiple myeloma. Postransplant lymphoproliferative disorder or monoclonal gammopathies of undetermined significance were excluded as cases.
Changes in diagnostic coding systems for lymphoma, particularly NHL	WHO classification system
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	All jobs held for >1 yr assigned to standardized occupation (5-digit code). Industrial hygienists at each center assigned exposure to 43 agents, including TCE and other solvents (benzene, toluene, xylene, chlorinated aliphatic hydrocarbons, and gasoline) to subjects according to confidence (possible, probable, certain), intensity (unexposed, low, medium, high), and frequency. Exposure surrogates for overall exposure and cumulative exposure (low, medium, high).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Face-to-face interview with questionnaire for information about medical history, lifestyle factors, lifetime occupational history (all jobs held >1 yr) and supplemental modules for specific occupations to gather additional details on jobs and exposures of a priori interest.
Blinded interviewers	Unblinded interviews. Blinded exposure assessment.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Not reported in published paper.

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	2,348 cases (88% participation rate) and 2,462 controls (81% participation rate, hospital controls, 52% participation rate, population controls). Exposure prevalence, subjects with high confidence overall TCE exposure, 71 (4%) all B-cell lymphoma, 6 (7%) T-cell lymphoma, and 48 (6%) NHL (B-cell diffuse and follicular subtypes and T-cell); subjects with high confidence high cumulative TCE exposure, 29 (2%) all B-cell lymphomas, 2 (2%) T-cell lymphoma, 14 (2%) NHL (B-cell diffuse and follicular subtypes and T-cell).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, education, and center.
Statistical methods	Unconditional logistic regression.
Exposure-response analysis presented in published paper	Yes, using cumulative exposure defined as low, medium, high.
Documentation of results	Yes.

B.3.2.6.4. Wang et al. (2009).

B.3.2.6.4.1. Author's abstract.

A population-based case-control study involving 601 incident cases of non-Hodgkin lymphoma (NHL) and 717 controls was conducted in 1996-2000 among Connecticut women to examine associations with exposure to organic solvents. A job-exposure matrix was used to assess occupational exposures. Increased risk of NHL was associated with occupational exposure to chlorinated solvents (odds ratio (OR) = 1.4, 95% confidence interval (CI): 1.1, 1.8) and carbon tetrachloride (OR = 2.3, 95% CI: 1.3, 4.0). Those ever exposed to any organic solvent in work settings had a borderline increased risk of NHL (OR = 1.3, 95% CI: 1.0, 1.6); moreover, a significantly increased risk was observed for those with average probability of exposure to any organic solvent at medium-high level (OR = 1.5, 95% CI: 1.1, 1.9). A borderline increased risk was also found for ever exposure to formaldehyde (OR = 1.3, 95% CI: 1.0, 1.7) in work settings. Risk of NHL increased with increasing average intensity (P = 0.01), average probability (p< 0.01), cumulative intensity (P = 0.01), and cumulative probability (p < 0.01) level of organic solvent and with average probability level (P = 0.02) and cumulative intensity level of chlorinated solvent (P = 0.02). Analyses by NHL subtype showed a risk pattern for diffuse large B-cell lymphoma similar to that for overall NHL, with stronger evidence of an association with benzene exposure. Results suggest an increased risk of NHL associated with occupational exposure to organic solvents for women.

B.3.2.6.4.2. Study description and comment.

This population case-control study of NHL in Connecticut women was designed to examine possible personal and occupational risk factors for NHL. The publication of Wang et al. (2009) examined solvent exposure and adopted a JEM to assign exposure potential to nine chemicals—benzene, formaldehyde, chlorinated solvents, chloroform, carbon tetrachloride, dichloromethane, methyl chloride, and TCE. Histologically-confirmed incident cases of NHL in women aged between 21 and 84 years of age and diagnosed in Connecticut between 1996 and 2000 were identified from the Connecticut Cancer Registry, a SEER reporting site, with population controls having Connecticut address identified from random digit dialing for women <65 years of age, or by random selection from Centers for Medicare and Medicaid Service files for women aged ≥65 years old. Controls were frequency matched to cases within 5-year age groups. Face-to-face interviews were completed for 601 (72%) cases and 717 controls (69% of those identified from random digit dialing and 47% identified using Health Care Financing Administration files).

Trained interviewers administered a structured questionnaire through in-person interviews with cases and controls to collect information on diet, nutrition, and alcohol intake; reproductive factors; hair dye use; and lifetime occupational history of all jobs held ≥1 year.

Jobs were coded to standardized occupational classification and standardized industry classification titles and assigned probability and intensity of exposure to formaldehyde and nine other solvents (benzene, any chlorinated solvents, DCE, chloroform, methylene chloride, dichloroethane, methyl chloride, TCE, and carbon tetrachloride) using a JEM developed by the NCI (Dosemeci et al., 1994; Gómez et al., 1994). All jobs held up to a year before cancer diagnosis were assigned blinded as to disease status potential exposure to each exposure of interest. Lifetime exposure potential for cases and controls was based on exposure duration and a weighted score for exposure intensity and probability of each occupational and industry and defined as a cumulative exposure metric, average metric, or ever/never metric. Of the 601 cases, 77 (13%) were assigned with potential TCE exposure over their lifetime; 8 cases were assigned potential for high intensity exposure, but with low probability and the 31 cases identified with medium and high probability of exposure were considered as having low intensity exposure potential. The low exposure prevalence to TCE, overall, and few subjects identified with confidence with high TCE exposure intensity or probability implies exposure misclassification bias is likely, and likely nondifferential, notably for high exposure categories (Dosemeci et al., 1990).

Association between NHL and individual occupational solvent exposure was assessed using unconditional logistic regression model which adjusted for age, family history of hematopoietic cancer, alcohol consumption, and race. Statistical analyses treated exposure defined as a categorical variable, divided into tertiles based on the distribution of controls, in logistic regression analyses and as a continuous variable, whenever possible, to test for linear trend. Polytomous logistic regression was used to evaluate the association between histologic subtypes of NHL (DLBCL, follicular lymphoma, or CLL/small lymphocytic lymphoma) and exposure. The largest number of cases was of the cell type DLBCL.

Strength of this study is assignment of TCE exposure potential to individual subjects using a validated JEM, although uncertainty accompanied exposure assignment and TCE exposure was largely of low intensity/low probability, and no cases with medium to high intensity/probability. Resultant misclassification bias would dampen observed associations for high exposure potential categories. Low prevalence of high intensity TCE exposure would reduce the study's statistical power.

Wang R, Zhang Y, Lan Q, Holford TR, Leaderer B, Zahm SH, Boyle P, Dosemeci M, Rothman N, Zhu Y, Qin Q, Zheng T. (2009). Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women. Am J Epidmiol 189:176–185.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This study evaluated multiple potential risk factors of NHL in a population-based case-control study of Connecticut women. Occupational exposure to TCE was not an a priori hypothesis.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	601 (832 eligible) cases of NHL, diagnosed between 1996 and 2000 among women, age 20–84 yrs and residents of Connecticut and histologically-confirmed, were identified from the Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource, a component of the Connecticut Tumor Registry; 717 (number of eligible controls not identified) population controls were randomly identified using random digit dialing, if age <65 yrs, or from Medicare and Medicaid Service files, for women aged ≥65 yrs old and stratified by sex and 5-yr age groups.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	NHL and chronic lymphatic leukemia incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-O-2 [Codes, M-9590-9642, 9690-9701, 9740-9750].
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	All jobs held for >1 yr were assigned to standardized occupation and industry classifications. Using JEM of NCI (Dosemeci et al., 1994; Gómez et al., 1994), probability of exposure level (low, medium and high) and intensity (very low, low, medium, and high) to TCE and other solvents (benzene, any chlorinated solvents, DCE, chloroform, methylene chloride, dichloroethane, methyl chloride, carbon tetrachloride, and formaldehyde) was assigned blinded as to case or control status.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Face-to-face interview with questionnaire for detailed information about medical history, lifestyle factors, education, lifetime occupational history (all jobs held >1 yr).
Blinded interviewers	Unblinded interviews.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	None.

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	601 cases (72% participation) and 717 controls (69% participation for random digit dialing controls and 47% participation for HCFA controls). Exposure prevalence, ever exposed to TCE, 77 (13%) NHL cases; medium to high TCE intensity, 13 NHL cases (2%); medium to high TCE probability, 34 cases (6%). All 34 cases with medium to high TCE probability assigned low intensity exposure.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, family history of hematopoietic cancer, alcohol consumption and race.
Statistical methods	Unconditional logistic regression.
Exposure-response analysis presented in published paper	Yes, by exposure intensity and by exposure probability.
Documentation of results	Yes.

B.3.2.6.5. Costantini et al. (2008), Miligi et al. (2006).

B.3.2.6.5.1. Costantini et al. (2008) abstract.

Background While there is a general consensus about the ability of benzene to induce acute myeloid leukemia (AML), its effects on chronic lymphoid leukemia and multiple myeloma (MM) are still under debate. We conducted a population-based case–control study to evaluate the association between exposure to organic solvents and risk of myeloid and lymphoid leukemia and MM.
Methods Five hundred eighty-six cases of leukemia (and 1,278 population controls), 263 cases of MM (and 1,100 population controls) were collected. Experts assessed exposure at individual level to a range of chemicals.
Results We found no association between exposure to any solvent and AML. There were elevated point estimates for the associations between medium/high benzene exposure and chronic lymphatic leukemia (OR: 1.8, 95% CI¼0.9–3.9) and MM (OR: 1.9, 95% CI: 0.9–3.9). Risks of chronic lymphatic leukemia were somewhat elevated, albeit with wide confidence intervals, from medium/high exposure to xylene and toluene as well.
Conclusions We did not confirm the known association between benzene and AML, though this is likely explained by the strict regulation of benzene in Italy nearly three decades prior to study initiation. Our results support the association between benzene, xylene, and toluene and chronic lymphatic leukemia and between benzene and MM with longer latencies than have been observed for AML in other studies.

B.3.2.6.5.2. Miligi et al. (2006) abstract.

BACKGROUND: A number of studies have shown possible associations between occupational exposures, particularly solvents, and lymphomas. The present investigation aimed to evaluate the association between exposure to solvents and lymphomas (Hodgkin and non-Hodgkin) in a large population-based, multicenter, case-control study in Italy. METHODS: All newly diagnosed cases of malignant lymphoma in men and women age 20 to 74 years in 1991-1993 were identified in 8 areas in Italy. The control group was formed by a random sample of the general population in the areas under study stratified by sex and 5-year age groups. We interviewed 1428 non-Hodgkin lymphoma cases, 304 Hodgkin disease cases, and 1530 controls. Experts examined the questionnaire data and assessed a level of probability and intensity of exposure to a range of chemicals. RESULTS: Those in the medium/high level of exposure had an increased risk of non-Hodgkin lymphoma with exposure to toluene (odds ratio = 1.8; 95% confidence interval = 1.1-2.8), xylene 1.7 (1.0-2.6), and benzene 1.6 (1.0-2.4). Subjects exposed to all 3 aromatic hydrocarbons (benzene, toluene, and xylene; medium/high intensity compared with none) had an odds ratio of 2.1 (1.1-4.3). We observed an increased risk for Hodgkin disease for those exposed to technical solvents (2.7; 1.2-6.5) and aliphatic solvents (2.7; 1.2-5.7). CONCLUSION: This study suggests that aromatic and chlorinated hydrocarbons are a risk factor for non-Hodgkin lymphomas, and provides preliminary evidence for an association between solvents and Hodgkin disease.

B.3.2.6.5.3. Study description and comment.

This series of papers of a population case-control study of lymphomas in 11 areas in Italy (Costantini et al., 2008) and occupation examines author's assigned exposure to TCE and other solvents using job-specific or industry-specific questionnaires and expert rating to cases and controls. Miligi et al. (2006) reported findings for NHL, a category that included CLL, NHL subtypes, and Hodgkin lymphoma in eight regions and Constantini et al. (2008) presented observations for specific leukemia subtypes and multiple myeloma in seven regions (eight regions for CLL). Exclusion of the regions in the original study does not appear to greatly reduce study power or to introduce a selection bias. For example, Miligi et al. (2006) included 1,428 of the 1,450 total NHL cases, the largest percentage of all lymphoma subtypes. The number of other lymphoma subtypes was much smaller compared to NHL; 304 cases of Hodgkin disease, 586 cases of leukemia, and 263 cases of multiple myeloma. All cases were identified from participating study centers and controls were randomly selected from the each area's population using stratified sampling for sex and age.

A face-to-face unblinded interview was conducted primarily at the interviewee's home with a high proportion of proxy responses among cases (19%) but not controls (5%). Bias is likely introduced by the lack of blinding of interviewers and from the high proportion of proxy interviews. A questionnaire was used to obtain information on medical history, lifestyle factors, occupational exposure, and nonoccupational solvent exposures. Industrial hygiene professionals assessed the probability and intensity of exposure to individual and classes of solvents using information provided by questionnaire. Probability was classified into three levels (low, medium, and high) with a four-category scale for intensity (very low, low, medium, and high). These qualitative scales lacked information on exposure concentrations and likely introduces misclassification bias that can either dampen or inflate observed risks given the study's use of multiple exposure groupings. "Very low level" was used for subjects with occupational exposure intensities judged to be comparable to the upper end of the normal range for the general population; "low-level intensity" when workplace exposure was judged to be low because of control measures but higher than background; "medium exposure" for occupational environments with moderate or poor control measures; and "high exposure" for workplaces lacking any control measures. Groupings of "very low/low" and "medium/high" exposure was used to examine association with NHL. Prevalence of medium to high TCE exposure among NHL cases was low, 3% for NHL cases and 2% for all leukemia subtypes. Whether temporal changes in TCE exposure concentrations were considered in assigning level and intensity is not known. Overall, this study has low sensitivity for examining TCE and lymphoma given the low prevalence of exposure, particularly to medium to high TCE intensity, the high proportion of proxy interviews among cases, particularly NHL cases (15%), and qualitative exposure assessment approach.

Costantini AS, Benvenuti A, Vineis P, Kriebel D, Tumino R, Ramazzotti V, Rodella S, et al. (2008). Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: evidence from the Italian multicenter case-control study. Am J Ind Med 51:803–811.

Miligi L, Costantini AS, Benvenuti A, Kreibel D, Bolejack V, et al. (2006). Occupational exposure to solvents and the risk of lymphomas. Epidemiol 17:552–561.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This study evaluated TCE and other solvent exposures and lymphoma in a large population-based, multicenter, case-control study.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	1,732 (2,066 eligible) cases of NHL, chronic lymphatic leukemia, and Hodgkin lymphoma, diagnosed between 1991 and 1993 among men and women, age 20–74 yrs and residents of eight regions in Italy, were identified from; 1,530 (2,086 eligible) population controls were randomly selected from demographic files or from sampling of National Health Service files and stratified by sex and 5-yr age groups. 586 leukemia and 263 multiple myeloma among men and women, age 20–74 in the period 1991–1993, from seven regions (eight regions for CLL) in Italy, were identified from hospital or pathology department records or a regional cancer registry; and 1,100 population controls selected from demographic files or from sampling of National Health Service files and stratified by sex and 5-yr age groups.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	NHL and Hodgkin lymphoma incidence (Miligi et al., 2006). Leukemia and multiple myeloma (Costantini et al., 2008).
Changes in diagnostic coding systems for lymphoma, particularly NHL	All NHL cases were defined following NCI Working Formulation Workgroup classification and Hodgkin lymphomas defined following the Rye classification. NHL diagnosis confirmed for 334 of 1,428 cases (23%).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	IH experts from each region using information collected on questionnaires assigned the probability of exposure level (low, medium, and high) and intensity (very low, low, medium, and high) to TCE and other solvents. Exposure was assigned blinded as to case or control status.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	

CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Face-to-face interview with questionnaire for detailed information about medical history, lifestyle factors, education, occupational history (period is not identified in published paper), and nonoccupational exposures including solvent exposure.
Blinded interviewers	Unblinded interviews.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	19% of all lymphoma cases and 5% of controls were with proxy respondents (Costantini et al., 2008).
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	1,732 cases (83% participation) and 1,530 controls (73% participation) (Miligi et al., 2006); no information on participation rate for leukemia or multiple myeloma cases or their controls in Costantini et al. (2008). Exposure prevalence, medium to high TCE intensity, 35 NHL cases (3%) (Miligi et al., 2006); 11 leukemia cases (2%), and 5 multiple myeloma cases (2%) (Costantini et al., 2008).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, region, education, and region.
Statistical methods	Multiple logistic regressions.
Exposure-response analysis presented in published paper	Yes, by exposure intensity and by duration (years) of exposure.
Documentation of results	Yes.

B.3.2.6.6. Seidler et al. (2007).

B.3.2.6.6.1. Author's abstract.

AIMS: To analyze the relationship between exposure to chlorinated and aromatic organic solvents and malignant lymphoma in a multi-centre, population-based case-control study. METHODS: Male and female patients with malignant lymphoma (n = 710) between 18 and 80 years of age were prospectively recruited in six study regions in Germany (Ludwigshafen/Upper Palatinate, Heidelberg/Rhine-Neckar-County, Würzburg/Lower Frankonia, Hamburg, Bielefeld/Gütersloh, and Munich). For each newly recruited lymphoma case, a gender, region and age-matched (+/-1 year of birth) population control was drawn from the population registers. In a structured personal interview, we elicited a complete occupational history, including every occupational period that lasted at least one year. On the basis of job task-specific supplementary questionnaires, a trained occupational physician assessed the exposure to chlorinated hydrocarbons (trichloroethylene, tetrachloroethylene, dichloromethane, carbon tetrachloride) and aromatic hydrocarbons (benzene, toluene, xylene, styrene). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression analysis, adjusted for smoking (in pack years) and alcohol consumption. To increase the statistical power, patients with specific lymphoma subentities were additionally compared with the entire control group using unconditional logistic regression analysis. RESULTS: We observed a statistically significant association between high exposure to chlorinated hydrocarbons and malignant lymphoma (Odds ratio = 2.1; 95% confidence interval 1.1–4.3). In the analysis of lymphoma subentities, a pronounced risk elevation was found for follicular lymphoma and marginal zone lymphoma. When specific substances were considered, the association between trichloroethylene and malignant lymphoma was of borderline statistical significance. Aromatic hydrocarbons were not significantly associated with the lymphoma diagnosis. CONCLUSION: In accordance with the literature, this data point to a potential etiologic role of chlorinated hydrocarbons (particularly trichloroethylene) and malignant lymphoma. Chlorinated hydrocarbons might affect specific lymphoma subentities differentially. Our study does not support a strong association between aromatic hydrocarbons (benzene, toluene, xylene, or styrene) and the diagnosis of a malignant lymphoma.

B.3.2.6.6.2. Study description and comment.

This population case-control study of NHL and Hodgkin lymphoma patients in six Germany regions is part of a larger multiple-center and -country case-control study of lymphoma and environmental exposures, the EPILYMPH study (see Cocco et al. (2010) in B.3.2.6.3). A total of 710 cases and 710 controls that were matched to cases on age, sex, and region, participated in this study. Participation rates were 88% for cases and 44% for controls. Potential for selection bias may exist given the low control response rate. Strength of this study is the use of WHO classification scheme for classifying lymphomas and the high percentage of cases with histologically-confirmed diagnoses. An industrial physician blinded to case and control status

assigned exposure to specific solvents (i.e., TCE, perchloroethylene, carbon tetrachloride, etc.) using a JEM developed for the EPILYMPH investigators, a modification of Bolm-Audorff et al.(1988). Exposure prevalence to TCE among cases was 13%. A cumulative exposure score was calculated and was the sum for every job held of intensity of solvent exposure, frequency of exposure, and duration of exposure. High exposure to TCE was defined as >35 ppm-years; 3% of cases had high cumulative exposure to TCE. Intensity of TCE exposure was assessed on a semiquantitative scale with the following categories: low intensity, 2.5 ppm (0.5–5); medium intensity, 25 ppm (>5–50), high intensity, 100 ppm (>50). The frequency of exposure was the percentage of working time during which the exposure occurred based upon a 40-hour week. A semiquantitative scale was adopted for frequency of exposure with the following categories: low frequency, 3% of working time (range, 1–5%), medium frequency, 17.5 % (range, >5–30%), high frequency, 65% of working time (>30%). A cumulative Prevalence of TCE exposure among cases was 13% overall with 3% of cases identified with cumulative exposure >35 ppm-years.

Overall, the use of expert assessment for exposure and WHO classification for disease coding likely reduce misclassification bias in this study. This population case-control study, like other population case-control studies of lymphoma and TCE, has a low prevalence of TCE exposure and limits statistical power to detect risk factors.

Seidler A, Mohner M, Berger J, Mester B, Deeg E, Eisner G, Neiters A, Becker N. (2007). Solvent exposure and malignant lymphoma: a population-based case-control study in Germany. J Occup Med Toxicol 2:2. Accessed August 27, 2007, http://www.occup-med.com/content/2/1/2.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This case-control study of NHL and Hodgkin lymphomas was designed to investigate association between specific exposure and distinct lymphoma classifications which are defined by REAL and WHO classifications.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	812 male and female lymphoma patients between the ages of 18 and 80 yrs were identified from a six German study regions from 1999 to 2003. 1,602 controls were identified from population registers and matched (1:1) to cases on sex, region, and age. 710 cases and 710 controls were interviewed.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	NHL and Hodgkin lymphoma incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	WHO classification. Diagnosis confirmed by pathological report for 691 cases.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Blinded assignment of intensity and frequency of exposure to specific chlorinated hydrocarbons (includes TCE) and to aromatic hydrocarbons based upon questionnaire information on complete occupational history for all jobs of ≥1-yr duration. Exposure assessment approach based on a modification of Bolm-Audorff et al. (1988)
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Face-to-face interview with questionnaire for detailed information about medical history, lifestyle factors, and occupation. Job-task-specific supplementary questionnaire administered to subjects having held jobs of interest; e.g., painters, metal workers and welders, dry cleaners, chemical workers, shoemakers and leather workers, and textile workers.
Blinded interviewers	Unblinded interviews.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	No information provided in paper.

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	710 cases (87.4%) and 710 controls (44.3%). Exposure prevalence: Any TCE exposure, Cases, 13%, Controls, 15%. High cumulative exposure (>35 ppm-yr), Cases, 3%, Controls, 1%.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, region, pack years of smoking, and # grams of alcohol consumed per day.
Statistical methods	Conditional logistic regression.
Exposure-response analysis presented in published paper	Yes, by ppm-yr as continuous variable.
Documentation of results	Yes.

B.3.2.6.7. Persson and Fredrikson (1999), Persson et al. (1993; 1989).

B.3.2.6.7.1. Author's abstract.

Non-Hodgkin's lymphoma (NHL) has been subject to several epidemiological studies and various occupational and non-occupational exposures have been identified as determinants. The present study is a pooled analysis of two earlier methodologically similar case-referent studies encompassing 199 cases of NHL and 479 referents, all alive. Exposure information, mainly on occupational agents, was obtained by mailed questionnaires to the subjects. Exposure to white spirits, thinner, and aviation gasoline as well as work as a painter was connected with increased odds ratios, whereas no increased risk was noted for benzene. Farming was associated with a decreased odds ratio and exposure to phenoxy herbicides, wood preservatives, and work as a lumberjack showed increased odds ratios. Moreover, exposure to plastic and rubber chemicals and also contact with some kinds of pets appeared with increased odds ratios. Office employment and housework showed decreased odds ratios. This study indicates the importance of investigating exposures not occurring very frequently in the general population. Solvents were studied as a group of compounds but were also separated into various specific compounds. The present findings suggest that the carcinogenic property of solvents is not only related to the aromatic ones or to the occurrence of benzene contamination, but also to other types of compounds.

B.3.2.6.7.2. Study description and comment.

The exposure assessment approach of Persson and Fredriksson (1999), a pooled analysis of NHL cases and referents in Persson et al. (1993), and Persson et al. (1989), was based upon self-reported information obtain from a mailed questionnaire to cases and controls. Ten of 17 main questions of the detailed multiple-page questionnaire concerned occupational exposure, with additional questions on specific job and exposure details. These studies of the Swedish population considered exposure durations of ≥1 years and those received 5–45 years before NHL diagnosis for cases and before the point in time of selection for controls. The period of TCE exposure assessed in the between 1964 and 1986, a time period similar to that of Axelson et al. (1994). Semiqualitative information about solvent exposure was obtained directly from the questionnaires. Assignment of exposure potential to individual solvents such as TCE and white spirit is not described nor does the paper describe whether assignment was done blinded as to case or control status. A five-category classification for intensity was developed although statistical analyses grouped the TCE categories as intensity scores of >2 compared to 0/1. TCE exposure prevalence among cases was 8% (16 of 199) and 7% among referents (32 of 479).

This small study of 199 NHL cases diagnosed between 1964 and 1986 at a regional Swedish hospital (Orebro) and alive at the time of data acquisition in 1986 was similar in design to other lymphoma (CLL, multiple myeloma) and occupational studies from these investigators (Flodin et al., 1987). A series of 479 referents from the same catchment area and from the same time period, identified previously from the multiple myeloma and CLL studies, served as the

source for controls in Persson and Fredrikson (1999) for the NHL analysis and in Persson et al. (1993; 1989) for the Hodgkin lymphoma analysis. Given the study's entrance date as 1964, with interviews carried out in the 1980s, some cases were deceased with information likely provided by proxy respondents. The paper does not identify the percentage of deceased cases and the magnitude of potential bias associated with proxy respondents cannot be determined. Little information is provided in the published paper on controls; however, the paper notes that 17% of eligible controls were not able or unwilling to respond to the questionnaire. Case and control series appear to differ given only subjects 40 to 80 years of age were included in the statistical analysis. Cases in Perrson et al. (1993) were histologically confirmed diagnosis of NHL; this was not so for Persson et al. (1989). Misclassification associated with misdiagnosis is not expected to be large given observation in Perrson et al. (1993) of 2% of lymphoma cases were misclassified.

Overall, the study's 20-year period between initial case and control identification and interview suggests some subjects were either survivors or information was obtained from proxy respondents. In both instances, misclassification bias is likely. No information is provided on job titles or the nature of TCE exposure, which was defined in the exposure assessment as "exposed or unexposed." Exposure prevalence to TCE in this study is higher than that found in community population studies of Miligi et al. (2006), Seidler et al. (2007), and Costantini et al. (2008).

Persson B, Fredrikson M. (1999). Some risk factors for non-Hodgkin's lymphoma. Int J Occup Med Environ Health 12:135–142.

Persson B, Fredriksson M, Olsen K, Boeryd B, Axelson O. (1993). Some occupational exposure as risk factors for malignant lymphomas. Cancer 72:1773–1778.

Persson B, Dahlander A-M, Fredriksson M, Brage HN, Ohlson C-G, Axelson O. (1989). Malignant lymphomas and occupational exposures. Br J Ind Med 46:516–520.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	These studies of Hodgkin lymphoma and NHL investigated occupational associations. Examination of TCE is not stated as a priori hypothesis.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Incident NHL and Hodgkin lymphoma cases reported to a regional cancer registry between 1975 and 1984, n = 148 (Persson et al., 1993), or identified from hospital records (Orebro Medical Center Hospital) for the period 1964 and 1986, n = 175 (Persson et al., 1989). Population controls from the same geographical area as cases were identified from previous case-control studies of leukemia and multiple myeloma and matched on age and sex. Analysis of NHL and Hodgkin lymphoma each used the same set of controls. Persson and Fredrikson (1999)—199 cases of NHL, 479 controls. Persson et al. (1993)—93 NHL and 31 Hodgkin lymphoma (90% participation); 204 controls. Persson et al. (1989)—106 NHL and 54 Hodgkin lymphoma (91%); 275 controls.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Classification system not identified in papers.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Self-reported occupational exposures as obtained from a mailed questionnaire.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Mailed questionnaire, only.
Blinded interviewers	N/A

CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	No information provided in paper.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	Exposure prevalence to TCE Persson and Fredrikson (1999)—16 NHL cases (8%) and 32 controls (7%). Persson et al. (1993)—8 NHL cases (8%) and 5 Hodgkin lymphoma cases (16%); 18 controls (9%). Persson et al. (1989)—8 NHL cases (8%) and 7 Hodgkin lymphoma cases (13%); 14 controls (5%).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Cases and controls are matched on age and sex. Statistical analyses do not control for other possible confounders.
Statistical methods	Only crude ORs are presented for TCE exposure, although logistic regression was used to examine other occupational exposure and NHL/Hodgkin lymphoma.
Exposure-response analysis presented in published paper	No.
Documentation of results	Poor, unable to determine response rate in control population, if controls were similar to cases on demographic variables such as sex and age, and whether controls were identified from same time period as cases.

B.3.2.6.8. Nordstrom et al. (1998).

B.3.2.6.8.1. Author's abstract.

To evaluate occupational exposures as risk factors for hairy cell leukemia (HCL), a population-based case-control study on 121 male HCL patients and 484 controls matched for age and sex was conducted. Elevated odds ratio (OR) was found for exposure to farm animals in general: OR 2.0, 95% confidence interval (CI) 1.2-3.2. The ORs were elevated for exposure to cattle, horse, hog, poultry and sheep. Exposure to herbicides (OR 2.9, CI 1.4-5.9), insecticides (OR 2.0, CI 1.1-3.5), fungicides (OR 3.8, CI 1.4-9.9) and impregnating agents (OR 2.4, CI 1.3-4.6) also showed increased risk. Certain findings suggested that recall bias may have affected the results for farm animals, herbicides and insecticides. Exposure to organic solvents yielded elevated risk (OR 1.5, CI 0.99-2.3), as did exposure to exhaust fumes (OR 2.1, CI 1.3-3.3). In an additional multivariate model, the ORs remained elevated for all these exposures with the exception of insecticides. We found a reduced risk for smokers with OR 0.6 (CI 0.4-1.1) because of an effect among non-farmers.

B.3.2.6.8.2. Study description and comment.

This population case-control of hairy cell leukemia, a B-cell lymphoid neoplasm and NHL, examined occupational organic solvent and pesticide exposures among male cases reported to the Swedish Cancer Registry between 1987 and 1992. A total of 121 cases, including 1 case one case, originally thought to have a diagnosis within the study's window, but latter learned as in 1993, and four controls per case matched on age and county of residence from the Swedish Population Registry. Occupational exposure was assessed based upon self-reported information provided in a mailed questionnaire with telephone follow-up by trained interviewer blinded to case or control status. Chemical-specific exposures of at least 1-day duration and occurring 1 year prior to case diagnosis were assigned to study subjects; however, the procedure for doing this was not described in the paper. Potential for organic solvents exposure included exposure received during leisure activities and work-related activities. Exposure prevalence to TCE among cases is 8 and 7% among controls. The low exposure prevalence and study size limit the statistical power of this study for detecting RRs <2.0.

ORs and 95% CIs are presented for chemical-specific exposures, including TCE, from logistic regression models in two separate analyses, univariate analysis and multivariate analysis adjusting for age. The OR for TCE exposure is presented only from univariate analysis. Age may not greatly confound or bias the observed association; an examination of risk estimates from univariate and multivariate analyses of the aggregated exposure category for organic solvents showed similar ORs, indicating age was not a significant source of bias in the statistical analyses because age was controlled in the study's design, a control was matching to a case on age.

Nordstrom M, Hardell L, Hagberg H, Rask-Andersen A. (1998). Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukemia evaluated in a case-control study. Br J Cancer 77:2048–2052.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Abstract—To evaluate occupational exposure as risk factors for hairy cell leukemia.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	121 cases of hairy cell leukemia in males reported to the Swedish Cancer Registry between 1987 and 1992. 484 controls (1:4 matching) identified from Swedish Population Registry and matched for age and county of residence.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Not identified in paper, likely ICD-9 (http://www.socialstyrelsen.se/, accessed February 6, 2009).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Self-reported information on occupational exposure as obtained from a mailed questionnaire to study participants. Questionnaire sought information on complete working history, other exposures, and leisure time activities with telephone interview in cases of incomplete information. Paper does not describe the procedure for assigning chemical exposures from job title information.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Mailed questionnaire.
Blinded interviewers	Follow-up telephone interview and job/exposure coding were done blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Proxy responses: 4%, cases; 1% controls.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	111 hairy cell leukemia cases, 400 controls. Response rate: 91% cases and 83% controls. Exposure prevalence among cases is 8 and 7% among controls.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Cases and controls are matched for age, sex, and county of residence. Effect measure for TCE exposure from univariate analysis presented in paper; other possible confounders or covariates not included in statistical analysis.
Statistical methods	Logistic regression.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.6.9. Fritschi and Siemiatycki (1996a), Siemiatycki (1991).

B.3.2.6.9.1. Author's abstract.

The known risk factors for lymphoma and myeloma cannot account for the current incidence rates of these cancers, and there is increasing interest in exploring occupational causes. We present results regarding lymphoma and myeloma from a large case-control study of hundreds of occupational exposures and 19 cancer sites. We examine in more detail those exposures previously considered to be related to these cancers, as well as exposures which were strongly related in our initial analyses. Lymphoma was not associated in our data with exposure to solvents or pesticides, or employment in agriculture or wood-related occupations, although numbers of exposed cases were sometimes small. Hodgkin's lymphoma was associated with exposure to fabric dust, and non-Hodgkin's lymphoma was associated with exposure to copper dust, ammonia and a number of fabric and textile-related occupations and exposures. Employment as a sheet metal worker was associated with development of myeloma.

B.3.2.6.9.2. Study description and comment.

This population study of several cancer sites included histologically-confirmed cases of NHL, Hodgkin lymphoma and myeloma ascertained from 16 Montreal-area hospitals between 1979 and 1985 and part of a larger study of 10 other cancer sites. This study relies on the use of expert assessment of occupational information on a detailed questionnaire and face-to-face interview. Fritschi and Siemiatycki (1996a) present observations of analyses examining industries, occupation, and some chemical-specific exposures, including solvents, but not TCE. Observations on TCE are found in the original report of Siemiatycki (1991).

A total of 215 NHL cases (83% response) were identified from 19 Montreal-area hospitals and while this case group is larger than that in Swedish lymphoma case-control studies, there are fewer NHL cases than other multicenter studies published since 2000. The 533 population controls (72% response), identified through the use of random digit dialing, and were used for each site-specific cancer case analyses. All controls were interviewed using face-to-face methods; however, 20% of the NHL cases were either too ill to interview or had died and, for these cases, occupational information was provided by a proxy respondent. The quality of interview conducted with proxy respondents was much lower, increasing the potential for misclassification bias, than that with the subject. The direction of this bias would diminish observed risk towards the null. Interviewers were unblinded, although exposure assignment was carried out blinded as to case and control status. The questionnaire sought information on the subject's complete job history and included questions about the specific job of the employee and work environment. Occupations considered with possible TCE exposure included machinists, aircraft mechanics, and industrial equipment mechanics. An additional specialized questionnaire was developed for certain job title of a prior interest that sought more detailed information on

tasks and possible exposures. For example, the supplemental questionnaire for machinists included a question on TCE usage.

A team of industrial hygienists and chemicals assigned exposures blinded based on job title and other information obtained by questionnaire. A semiquantitative scale was developed for 294 exposures and included TCE (any, substantial). Any exposure to TCE was 3% among cases but <1% for substantial TCE exposure; "substantial" is defined as ≥10 years of exposure for the period up to 5 years before diagnosis. The TCE exposure frequencies in this study are lower than those in more recent NHL case-control studies examining TCE. The expert assessment method is considered a valid and reliable approach for assessing occupational exposure in community-base studies and likely less biased from exposure misclassification than exposure assessment based solely on self-reported information (Fritschi et al., 2003; IOM, 2003; Siemiatycki et al., 1997).

Logistic regression models adjusted for age, ethnicity, income, and respondent status (Fritschi and Siemiatycki, 1996a) or Mantel-Haenszel χ^2 stratified on age, family income, and cigarette smoking (Siemiatycki, 1991). Odds ratios for TCE exposure are presented with 90% CIs in Siemiatycki (1991) and with 95% CIs in Fritschi and Siemiatycki (1996).

The strengths of this study were the large number of incident cases, specific information about job duties for all jobs held, and a definitive diagnosis of NHL. However, the use of the general population (rather than a known cohort of exposed workers) reduced the likelihood that subjects were exposed to TCE, resulting in relatively low statistical power for the analysis. The JEM, applied to the job information, was very broad since it was used to evaluate 294 chemicals. Overall, a reasonably good exposure assessment is found in this analysis; however, examination of NHL and TCE exposure is limited by statistical power considerations related to low exposure prevalence, particularly for "substantial" exposure. For the exposure prevalence found in this study to TCE and for NHL, the minimum detectable OR was 3.0 when $\beta = 0.02$ and $\alpha = 0.05$ (one-sided). The low statistical power to detect a doubling of risk and an increased possibility of misclassification bias associated with case occupational histories resulting from proxy respondents suggests this study is less sensitive than other NHL case-controls published since 2000 for examining NHL and TCE.

Fritschi L, Siemiatycki J. (1996a). Lymphoma, myeloma and occupation: Results of a case-control study. Int J Cancer 67: 498–503.

Siemitycki J. (1991). Risk Factors for Cancer in the Workplace. J Siemiatycki, Ed. Baca Raton: CRC Press.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This population case-control study of NHL was designed to investigate association between specific exposure and cancers at 20 sites using expert assessment method for exposure assignment.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	258 histologically-confirmed NHL cases were identified among Montreal area males, aged 35–70 yrs, diagnosed in 16 Montreal hospitals between 1979 and 1985. 740 male population controls were identified from the same source population using random digit dialing methods.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	NHL.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICDO-0, 200 and 202, International Statistical Classification of Diseases for Oncology (WHO, 1977). ICDO-0 is based upon rubrics of ICD, 9th Revision.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Unblinded interview using questionnaire sought information on complete job history with supplemental questionnaire for jobs of a priori interest (e.g., machinists, painters). Team of chemist and industrial hygienist assigned exposure using job title with a semiquantitative scale developed for 300 exposures, including TCE. For each exposure, a three-level ranking was used for concentration (low or background, medium, high) and frequency (percent of working time: low, 1–5%; medium, >5–30%; and high, >30%).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Yes, 82% of case interviews were face-to-face; 100% of control interviews were with subject.
Blinded interviewers	Interviews were unblinded but exposure coding was carried out blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Yes, ~20% of cases had proxy respondents. Interviews were completed with all control subjects.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	215 cases (83% response), 533 population controls (71%). Exposure prevalence: Any TCE exposure, 3% cases; substantial TCE exposure (exposure for ≥10 yrs and up to 5 yrs before disease onset), <1% cases.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, income, index for cigarette smoking (Siemiatycki, 1991). Age, proxy status, income, ethnicity (Fritschi and Siemiatycki, 1996a).
Statistical methods	Mantel-Haenszel (Siemiatycki, 1991). Unconditional logistic regression (Fritschi and Siemiatycki, 1996a).
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.6.10. Hardell et al. (1994; 1981).

B.3.2.6.10.1. Author's abstract.

> Results on 105 cases with histopathologically confirmed non-Hodgkin's lymphoma (NHL) and 335 controls from a previously published case-control study on malignant lymphoma are presented together with some extended analyses. No occupation was a risk factor for NHL. Exposure to phenoxyacetic acids yielded, in the univariate analysis, an odds ratio of 5.5 with a 95% confidence interval of 2.7-11. Most cases and controls were exposed to a commercial mixture of 2, 4-dichlorophenoxyacetic acid and 2, 4, 5-trichlorophenoxyacetic acid. Exposure to chlorophenols gave an odds ratio of 4.8 (2.7-8.8) with pentachlorophenol being the most common type. Exposure to organic solvents yielded an odds ratio of 2.4 (1.4-3.9). These results were not significantly changed in the multivariate analysis. Dichlorodiphenyltrichloroethane, asbestos, smoking, and oral snuff were not associated with an increased risk for NHL. The results regarding increased risk for NHL following exposure to phenoxyacetic acids, chlorophenols, or organic solvents were not affected by histopathological type, disease stage, or anatomical site of disease presentation. Median survival was somewhat longer in cases exposed to organic solvents than the rest. This was explained by more prevalent exposure to organic solvents in the group of cases with good prognosis NHL histopathology.
>
> A number of men with malignant lymphoma of the histiocytic type and previous exposure to phenoxy acids or chlorophenols were observed and reported in 1979. A matched case-control study has therefore been performed with cases of malignant lymphoma (Hodgkin's disease and non-Hodgkin lymphoma). This study included 169 cases and 338 controls. The results indicate that exposure to phenoxy acids, chlorophenols, and organic solvents may be a causative factor in malignant lymphoma. Combined exposure of these chemicals seemed to increase the risk. Exposure to various other agents was not obviously different in cases and in controls.

B.3.2.6.10.2. Study description and comment.

Exposure in these case-control studies of histologically-confirmed lymphoma (NHL and Hodgkin lymphoma) (Hardell et al., 1981) or only the NHL cases only (Hardell et al., 1994) over a 4-year period, 1974–1978, in Umea, Sweden was assessed based upon information provided in a self-administered questionnaire. The questionnaire obtained information on a complete working history over the life of the subjects along with information on various other exposures and leisure time activities. Organic solvent exposures were examined secondary to this study's primary hypothesis examining phenoxy acid or chlorophenol exposures and lymphoma. The extent of recall bias related to self-reported information cannot be determined nor is information provided in the published papers misclassification bias resulting from next-of-kin interviews. Occupations were classification according to the Nordic Working Classification system. Chemical-specific exposures assignment was not described but appears to have been carried out

blinded as to case or control status. A semiquantitative classification scheme based on intensity and duration of exposure was used to categorize solvent exposure into two groupings: low grade—<1 week continuously or <1 month in total—and high grade for all other exposure scenarios. TCE exposure prevalence is similar in both studies; 4% for cases and 1% for controls. The low exposure prevalence and small numbers of cases with TCE exposure (n = 4) limits the statistical power of these analyses and results in wide CIs around the estimated OR for TCE exposure (95% CI, 1.3–42).

The Rappaport Classification was used to identify NHL and Hodgkin lymphoma cases. The Rappaport Classification was in widespread use until the 1970s and was based on a cell's pathologic characteristics. Equivalence of NHL groupings according to Rappaport Classification system to ICDA-8 groupings, also in use during this time period, is 200 "Lymphosarcoma and reticulum-cell sarcoma" and 202 "Other neoplasms of lymphoid tissue."

Hardell L, Eriksson M, Degerman A. (1994). Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. Cancer Res 54:2386–2389.

Hardell L, Eriksson M, Lenner P, Lundgren E. (1981). Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br J Cancer 43:169–176.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	NHL cases from a case-control study of lymphoma (NHL and Hodgkin lymphoma) are analyzed separately to evaluate herbicide and organic solvents exposure.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	105 cases of histologically-confirmed NHL among males aged 25–85 yrs admitted to local hospital's oncology department between 1974 and 1978. A total of 335 male controls identified from the Swedish Population Registry, for living cases, and from the Swedish Registry for Causes of Death, for dead cases. Controls matched to cases by age, residence municipality, and year of death, for dead cases.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Rappaport Classification; equivalent to ICDA-8 Codes, 200, and 202.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Self-reported information on occupational exposure as obtained by questionnaire, with a telephone interview for incomplete or unclear information. Questionnaire sought information on complete working history, other exposures and leisure time activities. Paper does not describe the procedure for assigning chemical exposures from job title information.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	No information in paper.
Blinded interviewers	Follow-up telephone interview was done blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	No information in paper.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	105 NHL cases, 332 controls. Response rates could not be calculated given insufficient information in paper. Prevalence of TCE exposure, 4% cases, 1% controls.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Cases and controls matched on sex, age, place of residence, and vital status. Deceased controls are matched to deceased cases on year of death.
Statistical methods	Mantel-Haenszel stratified by age and vital status.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.7. Childhood Leukemia

B.3.2.7.1. Shu et al. (2004; 1999)

B.3.2.7.1.1. Author's abstract.

Ras proto-oncogene mutations have been implicated in the pathogenesis of many malignancies, including leukemia. While both human and animal studies have linked several chemical carcinogens to specific ras mutations, little data exist regarding the association of ras mutations with parental exposures and risk of childhood leukemia. Using data from a large case control study of childhood acute lymphoblastic leukemia (ALL; age <15 years) conducted by the Children's Cancer Group, we used a case-case comparison approach to examine whether reported parental exposure to hydrocarbons at work or use of specific medications are related to ras gene mutations in the leukemia cells of children with ALL. DNA was extracted from archived bone marrow slides or cryopreserved marrow samples for 837 ALL cases. We examined mutations in K-ras and N-ras genes at codons 12, 13, and 61 by PCR and allele-specific oligonucleotide hybridization and confirmed them by DNA sequencing. We interviewed mothers and, if available, fathers by telephone to collect exposure information. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from logistic regression to examine the association of parental exposures with ras mutations. A total of 127 (15.2%) cases had ras mutations (K-ras 4.7% and N-ras 10.68%). Both maternal (OR 3.2, 95% CI 1.7-6.1) and paternal (OR 2.0, 95% CI 1.1-3.7) reported use of mind-altering drugs were associated with N-ras mutations. Paternal use of amphetamines or diet pills was associated with N-ras mutations (OR 4.1, 95% CI 1.1-15.0); no association was observed with maternal use. Maternal exposure to solvents (OR 3.1, 95% CI 1.0-9.7) and plastic materials (OR 6.9, 95% CI 1.2-39.7) during pregnancy and plastic materials after pregnancy (OR 8.3, 95% CI 1.4-48.8) were related to K-ras mutation. Maternal ever exposure to oil and coal products before case diagnosis (OR 2.3, 95% CI 1.1-4.8) and during the postnatal period (OR 2.2, 95% CI 1.0-5.5) and paternal exposure to plastic materials before index pregnancy (OR 2.4, 95% CI 1.1-5.1) and other hydrocarbons during the postnatal period (OR 1.8, 95% CI 1.0-1.3) were associated with N-ras mutations. This study suggests that parental exposure to specific chemicals may be associated with distinct ras mutations in children who develop ALL.

Parental exposure to hydrocarbons at work has been suggested to increase the risk of childhood leukemia. Evidence, however, is not entirely consistent. Very few studies have evaluated the potential parental occupational hazards by exposure time windows. The Children's Cancer Group recently completed a large-scale case-control study involving 1842 acute lymphocytic leukemia (ALL) cases and 1986 matched controls. The study examined the association of self-reported occupational exposure to various hydrocarbons among parents with risk of childhood ALL by exposure time window, immunophenotype of ALL, and age at diagnosis. We found that maternal exposure to solvents [odds ratio (OR), 1.8; 95% confidence interval (CI), 1.3-2.5] and paints or thinners (OR, 1.6; 95% CI, 1.2-2.2) during the preconception period (OR, 1.6; 95% CI, 1.1-2.3) and during pregnancy (OR, 1.7; 95% CI, 1.2-2.3) and to plastic materials during the postnatal period (OR, 2.2; 95% CI, 1.0-4.7) were related to an increased risk of childhood ALL. A positive association between ALL and paternal exposure to plastic

materials during the preconception period was also found (OR, 1.4; 95% CI, 1.0-1.9). The ALL risk associated with parental exposures to hydrocarbons did not vary greatly with immunophenotype of ALL. These results suggest that the effect of parental occupational exposure to hydrocarbons on offspring may depend on the type of hydrocarbon and the timing of the exposure.

B.3.2.7.1.2. Study description and comment.

Parent hydrocarbon occupational exposure in this case-control study of acute lymphatic leukemia in children <15 years of age was assessed from telephone questionnaire to mothers and, whenever available, fathers of cases and controls who were part of the large-scale incidence study by the Children's Cancer/Oncology Group. A recent paper examines hydrocarbon exposures and relationship with the ras proto-oncogene (Shu et al., 2004). Nearly 50% of childhood leukemia cases in the United States were treated by a Children's Cancer Group hospital or institution and between January 1, 1989 and June 15, 1993, the study period, a total of 2,081 incident childhood leukemia cases were identified with 1,914 interviews with mothers. Controls were randomly selected using a random digit dialing procedure and matched to cases on age, race, and geographic location. Using structured questionnaires, parents or a surrogate when unavailable were asked about job title, industry, duties, starting and stopping date for all jobs held by the father for >6 months beginning at age 18 years and by the mother for all jobs held at least 6 months in the period from 2 year prior to the index pregnancy to date of diagnosis of leukemia case or the reference date of the controls. The questionnaire sought information on specific exposures to solvents (carbon tetrachloride, TCE, benzene, toluene, and xylene), plastic materials, paints, pigments or thinners, and oil or coal products. Exposure quantitative was not possible. Statistical analyses use self-reported exposure to specific hydrocarbons as defined as a dichotomous variable (yes/no). The potential for misclassification bias is greater with exposure assessment based upon self-reports compared to that by expert assessment (Teschke et al., 2002). Exposure information was linked to start and stop data of the relevant job to determine the timing of exposure related to specific windows of possible susceptibility for ALL. The author's do not describe jobs associated with possible TCE exposure.

The father's questionnaire was completed for 1,801 of the 2,081 eligible cases and 1,813 of the 2,597 eligible controls. Of the 1,618 matched sets, direct interview with fathers were obtained for 83% of cases and 68% of controls. Maternal interview were completed for 1,914 of the 2,081 eligible cases (92%). The low prevalence of any exposure to TCE, 1% for mothers (15 cases of 1,842 matched pairs with maternal exposure information) and 8% for fathers (136 cases out 1,618 matched pairs), limits the statistical power of this study to detect low to moderate risk.

Shu Xo, Perentesis JP, Wen W, Buckley JD, Boyle E, Ross, JA, Robison LL. (2004). Parental exposure to medications and hydrocarbons and ras mutations in children with acute lymphoblastic leukemia: A report from the Children's Oncology Group. Cancer Epidemiol Biomarkers Prev 13:1230–1235.

Shu XO, Stewart P, Wen W-Q, Han D, Potter JD, Buckley JD, Heineman E, Robison LL. (1999). Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring. Cancer Epidemiol Markers Prev 8:783–291.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Shu et al. (2004; 1999) examine possible association with a number of maternal and paternal exposures among cases and controls identified from the Children's Cancer/Oncology Group. The Children's Cancer/Oncology Group is an association of >120 centers in the United States, Canada, and Australia who collaboratively carry out research on risk factors and treatment of childhood cancers.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	848 children with acute lymphatic leukemia of ages 0–9 yrs of age at diagnosis from 1980 to 1993 and ≤14 yrs old at diagnosis between 1994 and 2000 were identified from cancer care centers in Québec, Canada. Controls are concurrently identified from population, from 1980 to 1993, from family allowance files and from 1994 to 2000, from universal health insurance files; and, matched (1:1 matching ratio) to cases on sex and age at the time of diagnosis (calendar date). Participation rates- 93.1% cases (790 of 849 eligible cases); 86.2% controls (790 of 916 eligible controls).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Childhood leukemia incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD, 9th revision, Code 204.0.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Telephone interviews of mothers of cases and controls using structured questionnaire were administered to obtain information on general risk factors and potential confounders. Questionnaire also sought information on a complete job history, for the mother from 18 yrs of age to the end of pregnancy and included for each job, job title, dates of employment, type of industry, and location of employer. Statistical analyses based on self-reported occupational exposure to hydrocarbons as defined by broad groups and individual hydrocarbons.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	

CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Telephone interview, >99% response.
Blinded interviewers	Telephone interviews were not blinded, but exposure assignment and coding was carried out blinded to case and control status by chemists and industrial hygienists.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	100% of cases and controls had maternal history provided by direct interview with mothers. 13% of cases and 30% of controls had paternal information provided by proxy respondent (e.g., through maternal interview).
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	15 cases (2% exposure prevalence) and 9 controls (1% exposure prevalence) with maternal TCE exposure. 136 cases (8% exposure prevalence) and 104 controls (13% exposure prevalence) with paternal TCE exposure.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Child's age at time of diagnosis, sex, and calendar year of diagnosis, maternal age and level of schooling.
Statistical methods	Conditional logistic regression By two time periods; 2 yrs before pregnancy up to birth, during specific pregnancy period. By level of exposure; Level 1 (some exposure) compared to no exposure, and Level 2 (greater exposure potential) compared to no exposure.
Exposure-response analysis presented in published paper	Yes.
Documentation of results	Yes.

B.3.2.7.2. Costas et al. (2002), MDPH (1997b).

B.3.2.7.2.1. Author's abstract.

A 1981 Massachusetts Department of Public Health study confirmed a childhood leukemia cluster in Woburn, Massachusetts. Our follow-up investigation attempts to identify factors potentially responsible for the cluster. Woburn has a 130-year industrial history that resulted in significant local deposition of tannery and chemical manufacturing waste. In 1979, two of the city's eight municipal drinking water wells were closed when tests identified contamination with solvents including trichloroethylene. By 1986, 21 childhood leukemia cases had been observed (5.52 expected during the seventeen year period) and the case-control investigation discussed herein was begun. Nineteen cases and 37 matched controls comprised the study population. A water distribution model provided contaminated public water exposure estimates for subject residences. Results identified a non-significant association between potential for exposure to contaminated water during maternal pregnancy and leukemia diagnosis, (odds RATIO=8.33, 95% CI 0.73–94.67). However, a significant dose-response relationship (P<0.05) was identified for this exposure period. In contrast, the child's potential for exposure from birth to diagnosis showed no association with leukemia risk. Wide confidence intervals suggest cautious interpretation of association magnitudes. Since 1986, expected incidence has been observed in Woburn including 8 consecutive years with no new childhood leukemia diagnoses.

B.3.2.7.2.2. Study description and comment.

Exposure in this case-control study of childhood leukemia over a 20-year period in Woburn, Massachusetts was assessed based upon the potential for a residence at the time of diagnosis to receive water from wells G and H, wells with a hydraulic mixing model of Murphy (Murphy, 1990), which described the town's water distribution system. Monitoring of wells G and H in 1979 showed the presence of several VOCs; TCE and perchloroethylene (PERC) were found to exceed drinking water guidelines, at 267 and 21 ppb, respectively. Low levels of other contaminates were detected including chloroform, 1,2-DCE methyl chloroform, trichlorotrifluoroethane, and inorganic arsenic. The Murphy model described the water flow through Woburn during the lifetime of wells G and H. The model uses data describing the physical layout of Woburn's municipal water system and information regarding the pumping cycles of wells G and H and other active uncontaminated wells that supplied the municipal water system. Model accuracy showed distribution of water from wells G and H to a block area with predicted mixture concentrations with an average error within 10% of the know concentration. Nearly 70% of the model predictions were within 20% of the know validation concentrations. An exposure value for cases and controls by exposure period was the sum of the model-predicted water concentration for each residence in Woburn as assigned to a hydrologically-distinct area along the water distribution network. Both cumulative and average exposure estimates were derived using the model.

Costas K, Knorr RS, Condon SK. (2002). A case-control study of childhood leukemia in Woburn, Massachusetts: the relationship between leukemia incidence and exposure to public drinking water. Sci Total Environ 300:23–25.

Massachusetts Department of Public Health (MDPH). (1997b). Woburn Childhood Leukemia Follow-up Study. Volumes I and II. Final Report.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Yes, "this follow-up investigation attempts to identify factors potentially responsible for the leukemia cluster in Woburn, MA" and the primary exposure of concern for investigation is "the potential consumption of contaminated water from Wells G and H by Woburn residents."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	21 cases of leukemia diagnosed in children <19 yrs between 1969 and 1989 who were residents of Woburn Massachusetts. Cases diagnosed from 1982 and latter were provided by the Massachusetts Cancer Registry. Cases diagnosed prior to 1982 were identified from local pediatric health professionals and by contacting all greater-Boston childhood oncology centers that treated children with leukemia. Two controls for each case were randomly selected from Woburn Public School records on a geographically basis and matched to cases on race, sex and date of birth (± 3 months).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Childhood leukemia incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-O (Acute Lymphatic Leukemia, Acute Myelogenous Leukemia, and Chronic Myelogenous Leukemia).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	In-person interviewers with mothers and fathers of cases and controls using questionnaire to gather information regarding demographics, residential information for the mother and child, occupational history, maternal medical and reproductive history, child's medical history, and lifestyle questions. The father's questionnaire contained questions concerning military and occupational history and also included duplicate questions on maternal occupational history, child's medical history, and lifestyle habits. A hydraulic mixing computer model describing Woburn's water distribution system was utilized to assign an exposure index expressed as cumulative number of months a household received contaminated drinking water from Wells G and H. Exposure Index = fraction of time during month when water from Wells G and H reached the user area + fraction of water from Wells G and H supplied to user area. No quantitative measures of TCE and other volatile organic solvents concentrations were included in hydraulic mixing model.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	

CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Personal interviews with cases and controls; 19 of 21 cases (91%) and 38 of possible 54 controls (70%) were interviewed.
Blinded interviewers	Interviewers were not blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	One parent interviewed for 21% of cases and 11% of controls.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	Participation rates- 93.1% cases (790 of 849 eligible cases); 86.2% controls (790 of 916 eligible controls).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Composite covariates used to control for SES, maternal smoking during pregnancy, maternal age at birth of child, and maternal alcohol consumption during pregnancy.
Statistical methods	Conditional logistic regression.
Exposure-response analysis presented in published paper	Yes.
Documentation of results	Yes and includes information in MDPH Final Report (1997b).

B.3.2.7.3. McKinney et al. (1991).

B.3.2.7.3.1. Author's abstract.

OBJECTIVE--To determine whether parental occupations and chemical and other specific exposures are risk factors for childhood leukemia. DESIGN--Case-control study. Information on parents was obtained by home interview. SETTING--Three areas in north England: Copeland and South Lakeland (west Cumbria); Kingston upon Hull, Beverley, East Yorkshire, and Holderness (north Humberside), and Gateshead. SUBJECTS--109 children aged 0-14 born and diagnosed as having leukemia or non-Hodgkin's lymphoma in study areas during 1974-88. Two controls matched for sex and date and district of birth were obtained for each child. MAIN OUTCOME MEASURES--Occupations of parents and specific exposure of parents before the children's conception, during gestation, and after birth. Other adults living with the children were included in the postnatal analysis. RESULTS--Few risk factors were identified for mothers, although preconceptional association with the food industry was significantly increased in case mothers (odds ratio 2.56; 95% confidence interval 1.32 to 5.00). Significant associations were found between childhood leukemia and reported preconceptional exposure of fathers to wood dust (2.73, 1.44 to 5.16), radiation (3.23, 1.36 to 7.72), and benzene (5.81, 1.67 to 26.44); ionizing radiation alone gave an odds ratio of 2.35 (0.92 to 6.22). Raised odds ratios were found for paternal exposure during gestation, but no independent postnatal effect was evident. CONCLUSION--These results should be interpreted cautiously because of the small numbers, overlap with another study, and multiple exposure of some parents. It is important to distinguish periods of parental exposures; identified risk factors were almost exclusively restricted to the time before the child's birth.

B.3.2.7.3.2. Study description and comment.

A population case-control study of ALL and NHL in children of <14 years of age and residing in three areas in the United Kingdom was carried out to identify possible risk factors for the region's observed increased background childhood leukemia rates. The Sellafield nuclear reprocessing plant was located in one of the areas and one hypothesis was an examination of parental radiation exposure and childhood lymphoma. Unblinded face-to-face interviews with cases, identified from regional tumor registries, and controls, identified using regional birth registers, used a structured questionnaire to ascertain a complete history of employment and exposure to specific substances and radiation from both child's biological parents, preferred, although, in the absence of one parent, surrogate information by the other parent was obtained from the date of first employment to end of the study period or, if earlier, the date the parent ceased seeing the child. The questionnaire additionally sought information on maternal and paternal exposure to 22 known chemical carcinogens. McKinney et al. (1991) noted that exposures were highly correlated. Information on job title and industry as reported in the questionnaire was coded independently by experts to occupational groupings and titles using a national classification scheme from the Office of Population Census and Surveys and is a

strength of this study. The category of metal refining industry and occupations was one of nine occupational groups identified a priori for hypothesis testing. Statistical analyses are based on exposure as defined by industry, occupational title, or chemical-specific exposure.

Interviewers with one or both parents were carried out for 109 of 151 eligible cases (72%) and with 206 of 269 eligible controls (77%), and the low exposure prevalence; no information was presented on the number of surrogate interviews, or, where only one parent responded for both parents. The low prevalence of TCE exposure, five discordant pairs (one subject with exposure and the matched subject without exposure) identified with maternal TCE exposure and 16 discordant pairs with paternal preconceptional TCE exposure, greatly limited the statistical power of this study.

McKinney PA, Alexander FE, Cartwright RA, Parker L. (1991). Parental occupations of children with leukemia in west Cumbria, north Humberside, and Gateshead. BMJ 302:681–687.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This study examines a number of risk factors (specific chemicals and occupational groups) as possibly associated with the high background rate of acute lymphatic leukemia and NHL in children ≤14 yrs in the three regions. 22 individual chemicals and 7 occupational groups for a priori hypothesis testing.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	151 case children identified from two tumor registries (Yorkshire and Northern Region). No information provided in paper on reporting accuracy of these registries. 269 population controls identified from District health authority birth registers and matched to cases on age, sex, and region of residency at time of case diagnosis. Participation rates- 72% of cases (n = 109) and 77% of controls (n = 206).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Childhood leukemia incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	No information provided in published paper.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Face-to-face interviews of mothers of cases and controls using structured questionnaire were administered to obtain information on general risk factors and potential confounders. Questionnaire also sought information on a maternal and paternal complete job history, from first employment to end of study and included for job title, dates of employment, and industry. Questionnaire administered to both parents, and, if one parent was unavailable, information was provided by proxy. Questionnaire also sought information on 22 specific chemicals. Expert assignment of occupation based upon National classification system. Statistical analyses industry of employment, job or occupation, and specific exposures.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	No, face-to-face interview with 72% of case parents and 77% of control parents.
Blinded interviewers	Face-to-face interviews were not blinded. Expert assignment of occupation was carried out blinded.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	No information provided in paper on percentage of proxy interviews.

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	Exposure prevalence to TCE—maternal exposure, 2 cases (2%) and 3 controls (2%); paternal exposure, 9 cases (9%) and 7 controls (4%).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Cases and control matched on age, sex, and region of residency at time of case diagnosis.
Statistical methods	Discordant pair analysis.
Exposure-response analysis presented in published paper	No.
Documentation of results	Limited reporting of ORs for job title and occupations.

B.3.2.7.4. Lowengart et al. (1987)

B.3.2.7.4.1. Author's abstract.

> A case-control study of children of ages 10 years and under in Los Angeles County was conducted to investigate the causes of leukemia. The mothers and fathers of acute leukemia cases and their individually matched controls were interviewed regarding specific occupational and home exposures as well as other potential risk factors associated with leukemia. Analysis of the information from the 123 matched pairs showed an increased risk of leukemia for children whose fathers had occupational exposure after the birth of the child to chlorinated solvents [odds ratio (OR) = 3.5, P = .01], spray paint (OR = 2.0, P = .02), dyes or pigments (OR = 4.5, P = .03), methyl ethyl ketone (CAS: 78-93-3; OR = 3.0, P = .05), and cutting oil (OR = 1.7, P = .05) or whose fathers were exposed during the mother's pregnancy with the child to spray paint (OR = 2.2, P = .03). For all of these, the risk associated with frequent use was greater than for infrequent use. There was an increased risk of leukemia for the child if the father worked in industries manufacturing transportation equipment (mostly aircraft) (OR = 2.5, P = .03) or machinery (OR = 3.0, P = .02). An increased risk was found for children whose parents used pesticides in the home (OR = 3.8, P = .004) or garden (OR = 6.5, P = .007) or who burned incense in the home (OR = 2.7, P = .007). The risk was greater for frequent use. Risk of leukemia was related to mothers' employment in personal service industries (OR = 2.7, P = .04) but not to specified occupational exposures. Risk related to fathers' exposure to chlorinated solvents, employment in the transportation equipment-manufacturing industry, and parents' exposure to household or garden pesticides and incense remains statistically significant after adjusting for the other significant findings.

B.3.2.7.4.2. Study description and comment.

Self-assessed parental exposure to chemical classes and to individual chlorinated solvents was assigned in this case-control study of leukemia in children ≤10 years old using information obtained through telephone interviews with mothers and fathers of cases and controls. Interviews were carried out for 79% of case mothers (159 or 202 cases) and 81% (124 of 154) case fathers. The number of potential controls was not identified in the paper, although it was reported that interviews were carried out for 136 referent mothers and 87 referent fathers. Mothers served as proxy respondents for paternal exposures in roughly 20% of cases and 30% of controls. The complete occupational history was sought for the period 1 year before the case diagnosis date, if the case was older than 2 years, 6 months before the diagnosis date, if the case was between the ages of 1 and 2 years, and the same as the date of diagnosis of the case was <1 year old. Questions on specific occupational exposures such as solvents or degreasers, metals, and other categories were included on the questionnaire, with self-reported information used to assign exposure potential. Exposure is defined only as a dichotomous variable (yes/no). In this study using a matched-pair design in the statistical analyses, there were six case-control pairs of paternal cases but not controls and three case-control pairs with paternal controls but not cases

with TCE exposure before pregnancy or during pregnancy. Few mothers reported exposure to chlorinated solvents. A strength of the study is the ability to examine exposure at a number of developmental periods, preconception, during pregnancy, and postnatal. Misclassification bias is likely strong in this study, introduced through the large number of proxy respondents and exposure assessment based upon self-reported information. Misclassification resulting from proxy information will dampen observed risks, where as misclassification of self-reported exposures may bias observed risks in either direction. For this reason and because of the low prevalence of exposure nature of exposure assessment approach, this study provides little information on childhood leukemia risks and TCE exposure.

Lowengart RA, Peters JM, Cicioni C, Buckley J, Bernstein L, Preston-Martin S, Rappaport E. (1987). Childhood leukemia and parents' occupational and home exposures. JNCI 79:39–46.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This case-control study of children ≤10 yrs of age was conducted to identify possible risk factors of childhood leukemia. TCE exposure was one of many occupational exposures assessed in this study.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	202 cases of acute lymphatic leukemia in children ≤10 yrs of age at time of diagnosis from 1980 through 1984 were identified from the Los Angeles County Cancer Surveillance Program, a population-based cancer registry. Controls were identified from among friends of cases with additional controls selected using random digit dialing from the same population as cases and were matched to cases on age, sex, race, and Hispanic origin. 123 cases (61% response rate) and 123 controls (not able to calculate response rate since number of possible controls not identified in paper).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Not identified in paper.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Telephone questionnaire sought information on maternal and paternal preconception, pregnancy, and postnatal (up to 1 yr before case diagnosis) exposures, including a full occupational history (job title, employers, and dates of employments) and on the child's exposure from birth to 1 yr before case diagnosis. Parents also provide self-reported information on specific exposures or occupational activities. Occupations grouped according to hydrocarbon exposure potential using definition of Zack et al. (1980).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Telephone interview with 159 of 202 (79%) case mothers and 124 of 202 case fathers (61%). Of controls, interviews were obtained from 136 mothers (65 friends of cases, 71 population controls) and 87 fathers.
Blinded interviewers	Unblinded interviews.

CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Yes, 19% of paternal exposure information on cases was provided by the mother. 43 of 130 control mothers provided information on paternal exposures (33%).
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	Paternal TCE exposure 1 yr before pregnancy, 1/0 discordant pairs During pregnancy, 6/3 discordant pairs After delivery 8/3 discordant pairs. No information is provided in paper on maternal TCE exposure.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, race, and Hispanic origin.
Statistical methods	Discordant pair analysis.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.8. Melanoma Case-Control Studies

B.3.2.8.1. Fritschi and Siemiatycki (1996b), Siemiatycki (1991).

B.3.2.8.1.1. Author's abstract.

OBJECTIVES: Associations between occupational exposures and the occurrence of cutaneous melanoma were examined as part of a large population based case-control study of 19 cancer sites. METHODS: Cases were men aged 35 to 70 years old, resident in Montreal, Canada, with a new histologically confirmed cutaneous melanoma (n = 103). There were two control groups, a randomly selected population control group (n = 533), and a cancer control group (n = 533) randomly selected from among subjects with other types of cancer in the large study. Odds ratios for the occurrence of melanoma were calculated for each exposure circumstance for which there were more than four exposed cases (85 substances, 13 occupations, and 20 industries) adjusting for age, ethnicity, and number of years of schooling. RESULTS: Significantly increased risk of melanoma was found for exposure to four substances (fabric dust, plastic dust, trichloroethylene, and a group containing paints used on surfaces other than metal and varnishes used on surfaces other than wood), three occupations (warehouse clerks, salesmen, and miners and quarrymen), and two industries (clothing and non-metallic mineral products). CONCLUSIONS: Most of the occupational circumstances examined were not associated with melanoma, nor is there any strong evidence from previous research that any of those are risk factors. For the few occupational circumstances which were associated in our data with melanoma, the statistical evidence was weak, and there is little or no supporting evidence in the scientific literature. On the whole, there is no persuasive evidence of occupational risk factors for melanoma, but the studies have been too small or have involved too much misclassification of exposure for this conclusion to be definitive.

B.3.2.8.1.2. Study description and comment.

Fritschi and Siemiatycki (1996b) and Siemiatycki (1991) reported data from a case-control study of occupational exposures and melanoma conducted in Montreal, Quebec (Canada) and part of a larger study of 10 other site-specific cancers and occupational exposures. The investigators identified 124 newly diagnosed cases of melanoma (ICD-O, 172), confirmed on the basis of histology reports, between 1979 and 1985; 103 of these participated in the study interview (83.1% participation). One control group (n = 533) consisted of patients with other forms of cancer recruited through the same study procedures and time period as the melanoma cancer cases. A population-based control group (n = 533, 72% response), frequency matched by age strata, was drawn using electoral lists and random digit dialing. Face-to-face interviews were carried out with 82% of all cancer cases with telephone interview (10%) or mailed questionnaire (8%) for the remaining cases. Twenty percent of all case interviews were provided by proxy respondents. The occupational assessment consisted of a detailed description of each job held during the working lifetime, including the company, products, nature of work at site, job

activities, and any additional information that could furnish clues about exposure from the interviews.

A team of industrial hygienists and chemists blinded to subject's disease status translated jobs into potential exposure to 294 substances with three dimensions (degree of confidence that exposure occurred, frequency of exposure, and concentration of exposure). Each of these exposure dimensions was categorized into none, any, or substantial exposure. Fritschi and Siemiatycki (1996b) present observations of logistic regression analyses examining industries, occupation, and some chemical-specific exposures, but not TCE. Observations on TCE from Mantel-Haenszel analyses are found in the original report of Siemiatycki (1991). Any exposure to TCE was 6% among cases (n = 8) and 4% for substantial TCE exposure (n = 4); "substantial" is defined as ≥10 years of exposure for the period up to 5 years before diagnosis.

Logistic regression models adjusted for age, ethnic origin, SES, Quetlet as an index of body mass, and respondent status (Fritschi and Siemiatycki, 1996b) or Mantel-Haenszel χ^2 stratified on age, family income, cigarette smoking, Quetlet, ethnic origin, and respondent status (Siemiatycki, 1991). Odds ratios for TCE exposure are presented with 90% CIs in Siemiatycki (1991) and 95% CIs in Fritschi and Siemiatycki (1996b).

The strengths of this study were the large number of incident cases, specific information about job duties for all jobs held, and a definitive diagnosis of melanoma. However, the use of the general population (rather than a known cohort of exposed workers) reduced the likelihood that subjects were exposed to TCE, resulting in relatively low statistical power for the analysis. The JEM, applied to the job information, was very broad since it was used to evaluate 294 chemicals.

Fritschi L, Siemiatycki J. (1996b). Melanoma and occupation: Results of a case-control study. 1996. Occup Environ Med 53:168–173.

Siemiatycki J. (1991). Risk Factors for Cancer in the Workplace. J Siemiatycki, Ed. Boca Raton: CRC Press.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This population case-control study was designed to generate hypotheses on possible association between 11 site-specific cancers and occupational title or chemical exposures.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	124 melanoma cases were identified among male Montreal residents between 1979 and 1985 of which 103 were interviewed. 740 eligible male controls identified from the same source population using random digit dialing or electoral lists; 533 were interviewed. A second control series consisted of other cancer cases identified in the larger study (n = 533). Participation rate: cases, 83.1%; population controls, 72%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-O, 172 (malignant neoplasm of skin).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Unblinded interview using questionnaire sought information on complete job history with supplemental questionnaire for jobs of a priori interest (e.g., machinists, painters). Team of chemist and industrial hygienist assigned exposure using job title with a semiquantitative scale developed for 294 exposures, including TCE. For each exposure, a three-level ranking was used for concentration (low or background, medium, high) and frequency (percent of working time: low, 1–5%; medium, >5–30%; and high, >30%).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	82% of all cancer cases interviewed face-to-face by a trained interviewer, 10% telephone interview, and 8% mailed questionnaire. Cases interviews were conducted either at home or in the hospital; all population control interviews were conducted at home.
Blinded interviewers	Interviews were unblinded but exposure coding was carried out blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Yes, 20% of all cancer cases had proxy respondents.

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	99 cases (76.7% response), 533 population controls (72%). Exposure prevalence: Any TCE exposure, 8% cases (n = 8); substantial TCE exposure (exposure for ≥10 yrs and up to 5 yrs before disease onset), 4% cases (n = 4).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, education, and ethnic origin (Fritschi and Siemiatycki, 1996b). Age, family income, cigarette smoking, and ethnic origin (Siemiatycki, 1991).
Statistical methods	Mantel-Haenszel (Siemiatycki, 1991). Logistic regression (Fritschi and Siemiatycki, 1996b).
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.9. Pancreatic Cancer Case-Control Studies

B.3.2.9.1. Kernan et al. (1999).

B.3.2.9.1.1. Author's abstract.

Background The relation between occupational exposure and pancreatic cancer is not well established. A population-based case-control study based on death certificates from 24 U.S. states was conducted to determine if occupations/ industries or work-related exposures to solvents were associated with pancreatic cancer death.
Methods The cases were 63,097 persons who died from pancreatic cancer occurring in the period 1984±1993. The controls were 252,386 persons who died from causes other than cancer in the same time period.
Results Industries associated with significantly increased risk of pancreatic cancer included printing and paper manufacturing; chemical, petroleum, and related processing; transport, communication, and public service; wholesale and retail trades; and medical and other health-related services. Occupations associated with significantly increased risk included managerial, administrative, and other professional occupations; technical occupations; and sales, clerical, and other administrative support occupations.
Potential exposures to formaldehyde and other solvents were assessed by using a job exposure matrix developed for this study. Occupational exposure to formaldehyde was associated with a moderately increased risk of pancreatic cancer, with ORs of 1.2, 1.2, 1.4 for subjects with low, medium, and high probabilities of exposure and 1.2, 1.2, and 1.1 for subjects with low, medium, and high intensity of exposure, respectively.
Conclusions The findings of this study did not suggest that industrial or occupational exposure is a major contributor to the etiology of pancreatic cancer. Further study may be needed to confirm the positive association between formaldehyde exposure and pancreatic cancer.

B.3.2.9.1.2. Study description and comment.

Kernan et al. (1999) reported data from a case-control study of occupational exposures and pancreatic cancer, coding usual occupation as noted on death certificates to assign potential TCE exposure to cases and controls. Deaths from pancreatic cancer from 1984 to 1993 were identified from 24 U.S. state and frequency-matched to nonpancreatitis or other pancreatic disease deaths by state, race, sex, and age (5-year groups); 63,097 pancreatic cancer deaths (case series) and 252,386 controls were selected for analysis.

Exposure assessment in this study group occupational (n = 509) and industry (n = 231) codes into 16 broad occupational and 20 industrial categories. Additionally, a JEM of Gomez et al. (1994) was applied to develop exposure surrogates for 11 chlorinated hydrocarbons, including TCE, and two larger groupings, all chlorinated hydrocarbons and organic solvents. A qualitative surrogate (ever exposed/never exposed) for TCE exposure is developed and no information is provided on death certifications on employment duration to examine exposure-response patterns.

Kernan et al. (1999) report mortality ORs from logistic regression for TCE exposure intensity and probability of exposure.

Overall, this is a large study that examined specific exposures using a generic JEM. Errors resulting from exposure misclassification are likely, not only introduced by the generic JEM, but through the use of usual occupation as coded on death certificates, which may not fully represent an entire occupational history.

Kernan GJ, Ji B-T, Dosemeci M, Silverman DT, Balbus J, Zahm SH. (1999). Occupational risk factors for pancreatic cancer: A case-control study based on death certificates from 24 U.S. states. Am J Ind Med 36:260–270.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This population case-control study was designed to generate hypotheses on possible association between pancreatic cancers and occupational title or chemical exposures.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	63,097 pancreatic cancer cases were identified using death certificates from 24 U.S. states between 1984 and 1993. 63,097 noncancer, nonpancreatitis or other pancreatic disease deaths (controls) identified from the same source population and frequency-matched to cases by state, race, sex, and age (1:4 matching).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Mortality.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-9, 157 (malignant neoplasm of pancreas).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Usual occupation coded on death certificate coded to 1980 U.S. census classification system for occupation and industry. 509 occupation codes and 231 industry codes grouped into 16 broad occupational and 20 industrial categories based on similarity of occupational exposures. JEM of Gomez et al. (1994) used to assign exposure surrogates for 11 chlorinated hydrocarbons, including TCE, and two broad categories, chlorinated hydrocarbons and organic solvents.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	This study did not use interviews, information reported on death certificate used to infer potential exposure.
Blinded interviewers	No interviews were conducted in this study.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	No.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	Exposure prevalence: Any TCE exposure (Low intensity exposure or higher), 14% cases (n = 9,068); High TCE exposure, 2% cases (n = 1,271).

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, metropolitan status, region of residence, and marital status.
Statistical methods	Logistic regression.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.10. Prostatic Cancer Case-Control Studies

B.3.2.10.1. Aronson et al. (1996), Siemiatycki (1991).

B.3.2.10.1.1. Author's abstract.

A population-based case-control study of cancer and occupation was carried out in Montréal, Canada. Between 1979 and 1986, 449 pathologically confirmed cases of prostate cancer were interviewed, as well as 1,550 cancer controls and 533 population controls. Job histories were evaluated by a team of chemist/hygienists using a checklist of 294 workplace chemicals. After preliminary evaluation, 17 occupations, 11 industries, and 27 substances were selected for multivariate logistic regression analyses to estimate the odds ratio between each occupational circumstance and prostate cancer with control for potential confounders. There was moderate support for risk due to the following occupations: electrical power workers, water transport workers, aircraft fabricators, metal product fabricators, structural metal erectors, and railway transport workers. The following substances exhibited moderately strong associations: metallic dust, liquid fuel combustion products, lubricating oils and greases, and polyaromatic hydrocarbons from coal. While the population attributable risk, estimated at between 12% and 21% for these occupational exposures, may be an overestimate due to our method of analysis, even if the true attributable fraction were in the range of 5–10%, this represents an important public health issue.

B.3.2.10.1.2. Study description and comment.

Aronson et al. (1996) and Siemiatycki (1991) reported data from a case-control study of occupational exposures and prostate cancer conducted in Montreal, Quebec (Canada) and was part of a larger study of 10 other site-specific cancers and occupational exposures. The investigators identified 557 newly diagnosed cases of prostate cancer (ICD-O, 185), confirmed on the basis of histology reports, between 1979 and 1985; 449 of these participated in the study interview (80.6% participation). One control group consisted of patients with other forms of cancer recruited through the same study procedures and time period as the prostate cancer cases. A population-based control group (n = 533, 72% response), frequency-matched by age strata, was drawn using electoral lists and random digit dialing. Face-to-face interviews were carried out with 82% of all cancer cases with telephone interview (10%) or mailed questionnaire (8%) for the remaining cases. Twenty percent of all case interviews were provided by proxy respondents. The occupational assessment consisted of a detailed description of each job held during the working lifetime, including the company, products, nature of work at site, job activities, and any additional information that could furnish clues about exposure from the interviews.

A team of industrial hygienists and chemists blinded to subject's disease status translated jobs into potential exposure to 294 substances with three dimensions (degree of confidence that exposure occurred, frequency of exposure, and concentration of exposure). Each of these

exposure dimensions was categorized into none, any, or substantial exposure. Aronson et al. (1996) presents observations of logistic regression analyses examining industries, occupation, and some chemical-specific exposures, but not TCE. Observations on TCE from Mantel-Haenszel analyses are found in the original report of Siemiatycki (1991). Any exposure to TCE was 2% among cases (n = 11) and <2% for substantial TCE exposure (n = 7); "substantial" is defined as ≥10 years of exposure for the period up to 5 years before diagnosis.

Logistic regression models adjusted for age, education, and ethnicity (Aronson et al., 1996) or Mantel-Haenszel χ^2 stratified on age, family income, cigarette smoking, coffee, and ethnic origin (Siemiatycki, 1991). Odds ratios for TCE exposure are presented with 90% CIs in Siemiatycki (1991) and 95% CIs in Aronson et al. (1996).

The strengths of this study were the large number of incident cases, specific information about job duties for all jobs held, and a definitive diagnosis of prostate cancer. However, the use of the general population (rather than a known cohort of exposed workers) reduced the likelihood that subjects were exposed to TCE, resulting in relatively low statistical power for the analysis. The JEM, applied to the job information, was very broad since it was used to evaluate 294 chemicals.

Aronson KJ, Siemiatycki J, Dewar R, Gérin M. (1996). Occupational risk factors for prostate cancer: Results from a case-control study in Montréal, Canada. Am J Epidemiol 143:363–373.

Siemitycki J. (1991). Risk Factors for Cancer in the Workplace. J Siemiatycki, Ed. Boca Raton: CRC Press.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This population case-control study was designed to generate hypotheses on possible association between 11 site-specific cancers and occupational title or chemical exposures.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	557 prostate cancer cases were identified among male Montreal residents between 1979 and 1985 of which 449 were interviewed. 740 eligible male controls identified from the same source population using random digit dialing or electoral lists; 533 were interviewed. A second control series consisted of other cancer cases identified in the larger study. Participation rate: cases, 83.1%; population controls, 72%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-O, 185 (malignant neoplasm of prostate).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Unblinded interview using questionnaire sought information on complete job history with supplemental questionnaire for jobs of a priori interest (e.g., machinists, painters). Team of chemist and industrial hygienist assigned exposure using job title with a semiquantitative scale developed for 294 exposures, including TCE. For each exposure, a three-level ranking was used for concentration (low or background, medium, high) and frequency (percent of working time: low, 1–5%; medium, >5–30%; and high, >30%).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	82% of all cancer cases interviewed face-to-face by a trained interviewer, 10% telephone interview, and 8% mailed questionnaire. Cases interviews were conducted either at home or in the hospital; all population control interviews were conducted at home.
Blinded interviewers	Interviews were unblinded but exposure coding was carried out blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Yes, 20% of all cancer cases had proxy respondents.

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	449 cases (80.6% response), 533 population controls (72%). Exposure prevalence: Any TCE exposure, 2% cases (n = 11); substantial TCE exposure (exposure for ≥10 yrs and up to 5 yrs before disease onset), <2% cases (n = 7).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, ethnic origin, SES, Quetlet as an index of body mass, and respondent status (Aronson et al., 1996). Age, family income, cigarette smoking, ethnic origin, and respondent status (Siemiatycki, 1991).
Statistical methods	Mantel-Haenszel (Siemiatycki, 1991). Logistic regression (Aronson et al., 1996).
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.11. RCC Case-Control Studies—Arnsberg Region of Germany

A series of studies (including Henschler et al. (1995), discussed in cohort study section) have been conducted in an area with a long history of TCE use in several industries. The main importance of these studies is that there is considerable detail on the nature of exposures, which made it possible to estimate the order of magnitude of exposure even though there were no direct measurements.

B.3.2.11.1. Brüning et al. (2003).

B.3.2.11.1.1. Author's abstract.

BACKGROUND: German studies of high exposure prevalence have been debated on the renal carcinogenicity of trichloroethylene (TRI). METHODS: A consecutive hospital-based case-control study with 134 renal cell cancer (RCC) cases and 401 controls was conducted to reevaluate the risk of TRI in this region which were estimated in a previous study. Exposure was self-assessed to compare these studies. Additionally, the job history was analyzed, using expert-based exposure information. RESULTS: The logistic regression results, adjusted for age, gender, and smoking, confirmed a TRI-related RCC risk in this region. Using the database CAREX for a comparison of industries with and without TRI exposure, a significant excess risk was estimated for the longest held job in TRI-exposing industries (odds ratio (OR) 1.80, 95% confidence interval (CI) 1.01-3.20). Any exposure in "metal degreasing" was a RCC risk factor (OR 5.57, 95% CI 2.33-13.32). Self-reported narcotic symptoms, indicative of peak exposures, were associated with an excess risk (OR 3.71, 95% CI 1.80-7.54). CONCLUSIONS: The study supports the human nephrocarcinogenicity of trichloroethylene.

B.3.2.11.1.2. Study description and comment.

This study is a second case-control follow-up of renal cell cancer in the Arnsberg area of Germany, which was intended to deal with some of the methodological issues present in the two earlier studies. The major advantage of studies in the Arnsberg area is the high prevalence of exposure to TCE because of the large number of companies doing the same kind of industrial work. An interview questionnaire procedure for self-assessment of exposures similar to the one used by Vamvakas et al. (1998) was used to obtain detailed information about solvents used, job tasks, and working conditions, as well as the occurrence of neurological symptoms. The industry and job title information in the subjects' job histories were also analyzed by two schemes of expert-rated exposure assignments for broad groups of jobs. The CAREX database from the European Union, for industry categories, and the British JEM developed by Pannett et al. (1985), for potential exposure to chemical classes or specific chemical, but not TCE, was adopted in an attempt to obtain a potentially less biased assessment of exposures.

Exposure prevalences for employment in industries with potential TCE and perchloroethylene exposures was high in both cases (87%) and controls (79%) using the CAREX

approach, but much lower using the JEM approach for potential exposure to degreasing agents (12% cases, 9% controls), self-reported exposure to TCE (18% cases, 10% controls), and TCE exposure with any symptom occurrence (14% cases, 4% controls). Both the CAREX and British JEM rating approaches are very broad and they have potentially high rates of misclassification of exposure intensity in job groupings and industry groupings. In an attempt to avoid reporting biases associated with the legal proceeding for compensation, analyses were conducted on self-reported exposure to selected agents (yes or no). The regional use of TCE and perchloroethylene (tetrachloroethylene) were so widespread that most individuals recognized the local abbreviations. If individuals claimed to be exposed when they were not, it would reduce the finding of a relationship if one existed. Similarly, subjects were grouped by frequency of perceived symptoms (any, less than daily, daily) associated with TCE or perchloroethylene exposure. Overreporting would also introduce misclassification and reduce evidence of any relationship. Self-reporting of exposure to chemicals in case-control studies, generally, is considered unreliable since, within the broad population, workers rarely know specific chemicals to which they have potential exposure. However, in cohort studies and case-control studies in which one industry dominates a local population such as in this study, this is less likely because the numbers of possible industries and job titles are much smaller than in a broad population. The Arnsberg area studies focused on a small area where one type of industry was very prevalent, and that industry used primarily just two solvents: TCE and tetrachloroethylene. As a result, it was common knowledge among the workers what solvent an individual was using, and, for most, it was TCE. Self-reported TCE exposure is considered to be less biased compared to possible misclassification bias associated with using the CAREX exposure assessment approach which identified approximately 90% of all cases as holding a job in an industry using TCE or perchloroethylene (see above discussion).

Some subjects in Brüning et al. (2003) are drawn from the underlying Arnsberg population as studied by Vamvakas et al. (1998) (reviewed below) and TCE exposures to these subjects would be similar—substantial, sustained high exposures to TCE at 400–600 ppm during hot dip cleaning and >100 ppm overall. However, the larger ascertainment area outside the Arnsberg region for case and control identification may have resulted in a lower exposure prevalence compared to Vamvakas et al. (1998).

Brüning T, Pesch B, Wiesenhütter B, Rabstein S, Lammert M, Baumüller A, Bolt H. (2003). Renal cell cancer risk and occupational exposure to trichloroethylene: results of a consecutive case-control study in Arnsberg, Germany. Am J Ind Med 23:274–285.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	From abstract—study aim was to "reevaluate the risk of TRI in this region which were estimated in a previous study."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	162 RCC cases identified from September 1999 to April 2000 and who had undergone nephrectomy between 1992 and 2000 (a time period preceding that adopted in Vamvakas et al., (1998)]) from a regional hospital urology department in Arnsberg, Germany; 134 of the recruited cases were interviewed. 401 hospital controls were interviewed between 1999 and 2000 from local surgery departments or geriatric departments and frequency matched to cases by sex and age. 134 of 162 (83%) cases; response rate among controls could not be calculated lacking information on the number of eligible controls.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	N/A
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Face-to-face interview with subjects or their next of kin using a structured questionnaire with questions to obtain information on a complete job history by job title, supplemental information on job tasks with suspected exposure to specific agents, medical history, and personal habits. Questionnaires also sought self-reported information on duration and frequency of exposure to TCE and perchloroethylene, and, for these individuals, frequency of narcotic symptoms as a marker of high peak exposure. Jobs titles were coded according to a British classification of occupations and industries with potential chemical-specific exposures identified for each occupation using CAREX, a carcinogen exposure database or the British JEM of Pannett et al. (1985) for chemical groupings (e.g., degreasing agents, organic solvents).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	

CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	100% of cases or their NOK and 100% controls with face-to-face interviews.
Blinded interviewers	No information on whether interviewers were blinded.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Yes, 17% of case interviews with next-of-kin; all controls were alive at time of interview.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancers in incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	CAREX Job-exposure-matrix 117 cases with TCE exposure (87% exposure prevalence among cases). 316 controls with TCE exposure (79% exposure prevalence among controls). Self-reported TCE exposure 25 cases with TCE exposure (18% exposure prevalence among cases). 38 controls with TCE exposure (9.5% exposure prevalence among controls).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, and tobacco smoking.
Statistical methods	Conditional logistic regression.
Exposure-response analysis presented in published paper	Yes, duration of exposure as 4 categories (no, <10 yrs, 10–<20 yrs, and 20+ yrs).
Documentation of results	Yes.

B.3.2.11.2. Pesch et al. (2000b).

B.3.2.11.2.1. Author's abstract.

BACKGROUND: This case-control study was conducted to estimate the renal cell cancer (RCC) risk for exposure to occupation-related agents, besides other suspected risk factors. METHODS: In a population-based multicentre study, 935 incident RCC cases and 4298 controls matched for region, sex, and age were interviewed between 1991 and 1995 for their occupational history and lifestyle habits. Agent-specific exposure was expert-rated with two job-exposure matrices and a job task-exposure matrix. Conditional logistic regression was used to calculate smoking adjusted odds ratios (OR). RESULTS: Very long exposures in the chemical, rubber, and printing industries were associated with risk for RCC. Males considered as 'substantially exposed to organic solvents' showed a significant excess risk (OR = 1.6, 95% CI : 1.1-2.3). In females substantial exposure to solvents was also a significant risk factor (OR = 2.1, 95% CI : 1.0-4.4). Excess risks were shown for high exposure to cadmium (OR = 1.4, 95% CI : 1.1-1.8, in men, OR = 2.5, 95% CI : 1.2-5.3 in women), for substantial exposure to lead (OR = 1.5, 95% CI : 1.0-2.3, in men, OR = 2.6, 95% CI : 1.2-5.5, in women) and to solder fumes (OR = 1.5, 95% CI : 1.0-2.4, in men). In females, an excess risk for the task 'soldering, welding, milling' was found (OR = 3.0, 95% CI : 1.1-7.8). Exposure to paints, mineral oils, cutting fluids, benzene, polycyclic aromatic hydrocarbons, and asbestos showed an association with RCC development.
CONCLUSIONS: Our results indicate that substantial exposure to metals and solvents may be nephrocarcinogenic. There is evidence for a gender-specific susceptibility of the kidneys.

B.3.2.11.2.2. Study description and comment.

This multicenter study of RCC and bladder cancer and in Germany, which included the Arnsberg region plus four others, identified two case series from participating hospitals, 1,035 urothelial cancer cases and 935 RCC cases with a single population control series matched to cases by region, sex, and age (1:2 matching ratio to urothelial cancer cases and 1:4 matching ratio to RCC cases). A strength of the study was the high percentage of interviews with RCC cases within 2 months of diagnosis (88.5%), reducing bias associated with proxy or next-of-kin interview, and few cases diagnoses confirmed by sonography only (5%). In all, 935 (570 males, 365 females) RCC cases were interviewed face-to-face with a structured questionnaire.

Two general JEMs, British and German, were used to assign exposures based on subjects' job histories reported in an interview. Researchers also asked about job tasks associated with exposure, such as metal degreasing and cleaning, and use of specific agents (organic solvents chlorinated solvents, including specific questions about carbon tetrachloride, TCE, and tetrachloroethylene) to evaluate TCE potential using a JTEM. A category of "any use of a solvent" mixes the large number with infrequent slight contact with the few noted earlier who have high intensity and prolonged contact. Analyses examining TCE exposure using either

the JEM of JTEM assigned a cumulative TCE exposure index of none to low, medium high and substantial, defined as the product of exposure probability x intensity x duration with the following cutpoints: none to low, <30th percentile of cumulative exposure scores; medium, 30th–<60th percentile; high, 60th–<90th percentile; and, substantial, ≥90th percentile. The use of the German JEM identified approximately twice as many cases with any potential TCE exposure (42%) compared to the JTEM (17%) and, in both cases, few cases identified with substantial exposure, 6% by JEM and 3% by JTEM. Pesch et al. (2000b) noted "exposure indices derived from an expert rating of job tasks can have a higher agent-specificity than indices derived from job titles." For this reason, the JTEM approach with consideration of job tasks is considered as a more robust exposure metric for examining TCE exposure and RCC due to likely reduced potential for exposure misclassification compared to TCE assignment using only job history and title.

While this case-control study includes the Arnsberg area, several other regions are included as well, where the source of the TCE and chlorinated solvent exposures are much less well defined. Few cases were identified as having substantial exposure to TCE and, as a result, most subjects identified as exposed to TCE probably had minimal contact, averaging concentrations of about 10 ppm or less (NRC, 2006).

Pesch B, Haerting J, Ranft U, Klimpet A, Oelschägel, Schill W, and the MURC Study Group. (2000b). Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. Int J Epidemiol 29:1014–1024.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This case-control study was conducted to estimate RCC risk for exposure to occupational-related agents; chlorinated solvents including TCE were identified as exposures of a priori interest.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	935 RCC cases were identified from hospitals in a five-region area in Germany between 1991 and 1995. Cases were confirmed histologically (95%) or by sonography (5%) and selected without age restriction. 4,298 population controls identified from local residency registries in the five-region area were frequency matched to cases by region, sex, and age. Participation rate: cases, 88%; controls, 71%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	N/A
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	A trained interviewer interviewed subjects using a structured questionnaire which covered occupational history and job title for all jobs held longer than 1 yr, medical history, and personal information. Two general JEMs, British and German, were used to assign exposures based on subjects' job histories reported in an interview. Researchers also asked about job tasks associated with exposure, such as metal degreasing and cleaning, and use of specific agents (organic solvents chlorinated solvents, including specific questions about carbon tetrachloride, TCE, and tetrachloroethylene) and chemical-specific exposure were assigned using a JTEM. Exposure index for each subject is the sum over all jobs of duration × probability × intensity. A four category grouping was used in statistical analyses defined by exposure index distribution of controls: no-low; medium, 30^{th} percentile; high, 60^{th} percentile; substantial, 90^{th} percentile.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Interviewers carried out face-to-face interview with all cases and controls. All cases were interviewed in the hospital; 88.5% of cases were interviewed within 2 months after diagnosis. All controls had home interviews.
Blinded interviewers	No, by nature of interview location.

CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	No.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancers in incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	JEM: 391 cases with TCE exposure index of medium or higher (42% exposure prevalence among cases). JTEM: 172 cases with TCE exposure index of medium or higher (18% exposure prevalence among cases). No information is presented in paper on control exposure prevalence.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, study center, and smoking.
Statistical methods	Conditional logistic regression.
Exposure-response analysis presented in published paper	Yes.
Documentation of results	Yes.

B.3.2.11.3. Vamvakas et al. (1998).

B.3.2.11.3.1. Author's abstract.

> A previous cohort-study in a cardboard factory demonstrated that high and prolonged occupational exposure to trichloroethene (C2HCl3) is associated with an increased incidence of renal cell cancer. The present hospital-based case/control study investigates occupational exposure in 58 patients with renal cell cancer with special emphasis on C2HCl3 and the structurally and toxicologically closely related compound tetrachloroethene (C2Cl4). A group of 84 patients from the accident wards of three general hospitals in the same area served as controls. Of the 58 cases, 19 had histories of occupational C2HCl3 exposure for at least 2 years and none had been exposed to C2Cl4; of the 84 controls, 5 had been occupationally exposed to C2HCl3 and 2 to C2Cl4. After adjustment for other risk factors, such as age, obesity, high blood pressure, smoking and chronic intake of diuretics, the study demonstrates an association of renal cell cancer with long-term exposure to C2HCl3 (odds ratio 10.80; 95% CI: 3.36-34.75).

B.3.2.11.3.2. Study description and comment.

In a follow-up to Henschler et al. (1995) (discussed below), a case-control study was conducted in the Arnsberg region of Germany where there has long been a high prevalence of small enterprises manufacturing small metal parts and goods, such as nuts, lamps, screws, and bolts. Both cases and controls were identified from hospital records; cases from of a large regional hospital in North Rhine Wetphalia during the period 1987 and 1992 and controls who were admitted to accident wards during 1993 at three other regional hospitals. Control selection was carried out independent of cases demographic risk factors (i.e., controls were not matched to cases). Controls may not be fully representative of the case series (NRC, 2006); they were selected from a time period after case selection, which may introduce bias if TCE use changes over time resulted in decreased potential for exposure among controls, and use of accident ward patients may be representative of the target population.

Exposures to TCE resulted from dipping metal pieces into vats, with room temperatures up to 60°C, and placing the wet parts on tables to dry. Some work rooms were noted to be small and poorly ventilated. These conditions are likely to result in high inhalation exposure to TCE (100–500 ppm). Cherrie et al. (2001) estimated the long-term exposures to be approximately 100 ppm. Some of the cases included in this study were also pending legal compensation. As a result, there had been considerable investigation of the exposure situation by occupational hygienists from the Employer's Liability Insurance Association and occupational physicians, including walk-through visits and interviews of long-term employees. The legal action could introduce a bias, a tendency to overreport some of the subjective reports by the subjects. However, the objective working conditions were assessed by knowledgeable professionals, who

corroborated the presence of the poorly controlled hot dip tanks, extensive use of TCE for all types of cleaning, and the process descriptions.

NRC (2006) discussed a number of criticisms in the literature on Vamvakas et al. (1998) by Green and Lash (1999), Cherrie et al. (2001), and Mandel (2001) and noted the direction of possible bias would be positive or negative depending on the specific criticism. Overall, cases in this study substantial, sustained exposures to high concentrations of TCE at 400–600 ppm during hot dip cleaning and >100 ppm overall and observations can inform hazard identification although the magnitude of observed association is uncertain give possible biases.

Vamvakas S, Brüning T, Thomasson B, Lammert M, Baumüller A, Bolt HM, Dekant W, Birner G, Henschler D, Ulm K. (1998). Renal cell cancer risk and occupational exposure to trichloroethylene: results of a consecutive case-control study in Arnsberg, Germany. Am J Ind Med 23:274–285.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Yes. From introduction—study aim was designed to investigate further the role of occupation exposure to TCE/perchloroethylene in the formation of renal cancer.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	73 RCC cases that had undergone nephrectomy between December 1987 and May 1992 from a hospital urology department in Arnsberg, Germany were contacted by mail; 58 of the recruited cases were. 112 controls identified from accident wards of three area hospitals were interviewed during 1993. Controls underwent abdominal sonography to exclude kidney cancer. 62 of 73 (85%) cases and 84 of 112 (75%) of controls participated in study.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	N/A
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Face-to-face interview with subjects or, if deceased, with their next of kin or former colleagues using a structured questionnaire with questions to obtain information on job tasks with selected exposure to specific agents and to self-reported selected exposures. A supplemental questionnaire on job conditions was administered to subjects reporting exposure to TCE and perchloroethylene. Subjects with TCE exposures were primarily exposed through degreasing operations in small businesses. Self-reported TCE exposure was ranked using a semiquantitative scale based upon total exposure time and frequency/duration of self-reported acute prenarcotic symptoms. **Cherrie et al. (2001) estimated that the machine cleaning exposures to TCE were ~400–600 ppm, with long-term average TCE exposure as ~100 ppm.**
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Personal physicians interviewed 100% of cases or their NOK/former colleague and 100% controls.
Blinded interviewers	Interviewers were not blinded nor was developments of exposure assessment semiquantitative scale.
CATEGORY F: PROXY RESPONDENTS	

>10% proxy respondents	No information provided in paper on number of cases with NOK interviews or interviews with former colleagues; all controls were alive and interviewed by their personal physician.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancers in incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	19 cases with TCE or perchloroethylene exposure (33% exposure prevalence) and 1 control with perchloroethylene exposure.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, obesity, high blood pressure, smoking, and diuretic use.
Statistical methods	Mantel-Haenszel χ^2.
Exposure-response analysis presented in published paper	Yes, semiquantitative scale of 4 categories (no, +, ++, +++).
Documentation of results	No information on number of eligible controls or number interviews with case NOK or former colleagues.

B.3.2.12. RCC Case-Control Studies—Arve Valley Region of France

A case-control study was conducted in the Arve Valley to examine the a priori hypothesis of an association with RCC and TCE exposure. The Arve Valley, like the Arnsburg Region in Germany, has a long history of TCE use in the screw-cutting industry. The Arve Valley, situated in the Rhône-Alpes region of eastern France is a major metalworking sector with around 800 small and medium-sized firms specializing in "screw-cutting" or the machining of small mechanical parts from bars, in small, medium, and large series on conventional automatic lathes or by digital control. This industry evolved around the time of World War I from the region's expertise in clock-making. A major point of this study is that it was designed as a follow-up study to the German renal cell cancer case-control studies but in a different population with similar exposure patterns and with high prevalence of exposure to TCE. For this reason, there is considerable detail on the nature of exposure, which made it possible to estimate the order of magnitude of exposure, even though there were not direct measurements.

B.3.2.12.1. Charbotel et al.(2009), Charbotel et al. (2007) Charbotel et al. (2006).

B.3.2.12.1.1. Charbotel et al. (2009) abstract.

Abstract Background– Several studies have investigated the association between trichloroethylene (TCE) exposure and renal cell cancer (RCC) but findings were inconsistent. The analysis of a case control study has shown an increased risk of RCC among subjects exposed to high cumulative exposure. The aim of this complementary analysis is to assess the relevance of current exposure limits regarding a potential carcinogenic effect of TCE on kidney.
Methods– Eighty-six cases and 316 controls matched for age and gender were included in the study. Successive jobs and working circumstances were described using a detailed occupational questionnaire. An average level of exposure to TCE was attributed to each job period in turn. The main occupational exposures described in the literature as increasing the risk of RCC were assessed as well as non-occupational factors. A conditional logistic regression was performed to test the association between TCE and RCC risk. Three exposure levels were studied (average exposure during the eight-hour shift): 35 ppm, 50 ppm and 75 ppm. Potential confounding factors identified were taken into account at the threshold limit of 10% ($p = 0.10$) (body mass index [BMI], tobacco smoking, occupational exposures to cutting fluids and to other oils).
Results– Adjusted for tobacco smoking and BMI, the odd-ratios associated with exposure to TCE were respectively 1.62 [0.77–3.42], 2.80 [1.12–7.03] and 2.92 [0.85–10.09] at the thresholds of 35 ppm, 50 ppm and 75 ppm. Among subjects exposed to cutting fluids and TCE over 50 ppm, the OR adjusted for BMI, tobacco smoking and exposure to other oils was 2.70 [1.02–7.17].
Conclusion– Results from the present study as well as those provided in the international literature suggest that current French occupational exposure limits for TCE are too high regarding a possible risk of RCC.

B.3.2.12.1.2. Charbotel et al. (2007) abstract.

Background: We investigated the association between exposure to trichloroethylene (TCE) and mutations in the von Hippel-Lindau (VHL) gene and the subsequent risk for renal cell carcinoma (RCC).
Methods: Cases were recruited from a case-control study previously carried out in France that suggested an association between exposures to high levels of TCE and increased risk of RCC. From 87 cases of RCC recruited for the epidemiological study, 69 were included in the present study. All samples were evaluated by a pathologist in order to identify the histological subtype and then be able to focus on clear cell RCC. The majority of the tumor samples were fixed either in formalin or Bouin's solutions. The majority of the tumors were of the clear cell RCC subtype (48 including 2 cystic RCC). Mutation screening of the 3 VHL coding exons was carried out. A descriptive analysis was performed to compare exposed and non exposed cases of clear cell RCC in terms of prevalence of mutations in both groups.
Results: In the 48 cases of RCC, four VHL mutations were detected: within exon 1 (c.332G>A, p.Ser111Asn), at the exon 2 splice site (c.463+1G>C and c.463+2T>C) and within exon 3 (c.506T>C, p.Leu169Pro). No difference was observed regarding the frequency of mutations in exposed vs. unexposed groups: among the clear cell RCC, 25 had been exposed to TCE and 23 had no history of occupational exposure to TCE. Two patients with a mutation were identified in each group.
Conclusion: This study does not confirm the association between the number and type of VHL gene mutations and exposure to TCE previously described.

B.3.2.12.1.3. Charbotel et al. (2006) abstract.

Background: We investigated the association between exposure to trichloroethylene (TCE) and mutations in the von Hippel-Lindau (VHL) gene and the subsequent risk for renal cell carcinoma (RCC).
Methods: Cases were recruited from a case-control study previously carried out in France that suggested an association between exposures to high levels of TCE and increased risk of RCC. From 87 cases of RCC recruited for the epidemiological study, 69 were included in the present study. All samples were evaluated by a pathologist in order to identify the histological subtype and then be able to focus on clear cell RCC. The majority of the tumor samples were fixed either in formalin or Bouin’s solutions. The majority of the tumors were of the clear cell RCC subtype (48 including 2 cystic RCC). Mutation screening of the 3 VHL coding exons was carried out. A descriptive analysis was performed to compare exposed and non-exposed cases of clear cell RCC in terms of prevalence of mutations in both groups.
Results: In the 48 cases of RCC, four VHL mutations were detected: within exon 1 (c.332G>A, p.Ser111Asn), at the exon 2 splice site (c.463+1G>C and c.463+2T>C) and within exon 3 (c.506T>C, p.Leu169Pro). No difference was observed regarding the frequency of mutations in exposed vs. unexposed groups: among the clear cell RCC, 25 had been exposed to TCE and 23 had no history of

occupational exposure to TCE. Two patients with a mutation were identified in each group.
Conclusion: This study does not confirm the association between the number and type of VHL gene mutations and exposure to TCE previously described.

To test the effect of the exposure to trichloroethylene (TCE) on renal cell cancer (RCC) risk, a case–control study was performed in the Arve Valley (France), a geographic area with a high frequency and a high degree of such exposure. Cases and controls were selected from various sources: local general practitioners and urologists practicing in the area and physicians (urologists and oncologists) from other hospitals of the region who might treat patients from this area. Blinded telephone interviews with cases and controls were administered by a single trained interviewer using occupational and medical questionnaires. The analysis concerned 86 cases and 316 controls matched for age and gender. Three approaches were developed to assess the link between TCE exposure and RCC: exposure to TCE for at least one job period (minimum 1 year), cumulative dose number of ppm of TCE per job period multiplied by the number of years in the job period) and the effect of exposure to peaks. Multivariate analysis was performed taking into account potential confounding factors. Allowing for tobacco smoking and Body Mass Index, a significantly 2-fold increased risk was identified for high cumulative doses: odds ratio (OR) = 2.16 (1.02–4.60). A dose-response relationship was identified, as was a peak effect; the adjusted OR for highest class of exposure-plus-peak being 2.73 (1.06–7.07). After adjusting for exposure to cutting fluids the ORs, although still high, were not significant because of lack of power. This study suggests an association between exposures to high levels of TCE and increased risk of RCC. Further epidemiological studies are necessary to analyze the effect of lower levels of exposure.

B.3.2.12.1.4. Study description and comment.

Cases in the population-based, case-control study were obtained retrospectively from regional medical practitioners or from teaching hospitals from 1993 to 2002, and prospectively from 2002 to mid-2003. One case was excluded from analysis because it was not possible to find a control subject. Controls were either selected from the same urology practice as cases or, for cases selected from teaching hospitals, from among patients of the case's general practitioner. Telephone interviews of 87 RCC cases and 316 controls matched for age and sex by a trained interviewer were used to obtain information on occupational and medical history for the case-control analysis of Charbotel et al. (2006). Of the 87 RCC cases, 67 cases provided consent for mutational analysis of which 48 cases were diagnosed with clear cell RCC, suitable for mutational analysis of the *VHL* gene (Charbotel et al., 2007). Tissue samples were paraffin-embedded or frozen tissues and ability to fully sequence the *VHL* gene depended on type of the fixative procedure; only 26 clear cell RCC cases (34% of 73 clear cell RCC cases in the case-control study) could full sequencing of the *VHL* gene occur.

Two occupational questionnaires were administered to both cases and controls, a questionnaire developed specifically to evaluate jobs and exposure potential in the screw-cutting

industry and a more general one for any other jobs. Interviewers were essentially blinded to subject status as case or control for the occupational questionnaires given the medical questionnaire was administered afterwards (Fevotte et al., 2006). The medical questionnaire included familial kidney disease and medical history, BMI, and history of smoking. A task/TCE-Exposure Matrix was designed using information obtained from questionnaires and routine atmospheric monitoring of workshops or biological monitoring (U-TCA) of workers carried out since the 1960s. Questionnaires were used to elicit from each subject the main tasks associated with each job, working conditions, activities, or jobs that might involve TCE exposures and possible exposure to other occupational risk factors for RCC.

The JEM linked to corresponding TCE-exposure levels using available industrial hygiene monitoring data on atmospheric TCE levels and from biological measurement on workers. Estimates reflected task duration, use of protective equipment, and distance from TCE source, as well, as both dermal and inhalation exposure routes. Estimated TCE intensities for jobs associated with open cold degreasing were 15–18 ppm, 120 ppm for jobs working near open hot degreasing machines, with up to 300 ppm for work directly above tank and for job and intensities of 300–600 ppm for emptying, cleaning, and refilling degreasers. Eight local physicians with knowledge of working conditions corroborated the working conditions for individual job periods after 1980 in screw-cutting shops. Overall, there was good agreement (72%) between physician and the JEM. Three exposure surrogates were assigned to each case and control: TWA exposure (Charbotel et al., 2009), cumulative exposure (Charbotel et al., 2006), and cumulative exposure with and without peak exposure (Charbotel et al., 2006).

An 8-hour TWA exposure concentration was developed for each job period from 1924 to 2003 and was the product of the task-specific estimated TCE intensity and duration of task. A subject's lifetime 8-hour TWA was the sum of each job period specific estimated TWA. Exposure peak, daily exposure reaching ≥200 ppm for at least 15 minutes, was assessed as an additive factor and was defined by frequency (seldom exposed, few times yearly to frequently exposure, few time weekly).

Over the study period, 19% (295 of 1,486) job periods were assessed as having TCE exposure with an 8-hour TWA of <35 ppm for 72% of exposed jobs and >75 ppm for 5% of exposed jobs. Exposure prevalence to TCE peaked in the 1970s with roughly 20% of job periods with TCE exposure and 8% of subjects identified with >75 ppm. By the 1990s, exposure prevalence had not only decreased to 7% but also exposure intensity, only 5% of job periods with >75 ppm.

Cumulative TCE exposure was the sum of 8-hour TWAs overall job periods with statistical analysis using four categories: no, low, medium, and high. These were defined as low, 5–150 ppm-years; medium, 155–335 ppm-year; and high, >335 ppm-years (HSIA, 2005). Analyses were also carried out examining peak exposure, classified as yes/no and without

assignment of quantitative level, as additional exposure to average TCE concentration; 33 subjects were exposed to peaks and very few to high peaks.

The high exposure prevalence and strong approach for exposure assessment provides Charbotel et al. (2009; 2006) more statistical power and ability to assess association of RCC and TCE exposure. However, the low participation rate, inability to fully sequence the *VHL* gene in all clear cell RCC cases, the lower background prevalence of mutations (15% in this study compared to roughly 50% in other series) in Charbotel et al. (2007) suggest a relative insensitivity of assay used and lack of a positive control limits the mutational analysis. These methodological limitations introduce bias with greater uncertainties for evaluating consistency of findings with somatic *VHL* mutations observed in other TCE-exposed RCC cases (Brauch et al., 1999; Brüning et al., 1997b). TCE exposure prevalence (>5 ppm-year) in Charbotel et al. (2006) was 43% among cases and is higher than that observed in other population-based case-control studies of RCC and TCE (e.g., Pesch et al., 2000a). While some subjects had jobs with exposures to high concentrations of TCE during the 1970s and 1980s, a large percentage of jobs were to TCE concentrations of <35 ppm (8-hour TWA). Jobs with high TCE concentrations also were identified as having frequent exposure to peak TCE concentrations, particularly before 1980. Peak TCE estimates in this study were judged to be lower than those in German studies of the Arnsberg region (Vamvakas et al., 1998; Henschler et al., 1995) but higher than those of Hill Air Force Base civilian workers (Blair et al., 1998; Stewart et al., 1991) due to a lower frequency of degreasing tasks in Blair et al. (1998) cohort and to slower technological changes in degreasing process in the French case-control study (Fevotte et al., 2006).

Charbotel B, Fevotte J, martin JL, Bergeret A. (2009). Cancer du rein et expositions au trichloroethylene: les valeurs limites d'exposition professionnelle fraçaises en vigueur sont-elles adaptées. Rev Epidemiol Sante Publique 57:41–47.

Charbotel B, Fevotte J, Hours M, Martin J-L, Bergeret A. (2006). Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological Aspects. Ann Occup Hyg 50:777–787.

Fevotte J, Charbotel B, Muller-Beaute P, Martin J-L, Hours, Bergeret A. (2006). Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part I: Exposure assessment. Ann Occup Hyg 50:765–775.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Yes. From abstract—study aim was to "test the effect of TCE exposure on renal cell cancer."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	117 cases of RCC patients were identified retrospectively from 1993 to June 2002, and prospectively from June 2002 to June 2003 from patients of urology practices and hospital urology and oncology departments in the region of Arve Valley, France. 404 controls were identified from the same urology practice or from the same general practitioner, for cases identified from hospital records and matched on residency in the geographic study area at time of case diagnosis, sex, and year of birth. Controls sought medical treatment for conditions other than kidney or bladder cancer. Case definition included clear cell and other subtypes of RCC including chromophil, chromophobe and collecting duct carcinomas. 87 or 117 (74%) cases and 316 of 404 (78%) controls participated in study.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	N/A

CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Occupational questionnaires sought information for each study subject a complete job history and was followed-up with either a questionnaire specific for jobs and exposures in the screw-cutting industry or a General Occupational Questionnaire, whichever was more applicable to subject. Questionnaires also sought self-reported information on potential TCE exposures. A medical questionnaire seeking information on medical history and familial kidney disease was administered after occupational questionnaires. Jobs titles were coded according to standardized classification of occupations and 1,486 job periods grouped into three categories (screw-cutting, nonscrew-cutting but job with possible TCE exposure, and no TCE exposure). An estimated 8-hr TWA was assigned to each job and job period using a JTEM. RCC and TCE was examined using three exposure approaches: exposure to at least 5 ppm for at least one job period (minimum 1 yr), cumulative dose or ∑ (TCE ppm per job × years) using quantitative ranking levels (no exposure, low, medium, and high), and potential for peak defined as any exposure 200+ ppm. **TCE concentrations associated with quantitative ranking are low, 5–150 ppm-yrs; medium, 155–335 ppm-yrs; high, >335 ppm-yrs.**
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Telephone interviews were conducted by a trained interviewer.
Blinded interviewers	The paper notes interviewers were blinded "as far as possible" since medical questionnaire was administered after the occupational questionnaires.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Yes, 22% of cases were dead at time of interview compared to 7% of controls.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancers in incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	37 cases with TCE exposure (43% exposure prevalence), 110 controls with TCE exposure (35% exposure prevalence). 16 cases with high level confidence TCE exposure (27% exposure prevalence), 37 controls with high level confidence TCE exposure (16%).

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, tobacco smoking, and BMI (Charbotel et al., 2006). Age, sex tobacco smoking, BMI, and exposure to cutting or petroleum oils (Charbotel et al., 2009).
Statistical methods	Conditional logistic regression on matched pairs.
Exposure-response analysis presented in published paper	Yes, cumulative exposure as four categories (no, low, medium and high exposure) and cumulative exposure plus peaks.
Documentation of results	Yes.

B.3.2.13. RCC Case-Control Studies in Other Regions

B.3.2.13.1. Moore et al. (2010)

B.3.2.13.1.1. Author's abstract.

Trichloroethylene (TCE) is a suspected renal carcinogen. TCE-associated renal genotoxicity occurs predominantly through glutathione S-transferase (GST) conjugation and bioactivation by renal cysteine beta-lyase (CCBL1). We conducted a case-control study in Central Europe (1,097 cases and 1,476 controls) specifically designed to assess risk associated with occupational exposure to TCE through analysis of detailed job histories. All jobs were coded for organic/chlorinated solvent and TCE exposure (ever/never) as well as the frequency and intensity of exposure based on detailed occupational questionnaires, specialized questionnaires, and expert assessments. Increased risk was observed among subjects ever TCE exposed [odds ratio (OR) = 1.63; 95% confidence interval (95% CI), 1.04-2.54]. Exposure-response trends were observed among subjects above and below the median exposure [average intensity (OR = 1.38; 95% CI, 0.81-2.35; OR = 2.34; 95% CI, 1.05-5.21; P(trend) = 0.02)]. A significant association was found among TCE-exposed subjects with at least one intact GSTT1 allele (active genotype; OR = 1.88; 95% CI, 1.06-3.33) but not among subjects with two deleted alleles (null genotype; OR = 0.93; 95% CI, 0.35-2.44; P(interaction) = 0.18). Similar associations for all exposure metrics including average intensity were observed among GSTT1-active subjects (OR = 1.56; 95% CI, 0.79-3.10; OR = 2.77; 95% CI, 1.01-7.58; P(trend) = 0.02) but not among GSTT1 nulls (OR = 0.81; 95% CI, 0.24-2.72; OR = 1.16; 95% CI, 0.27-5.04; P(trend) = 1.00; P(interaction) = 0.34). Further evidence of heterogeneity was seen among TCE-exposed subjects with >or=1 minor allele of several CCBL1-tagging single nucleotide polymorphisms: rs2293968, rs2280841, rs2259043, and rs941960. These findings provide the strongest evidence to date that TCE exposure is associated with increased renal cancer risk, particularly among individuals carrying polymorphisms in genes that are important in the reductive metabolism of this chemical, and provides biological plausibility of the association in humans.

B.3.2.13.1.2. Study description and comment.

The hospital case-control study of kidney cancer in men and women who were residents in areas of the sevens study centers evaluated nonoccupational and occupational risk factors and included a detailed exposure assessment for chlorinated organic solvents, including TCE. Histologically-confirmed incident cases of RCC (ICD-O-2, Code C.64) between 20 and 79 years of age and diagnosed between 1999 and 2003 at seven participating hospitals were eligible as cases, with hospital in-patient or out-patient controls admitted to the same hospital centers but with non-tobacco-related conditions, excluding genitourinary cancers, and frequency-matched to cases by sex and age, and by study center. The final study population included 1,097 cases and 1,476 controls for a participation rate, depending on study center of 90–98% and 90–96% for cases and controls, respectively. As part of the study, blood samples obtained from 925 cases

and 1,192 controls were assayed for deletion of the GSTT1 polymorphism and genetic variation across the renal cysteine β-lyase (CCBL1) gene.

Face-to-face interviews were conducted using standard questionnaires that asked about lifestyle habits and personal, familial medical history, and for each job held ≥1 year. For specific jobs or industries with likely exposure to know or suspected occupational carcinogens of interest, a specialized occupation questionnaires were used to gather more detailed information. For every job in a subject's work history, an exposure assessment team from each center, with extensive knowledge of industries in the region and blinded to case or control status, evaluated the frequency and intensity of exposure to organic and chlorinated solvents based on the general and job-specific questionnaires. The general category of aliphatic chlorinate organic solvents included perchloroethylene, methylene chloride, carbon tetrachloride, 1, 1, 1-trichloroethane, and TCE. Subjects identified as exposed to organic solvents were reevaluated by the team at a later date to confirm assignment as an attempt to reduce exposure misclassification. The reevaluation was performed blinded to case and controls status. For each exposed job, the frequency, intensity, and confidence of exposure to TCE, organic solvents, and chlorinated solvents. While TCE exposure was correlated with both chlorinated solvents and organic solvents exposure, it was not associated with other co-exposures. Exposure frequency was coded into three categories, representing the average percentage of a working day exposure was likely (1–4.9, 5–30, >30%), with midpoint weights for cumulative exposure calculations of 0.025, 0.175, and 0.50, respectively, and assuming a log-normal exposure distribution. TCE intensity was also coded into three categories (0–<5, 5–50, >50 ppm) with midpoint weights for cumulative exposure calculations of 2.5, 25, and 75 ppm, respectively. Exposure surrogates developed included cumulative exposure, the product of the midpoints for intensity and frequency and multiplied by duration. Average exposure intensity was a second exposure surrogate and defined as the quotient of cumulative exposure and duration. Last, confidence of exposure that represented the expected percentage of workers that would be exposed in that job was categorized as possible (<40%), probable (40–89%), or definite (≥90%). Among subjects with probable exposure (high confidence TCE exposure), the median intensity score was 0.076 ppm [25th and 75th percentile range among cases, 0.83–7.25 ppm] and median cumulative exposure scores were 1.58 (25th and 75th percentiles, 0.77–2.87 ppm-year) and 1.95 ppm-years (25th and 75th percentiles, 0.83–7.25 ppm-year) among cases and controls, respectively.

Association between RCC and organic solvents, chlorinated solvents, and TCE exposure for jobs with any confidence level and for holding a job with probable or definite exposure was assessed using unconditional logistic regression to estimate ORs and 95% CIs. All statistical models included covariates for sex, age, and study center. Analyses were also modeled to account for a 20-year lag. Almost all TCE exposure occurred at least 20 years before RCC onset and Moore et al. (2010) did not report these findings as OR estimates were similar to those from the models using unlagged exposure surrogate.

The strong exposure approach in Moore et al. (2010) and examination of exposure probability or confidence are strengths of the study. TCE used did not appear widespread as exposure prevalence was low, 6 % of cases had held a job of any exposure probability, compared to 29% of cases identified with any exposure to organic solvents. The percentage of cases was even lower, 4%, for higher confidence TCE exposure. Additionally, evaluation of GST polymorphisms provides assessment of susceptibility factors.

Moore LE, Buffetta P, Karami S, Brennan P, Stewart PS, Hung R, et al. (2010). Occupational trichloroethylene exposure and renal carcinoma risk: Evidence of genetic susceptibility by reductive metabolism gene variants. Cancer Res 20:6527–6536.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Study hypotheses of investigating risk association with occupation TCE exposure and kidney (excluding pelvis) cancers through analysis of job histories and use of detailed exposure assessment method.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Cases: 1,097 histologically-confirmed RCC cases in males and females, 20–79 yrs of age, 1999–2003, identified through seven hospital centers in four countries (Czech Republic, Poland, Romania, Russia). Controls: 1,476 in-patient or out-patient hospital controls admitted to same hospital as case with nontobacco-related conditions and frequency matched to cases by sex and age, and by study center.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	RCC incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-0-2 [Codes C.54].
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Job-specific questionnaire for job ≥1 year. Exposure assessment team from each center with knowledge of region's industries to assess frequency, intensity and confidence of exposure to TCE and organic solvent group (perchloroethylene, methylene chloride, carbon tetrachloride, and 1,1,1-trichloroethane). Exposure surrogates of frequency (three categories based on percentage of day), intensity (three groups), cumulative exposure (product of intensity, duration, frequency), and average exposure intensity (cumulative exposure score divided by the number of years exposed). Exposure confidence score (possible, probably, definite) defined as percentage of workers exposed at a job.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	In-person interview using questionnaire.
Blinded interviewers	No information in published paper if interviewers were blinded. Exposure assessment assigned blinded.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	No proxy interviews.

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	Cases: 90–99% participation rate; Controls: 90–96% participation rate. Exposure prevalence, ever exposed to TCE (6% of cases holding TCE job, any confidence level; 4% of cases with probable or definite exposure).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, and center. Place of residence, tobacco smoking, BMI, and hypertension also examined but did not alder OR estimate by >10%, and thus, were not included in final models.
Statistical methods	Unconditional logistic regression.
Exposure-response analysis presented in published paper	Test for trend reported for years, hours, cumulative and average intensity of exposure.
Documentation of results	Yes, study was well documented with supplemental material available on publisher's webpage.

B.3.2.13.2. Parent et al. (2000a), Siemiatycki (1991).

B.3.2.13.2.1. Author's abstract.

BACKGROUND: Little is known about the role of workplace exposures on the risk of renal cell cancer. METHODS: A population-based case-control study was undertaken in Montreal to assess the association between hundreds of occupational circumstances and several cancer sites, including the kidney. A total of 142 male patients with pathologically confirmed renal cell carcinoma, 1900 controls with cancer at other sites and 533 population-based controls were interviewed. Detailed job histories and relevant data on potential confounders were obtained. A group of chemists-hygienists evaluated each job reported and translated them into a history of occupational exposures using a checklist of 294 substances. Multivariate logistic regression models using either population, cancer controls, or a pool of both groups were used to estimate odds ratios. RESULTS: There were some indications of excess risks among printers, nursery workers (gardening), aircraft mechanics, farmers, and horticulturists, as well as in the following industries: printing-related services, defense services, wholesale trade, and retail trade. Notwithstanding the low precision of many of the odds ratio estimates, the following workplace exposures showed some evidence of excess risk: chromium compounds, chromium (VI) compounds, inorganic acid solutions, styrene-butadiene rubber, ozone, hydrogen sulphide, ultraviolet radiation, hair dust, felt dust, jet fuel engine emissions, jet fuel, aviation gasoline, phosphoric acid and inks. CONCLUSIONS: For most of these associations there exist no, or very little, previous data. Some associations provide suggestive evidence for further studies.

B.3.2.13.2.2. Study description and comment.

This population case-control study of histologically-confirmed kidney cancer among males who resided in the Montreal Metropolitan area relies on the use of expert assessment of occupational information on a detailed questionnaire and face-to-face interview and was part of a larger study of 10 other site-specific cancers and occupational exposures (Parent et al., 2000a; Siemiatycki, 1991). Interviewers were unblinded, although exposure assignment was carried out blinded as to case and control status. The questionnaire sought information on the subject's complete job history and included questions about the specific job of the employee and work environment. Occupations considered with possible TCE exposure included machinists, aircraft mechanics, and industrial equipment mechanics. An additional specialized questionnaire was developed for certain job title of a prior interest that sought more detailed information on tasks and possible exposures. For example, the supplemental questionnaire for machinists included a question on TCE usage. A team of industrial hygienists and chemicals assigned exposures blinded based on job title and other information obtained by questionnaire. A semiquantitative scale was developed for 300 exposures and included TCE (any, substantial). Parent et al. (2000a) presents observations of analyses examining job title, occupation, and some chemical-

specific exposures, but not TCE. Observations on TCE are found in the original report of Siemiatycki (1991). Any exposure to TCE was 3% among cases but <1% for substantial TCE exposure; "substantial" is defined as >10 years of exposure for the period up to 5 years before diagnosis. The TCE exposure frequencies in this study are lower than those in Brüning et al. (2003) and Charbotel et al. (2006), studies conducted in geographical areas with a high prevalence of industries using TCE. The expert assessment method is considered a valid and reliable approach for assessing occupational exposure in community-base studies and likely less biased from exposure misclassification than exposure assessment based solely on self-reported information (Fritschi et al., 2003; IOM, 2003; Siemiatycki et al., 1987). For example, Dewar et al. (1994) examine sensitivity of JEM of Siemiatycki et al. (1987) to exposure assessment by chemists and industrial hygienists using interview information and evaluation of job histories. Specific solvents are not examined, although, a sensitive 84% and specificity of 97% was found for the JEM for general solvent exposure.

This population study of several cancer sites included histologically-confirmed cases of kidney cancer (ICD-O 189, malignant neoplasm of kidney and other and unspecified urinary organs) ascertained from 16 Montreal-area hospitals between 1979 and 1985. A total of 227 eligible kidney cancer cases were identified were identified from 19 Montreal-area hospitals; 177 cases participated in the study (78% response). One control group (n = 1,295) consisted of patients with other forms of cancer (excluding lung cancer and other intestinal cancers) recruited through the same study procedures and time period as the rectal cancer cases. A population-based control group (n = 533), frequency matched by age strata, was drawn using electoral lists and random digit dialing. All controls were interviewed using face-to-face methods; however, 20% of the all cancer cases in the larger study were either too ill to interview or had died and, for these cases, occupational information was provided by a proxy respondent. The quality of interview conducted with proxy respondents was much lower, increasing the potential for misclassification bias, than that with the subject. The direction of this bias would diminish observed risk towards the null.

Statistical analysis are considered valid; logistic regression model, which included terms for respondent status, age, smoking, and BMI in Parent et al. (2000a) and Mantel-Haenszel χ^2 stratified on age, family income, cigarette smoking, and ethnic origin in Siemiatycki (1991). Odds ratios are presented with 90% CIs in Siemiatycki (1991) and 95% CIs in Parent et al. (2000a).

Overall, exposure assessment in this study adopted a superior approach, using expert knowledge and use of a JEM. However, examination of NHL and TCE exposure is limited by statistical power considerations related to low exposure prevalence, particularly for "substantial" exposure. For the exposure prevalence found in this study to TCE and for kidney cancer, the minimum detectable OR was 3.0 when $\beta = 0.02$ and $\alpha = 0.05$ (one-sided). The low statistical power to detect a doubling of risk and an increased possibility of misclassification bias

associated with case occupational histories resulting from proxy respondents suggests a decreased sensitivity in this study for examining kidney cancer and TCE.

Parent M-E, Hua Y, Siemiatycki J. (2000a). Occupational risk factors for renal cell carcinoma in Montreal. Am J Ind Med 38:609–618.

Siemiatycki J. (1991). Risk Factors for Cancer in the Workplace. Baca Raton: CRC Press.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This population case-control study was designed to generate hypotheses on possible association between 11 site-specific cancers and occupational title or chemical exposures.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	277 kidney cancer cases were identified among male Montreal residents between 1979 and 1985 of which 177 (147 RCCs) were interviewed. 740 male population controls were identified from the same source population using random digit dialing; 533 were interviewed. A second control series consisted of all other cancer controls excluding lung and bladder cancer cases. Participation rate: cases, 78%; population controls, 72%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD 189 (malignant neoplasm of the kidney and other and unspecified urinary organs) (Siemiatycki, 1991). ICD 189.0, RCC (Parent et al., 2000a).
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Unblinded interview using questionnaire sought information on complete job history with supplemental questionnaire for jobs of a priori interest (e.g., machinists, painters). Team of chemist and industrial hygienist assigned exposure using job title with a semiquantitative scale developed for 300 exposures, including TCE. For each exposure, a three-level ranking was used for concentration (low or background, medium, high) and frequency (percent of working time: low, 1–5%; medium, >5–30%; and high, >30%).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	100% of cases and controls were interviewed face-to-face by a trained interviewer. Cases interviews were conducted either at home or in the hospital; all population control interviews were conducted at home.
Blinded interviewers	Interviews were unblinded but exposure coding was carried out blinded as to case and control status.

CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Yes, 16% of cases, 13% of population controls, and 22% of cancer controls had proxy respondents.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancers in incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	177 cases (78% response), 533 population controls (72%). Exposure prevalence: Any TCE exposure, 2% cases; substantial TCE exposure (exposure for ≥10 yrs and up to 5 yrs before disease onset), 1% cases.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, income, index for cigarette smoking (Siemiatycki, 1991). Age, smoking, BMI, and proxy status (Parent et al., 2000b).
Statistical methods	Mantel-Haenszel (Siemiatycki, 1991). Logistic regression (Parent et al., 2000a).
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.13.3. Dosemeci et al. (1999).

B.3.2.13.3.1. Author's abstract.

BACKGROUND: Organic solvents have been associated with renal cell cancer; however, the risk by gender and type of solvents is nuclear. METHODS: We evaluated the risk of renal cell carcinoma among men and women exposed to all organic solvents-combined, all chlorinated aliphatic hydrocarbons (CAHC)-combined, and nine individual CAHC using *a priori* job exposure matrices developed by NCI in a population-based case-control study in Minnesota, U.S. We interviewed 438 renal cell cancer cases (273 men and 165 women) and 687 controls (462 men and 225 women). RESULTS: Overall, 34% of male cases and 21% of female cases were exposed to organic solvents in general. The risk of renal cell carcinoma was significantly elevated among women exposed to all organic solvents combined (OR = 2.3; 95% CI = 1.3-4.2), to CAHC combined (OR = 2.1; 95% CI = 1.1-3.9), and to trichloroethylene (TCE) (OR = 2.0; 95% CI = 1.0-4.0). Among men, no significant excess risk was observed among men exposed to any of these nine individual CAHCs, all CAHCs-combined, or all organic solvents-combined. DISCUSSION: These observed gender differences in risk of renal cell carcinoma in relation to exposure to organic solvents may be explained by chance based on small numbers, or by the differences in body fat content, metabolic activity, the rate of elimination of xenobiotics from the body, or by differences in the level of exposure between men and women, even though they have the same job title.

B.3.2.13.3.2. Study description and comment.

Dosemeci et al. (1999) reported data from a population-based case-control study of the association between occupation exposures and renal cancer risk. The investigators identified newly diagnosed patients with histologically confirmed RCC from the Minnesota Cancer Surveillance System from July 1, 1988 to December 31, 1990. The study was limited to white cases, and age and gender-stratified controls were ascertained using random digit dialing (for subjects ages 20–64) and from Medicare records (for subjects 65–85 years). Of the 796 cases and 796 controls initially identified, 438 cases (273 men, 165 women) and 687 controls (462 men, 225 women) with complete personal interviews were included in the occupational analysis.

Data were obtained using in-person interviews that included demographic variables, residential history, diet, smoking habits, medical history, and drug use. The occupational history included information about the most recent and usual industry and occupation (coded using the standard industrial and occupation codes, Department of Commerce), job activities, hire and termination dates, and full/part time status. A JEM developed by the NCI (Gómez et al., 1994) was used with the coded job data assign occupational exposure potential for 10 chlorinated aromatic hydrocarbons and organic solvents, and includes TCE.

Dosemeci et al. (1999) adopted logistic regression methods to evaluate renal cancer and occupational exposures. Odds ratios were adjusted for age, smoking, hypertension, and use of drugs for hypertension, and BMI.

Strengths of this study include the use of incident cases of renal cancer from a defined population area, with confirmation of the diagnosis using histology reports. The occupation history was based on usual and most recent job, in combination with a relatively focused JEM. In contrast to the type of exposure assessment that can be conducted in cohort studies within a specific workplace; however, exposure measurements, based on personal or workplace measurement, were not used, and a full lifetime job history was not obtained.

Dosemeci M, Cocco P, Chow W-H. (1999). Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons. Am J Ind Med 36:54–59.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Yes. From abstract—study aim was to evaluate effect of organic solvents on RCC risk using a priori JEMs.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	796 white males and females identified through the Minnesota Cancer Surveillance System with histological confirmed RCC between July 1, 1988 and December 31, 1990. Interviews were obtained for 690 subjects, of which 241 were with next-of-kin and excluded; 438 cases (273 males and 165 females) were included in analysis. 707 white population controls identified through random digit dialing, and matched to cases, aged 20–65 yrs old, by age and sex using a stratified random sample or, for cases aged 65–85, from Health Care Financing Administration list. 687 controls (462 males and 225 females) are included in the analysis. Participation rate: cases, 87%; controls, 86%. Occupational analysis: cases, 55%, controls 83%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence
Changes in diagnostic coding systems for lymphoma, particularly NHL	N/A
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	A trained interviewer blinded to case and control status interviewed subjects at home using a questionnaire which covered occupational, residential, and medical histories; demographic information; and personal information. Occupational history included self-reporting of the most recent job and usual occupation and industry, employment dates, and focused on 13 specific occupations or industries. Occupation and industry were coded according to a standard occupational classification or standard industrial classification with potential chemical-specific exposures to TCE and eight other chlorinated hydrocarbons identified using the JEM of Dosemeci et al. (1999) and Gomez et al. (1994).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	All cases and controls had face-to-face interviews.
Blinded interviewers	Yes, interviewers were blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	

>10% proxy respondents	No, subjects with next-of-kin interviews were excluded from the analysis.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancers in incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	55 cases with TCE exposure (13% exposure prevalence among cases). 69 controls cases with TCE exposure (10% exposure prevalence among controls).
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, smoking, BMI, and hypertension/ use of diuretics/use of anti-hypertension drugs.
Statistical methods	Logistic regression.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.2.14. Other Cancer Site Case-Control Studies

B.3.2.14.1. Siemiatycki (1991), Siemiatycki et al. (1987).

B.3.2.14.1.1. Author's abstract.

> A multi-cancer site, multi-factor, case-referent study was undertaken to generate hypotheses about possible occupational carcinogens. About 20 types of cancer were included. Incident cases among men aged 35-70 years and diagnosed in any of the major Montreal hospitals were eligible. Probing interviews were carried out for 3,726 eligible cases. The interview was designed to obtain detailed lifetime job histories and information on potential confounders. Each job history was reviewed by a team of chemists who translated it into a history of occupational exposures. These occupational exposures were then analyzed as potential risk factors in relation to the sites of cancer included. For each site of cancer analyzed, referents were selected from among the other sites in the study. The analysis was carried out in stages. First a Mantel-Haenszel analysis was undertaken of all cancer-substance associations, stratifying on a limited number of covariates, and, then, for those associations which were noteworthy in the initial analysis, a logistic regression analysis was made taking into account all potential confounders. This report describes the fieldwork and analytical methods.

B.3.2.14.1.2. Study description and comment.

Siemiatycki (1991) reported data from a case-control study of occupational exposures and several site-specific cancers, including lung and pancreas, conducted in Montreal, Quebec (Canada). Other cases included in this study were cancers of the bladder, colon, rectum, esophagus prostate, and lymphatic system (NHL); a description of the other case series are found in other sections in this appendix. The investigators identified 1,082 newly diagnosed cases of lung cancer (ICD-O, 162) and 165 newly diagnosed cases of pancreatic cancer (ICD-O, 157), confirmed on the basis of histology reports, between 1979 and 1985; 857 lung cancer (79.2%) and 117 pancreatic cancer cases (70.7%) participated in the study interview. One control group consisted of patients with other forms of cancer recruited through the same study procedures and time period as the melanoma cancer cases. The control series for lung cancer cases excluded other lung cancer cases; the control series for pancreatic cancer cases excluded all lung cancer cases. Additionally, a population-based control group (n = 533, 72% response), frequency-matched by age strata, was drawn using electoral lists and random digit dialing. Face-to-face interviews were carried out with 82% of all cancer cases with telephone interview (10%) or mailed questionnaire (8%) for the remaining cases. Twenty percent of all case interviews were provided by proxy respondents. The occupational assessment consisted of a detailed description of each job held during the working lifetime, including the company, products, nature of work at site, job activities, and any additional information that could furnish clues about exposure from the interviews.

A team of industrial hygienists and chemists blinded to subject's disease status translated jobs into potential exposure to 294 substances with three dimensions (degree of confidence that exposure occurred, frequency of exposure, and concentration of exposure). Each of these exposure dimensions was categorized into none, any, or substantial exposure. Any exposure to TCE was 2% among cases (n = 21 lung cancer cases, 2 pancreatic cancer cases) and 1% for substantial TCE exposure (n = 9 lung cancer cases); "substantial" is defined as ≥10 years of exposure for the period up to 5 years before diagnosis. None of the pancreatic cancer cases was identified with "substantial" exposure to TCE.

Mantel-Haenszel χ^2 analyses examined occupation exposures and lung cancer stratified on age, family income, cigarette smoking, ethnic origin, alcohol consumption, and respondent status or pancreatic cancer stratified on age, income, cigarette smoking, and respondent status (Siemiatycki, 1991). Odds ratios for TCE exposure in Siemiatycki (1991) are presented with 90% CIs.

The strengths of this study were the large number of incident cases, specific information about job duties for all jobs held, and a definitive diagnosis of cancer. However, the use of the general population (rather than a known cohort of exposed workers) reduced the likelihood that subjects were exposed to TCE, resulting in relatively low statistical power for the analysis. The JEM, applied to the job information, was very broad since it was used to evaluate 294 chemicals.

Siemitycki J. (1991). Risk Factors for Cancer in the Workplace. J Siemiatycki, Ed. Boca Raton: CRC Press.

Siemiatycki J, Wacholder S, Richardson L, Dewar R, Gérin M. (1987). Discovering carcinogens in the occupational environment. Scand J Work Environ Health 13:486–492.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This population case-control study was designed to generate hypotheses on possible association between 11 site-specific cancers and occupational title or chemical exposures.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	1,082 lung cases were identified among male Montreal residents between 1979 and 1985 of which 857 were interviewed; 165 cases were identified among male Montreal residents between 1979 and 1985 of which 117 were interviewed. 740 eligible male controls identified from the same source population using random digit dialing or electoral lists; 533 were interviewed. A second control series consisted of other cancer cases identified in the larger study. Participation rate: lung cancer cases, 79.2 %, pancreatic cancer cases, 70.7%; population controls, 72%.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-O, 122 (malignant neoplasm of trachea, bronchus and lung). ICD-O, 157 malignant neoplasm of pancreas.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Unblinded interview using questionnaire sought information on complete job history with supplemental questionnaire for jobs of a priori interest (e.g., machinists, painters). Team of chemist and industrial hygienist assigned exposure using job title with a semiquantitative scale developed for 294 exposures, including TCE. For each exposure, a three-level ranking was used for concentration (low or background, medium, high) and frequency (percent of working time: low, 1–5%; medium, >5–30%; and high, >30%).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	82% of all cancer cases interviewed face-to-face by a trained interviewer, 10% telephone interview, and 8% mailed questionnaire. Cases interviews were conducted either at home or in the hospital; all population control interviews were conducted at home.
Blinded interviewers	Interviews were unblinded but exposure coding was carried out blinded as to case and control status.
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Yes, 20% of all cancer cases had proxy respondents.

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	857 lung cancer cases (79.2% response), 117 pancreatic cancer cases (70.7% response); 533 population controls (72% response). Exposure prevalence: Any TCE exposure, 2% cancer cases (n = 21 lung cancer cases and 2 pancreatic cancer cases); substantial TCE exposure (exposure for ≥10 yrs and up to 5 yrs before disease onset), 1% lung cancer cases (n = 9), no pancreatic cancer cases assigned "substantial" TCE exposure.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Lung cancer—age, family income, cigarette smoking, ethnic origin, alcohol consumption, and respondent status. Pancreatic cancer—age, income, cigarette smoking, and respondent status.
Statistical methods	Mantel-Haenszel (Siemiatycki, 1991).
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.3. Geographic-Based Studies

B.3.3.1. Coyle et al. (2005)

B.3.3.1.1. Author's abstract.

Purpose. To investigate the role of environment in breast cancer development, we conducted an ecological study to examine the association of releases for selected industrial chemicals with breast cancer incidence in Texas.
Methods. During 1995–2000, 54,487 invasive breast cancer cases were reported in Texas. We identified 12 toxicants released into the environment by industry that: (1) were positively associated with breast cancer in epidemiological studies, (2) were Environmental Protection Agency (EPA) Toxics Release Inventory (TRI) chemicals designated as carcinogens or had estrogenic effects associated with breast cancer risk, and (3) had releases consistently reported to EPA TRI for multiple Texas counties during 1988–2000. We performed univariate, and multivariate analyses adjusted for race and ethnicity to examine the association of releases for these toxicants during 1988–2000 with the average annual age-adjusted breast cancer rate at the county level.
Results. Univariate analysis indicated that formaldehyde, methylene chloride, styrene, tetrachloroethylene, trichloroethylene, chromium, cobalt, copper, and nickel were positively associated with the breast cancer rate. Multivariate analyses indicated that styrene was positively associated with the breast cancer rate in women and men (b = 0.219, p =0.004), women (b = 0.191, p=0.002), and women ‡ 50 years old (b = 0.187, p=0.002).
Conclusion. Styrene was the most important environmental toxicant positively associated with invasive breast cancer incidence in Texas, likely involving women and men of all ages. Styrene may be an important breast carcinogen due to its widespread use for food storage and preparation, and its release from building materials, tobacco smoke, and industry.

B.3.3.1.2. Study description and comment.

Residential address in 254 Texas counties at time of cancer diagnosis was the exposure surrogate in this ecologic study of invasive breast cancer in over a 5-year period (1995–2000). Incident breast cancer cases in males and females were identified from Texas Cancer Registry. During the 5-year period, 54,487 cases were diagnosed, of which 53,910 were in females (99%). The association between median average annual age-adjusted breast cancer rates for women and men, all women, women <50 years old, and women ≥50 years old and 12 hazardous air pollutants identified as exposures of interested were examined using nonparametric tests (Mann-Whitney U test) and linear regression analyses. The 12 hazardous air pollutants were: carbon tetrachloride, formaldehyde, methylene chloride, styrene, perchloroethylene, TCE, arsenic, cadmium, chromium, cobalt, copper, and nickel. On-site atmospheric release data on individual hazardous air pollutants was identified from EPA's Toxics Release Inventory (TRI) for a 13-year period, 1998–2000 with an exposure surrogate as the annual total release in pounds/year for the 12 hazardous air pollutants.

Coyle et al. (2005) compared average annual age-adjusted breast cancer rate for counties reporting a release to that rate for non-reporting counties using Mann-Whitney U test. Additionally, multiple linear regression analyses was used to determine the association of the average annual age-adjusted breast cancer rates with the 12 hazardous air pollutants, adjusting for race and ethnicity when associated with the study's outcome variable.

While this study provides insight on cancer rates in studied population, TCE and other hazardous air pollutant exposures are poorly defined and the exposure surrogate unable to distinguish subjects more with higher exposure potential from those with low or minimal exposure potential. Some information may be provided through examination of inter-county release rates; however, no information is provided by Coyle et al. (2005). Furthermore, the ecologic design of the study does not address residential history or other information on an individual-subject level and is subject to bias from "ecologic fallacy" or improper inference about individual-level associations based on aggregate-level analysis. Overall, this study is not able to identify risk factors (etiologic exposures), has low sensitivity for examining TCE, and provides little weight in an overall weight of evidence evaluation of TCE and cancer.

Coyle YM, Hynan LS, Euhus DM, Minhajuddin ATM. (2005). An ecological study of the association of environmental chemicals on breast cancer incidence in Texas. Breast Cancer Res Treat.92:107–114.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Hypothesis of this study was to evaluate breast risks in Texas counties and hazardous air pollutants.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Cases are incident breast cancers in males and females over a 5-yr period (1995–2000) in subjects residing in Texas and reported to the Texas Cancer Registry.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Not identified in paper.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Residence in Texas county as time of diagnosis is exposure surrogate. Annual release by county of 12 hazardous air pollutants (carbon tetrachloride, formaldehyde, methylene chloride, styrene, perchloroethylene, TCE, arsenic, cadmium, chromium, cobalt, copper, and nickel) are obtained from EPA's TRI database.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	54,487 incident breast cancer cases in males and females.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, and race/ethnicity.
Statistical methods	Mann-Whitney U test (nonparametric) to compared average annual age-adjusted breast cancer rate between counties reported hazardous air pollutant release to that for non-reporting counties. Linear logistic regression
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.3.2. Morgan and Cassady (2002)

B.3.3.2.1. Author's abstract.

In response to concerns about cancer stemming from drinking water contaminated with ammonium perchlorate and trichloroethylene, we assessed observed and expected numbers of new cancer cases for all sites combined and 16 cancer types in a California community (1988 to 1998). The numbers of observed cancer cases divided by expected numbers defined standardized incidence ratios (SIRs) and 99% confidence intervals (CI). No significant differences between observed and expected numbers were found for all cancers (SIR, 0.97; 99% CI, 0.93 to 1.02), thyroid cancer (SIR, 1.00; 99% CI, 0.63 to 1.47), or 11 other cancer types. Significantly fewer cases were observed than expected for cancer of the lung and bronchus (SIR, 0.71; 99% CI, 0.61 to 0.81) and the colon and rectum (SIR, 0.86; 0.74 to 0.99), whereas more cases were observed for uterine cancer (SIR, 1.35; 99% CI, 1.06 to 1.70) and skin melanoma (SIR, 1.42; 99% CI, 1.13 to 1.77). These findings did not identify a generalized cancer excess or thyroid cancer excess in this community.

B.3.3.2.2. Study description and comment.

Residential address in 13 census tracts in Redlands (San Bernardino County, California) at time of cancer diagnosis was the exposure surrogate in this ecologic study of cancer incidence over a 10-year period (1988–1998). Seventeen cancers in adults (all cancers, bladder, brain and other nervous system, breast [females only], cervix, colon and rectum, Hodgkin lymphoma, kidney and renal pelvis, leukemia [all], liver and bile duct, lung and bronchus, NHL, melanoma, ovary, prostate, thyroid and uterus) and three site-specific incident cancers in children under 15 years of age (leukemia [all], brain/CNS, and thyroid) were identified from the Desert Sierra Cancer Surveillance Program, a regional cancer registry reporting to the California Cancer Registry, with expected numbers of site-specific cancer using age-race annual site-specific cancer incidence rates between 1988 and 1992 to 1990 census-reported information on population size and demographics. The use of the Desert Sierra Cancer Surveillance Program rates which include the studied population would inflate the number of site-specific cancer expected; however, the potential magnitude of bias is likely minimal given the Redlands populations was estimated as 2% of the total population of the regional cancer registries ascertainment area (Morgan and Cassady, 2002). This is a record-based study and information on personal habits and potential risk factors other than race, sex, and age are lacking for individual subjects.

Morgan and Cassidy (2002) identified TCE and perchlorate from drinking water as exposures of interest. Limited monitoring data from the 1,980 identified TCE concentrations in Redlands wells as between 0.09 and 97 ppb TCE and drinking water concentrations as below the maximum contaminant level (5 ppb) since 1991. The paper lacks information if water monitoring represented wells in the 13-census tract study area. Furthermore, the paper does not

include information on water treatment and distribution networks to provide an estimate of TCE concentration in finished tap water to individual homes. These authors noted their inability to identify higher or lower exposed subjects, as well, as minimally exposed subjects as a source of uncertainty. No data are presented on perchlorate concentrations in well or drinking water. The assumption of residence in 13 census tracts is insufficient as a surrogate of potential exposure to TCE and perchlorate in the absence of exposure modeling and data on water distribution patterns. Exposure misclassification bias is highly likely and of a nondifferential nature which would dampen observed associations.

While this study provides insight on cancer rates in studied population, TCE exposure is poorly defined and the exposure surrogate unable to distinguish subjects more with higher exposure potential from those with low or minimal exposure potential. Furthermore, the ecologic design of the study does not address residential history or other information on an individual-subject level and is subject to bias from "ecologic fallacy" or improper inference about individual-level associations based on aggregate-level analysis. Morgan and Cassidy (2002) furthermore discuss the relatively high education and income levels in the Redlands population compared with the average for the referent population may lead to lower tobacco use and higher than average access to health care, biases that would dampen risks for lung and other tobacco-related cancers, but may also increase risks for colon and cervical cancers. Overall, this study is not able to identify risk factors (etiologic exposures), has low sensitivity for examining TCE, and provides little weight in an overall weight of evidence evaluation of TCE and cancer.

Morgan JW, Cassady RE. (2002). Community cancer assessment in response to long-time exposure to perchlorate and trichloroethylene in drinking water. J Occup Environ Med 44:616–621.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Hypothesis of this study was to evaluate cancer risks in a California community, not to evaluate TCE and cancer explicitly.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Cases are incident cancers over a 10-yr period (1988–1989) in subjects residing in 13 Redlands (California) census tracts at time of diagnosis. 17 site-specific cancers are identified in adults and 3 site-specific cancers in children <15 yrs old. Cancer cases identified from Desert Sierra Cancer Surveillance Program (DSCSP), a regional cancer registry. Annual age-race-site specific cancer rates from DSCSP for 1988 and 1992 and age-race-sex specific population estimates for 1990.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Not identified in paper.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Residence in a 13-census tract area of Redlands, California is exposure surrogate. No data are presented on TCE or perchlorate concentrations in treated drinking water supplied to residents.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	3,098 incident cancers, the largest number from 536 breast cancer and fewest number from Hodgkin disease.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, and race/ethnicity.
Statistical methods	SIR with indirect standardization of estimated expected numbers of site-specific cancers adjusted for population growth; 90% CIs presented in tables.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.3.3. Cohn et al. (1994b)

B.3.3.3.1. Author's abstract.

> A study of drinking water contamination and leukemia and non-Hodgkin's lymphoma (NHL) incidence (1979-1987) was conducted in a 75-town study area. Comparing incidence in towns in the highest trichloroethylene (TCE) stratum (>5 microg/L) to towns without detectable TCE yielded an age-adjusted rate ratio (RR) for total leukemia among females of 1.43 (95% CI 1.07-1.90). For females under 20 years old, the RR for acute lymphocytic leukemia was 3.26 (95% CI 1.27-8.15). Elevated RRs were observed for chronic myelogenous leukemia among females and for chronic lymphocytic leukemia among males and females. NHL incidence among women was also associated with the highest TCE stratum (RR = 1.36; 95% CI 1.08-1.70). For diffuse large cell NHL and non-Burkitt's high-grade NHL among females, the RRs were 1.66 (95% CI 1.07-2.59) and 3.17 (95% CI 1.23-8.18), respectively, and 1.59 (95% CI 1.04-2.43) and 1.92 (95% CI 0.54-6.81), respectively, among males. Perchloroethylene (PCE) was associated with incidence of non-Burkitt's high-grade NHL among females, but collinearity with TCE made it difficult to assess relative influences. The results suggest a link between TCE/PCE and leukemia/NHL incidence. However, the conclusions are limited by potential misclassification of exposure due to lack of individual information on long-term residence, water consumption, and inhalation of volatilized compounds.

B.3.3.3.2. Study description and comment.

This expanded study of a previous analysis of TCE and perchloroethylene in drinking water in a 27-town study area (Fagliano et al., 1990)examined leukemia and NHL incidence from 1979 to 1987 in residents and TCE and other VOCs in drinking water delivered to 75 municipalities. Exposure estimates were developed from data generated by a mandatory monitoring program for 4 trihalomethane chemicals and 14 other volatile organic chemicals in 1984–1985 for public water supplies and from historical monitoring data conducted in 1978–1984 by the New Jersey Department of Environmental Protection and Energy and the New Jersey Department of Health, which was the mean of monthly averages for this period. The average and maximum concentration of TCE and other chemicals were estimated by considering together, for the period prior to 1985, details of the distribution system size, well or surface water use, patterns of water purchases among systems, and significant changes in water supply, and for years after 1985, samples of finished water from the plant and samples taken from the distribution system under the assumption of homogeneous mixing. The number of distribution system samples for each supply varied from 2 to 50. Additionally, a dilution factor assuming complete mixing was used to adjust for water purchased from another source. A single summary average and maximum concentration for each contaminate for a municipality was assigned to all cases residing in that municipality at the time of cancer diagnosis. Concentrations of TCE and perchloroethylene were highly correlated (r = 0.63). A ranking of municipalities was the same

when using average or maximum concentration and the maximum concentration of TCE or perchloroethylene used in statistical analyses was grouped into three strata: <0.1 (referent group), 0.1–5, >5–20, and >20 ppb.

Incident cases of NHL and forms of leukemia reported to the New Jersey State Cancer Registry were identified from 1979 and 1987. Incidence rate ratios were estimated using Poisson regression models fitted to age- and sex-specific numbers of cases by exposure strata and the stratum-specific population. Statistical treatment considered exposure to other drinking water contaminants, atmospheric emissions of hazardous air pollutants as reported to U.S. EPA's TRI by municipality and two socioeconomic variables measured as municipal—average annual household income and percentage of high school graduates. None of the water trihalomethane or VOCs other than perchloroethylene was shown to be associated with childhood leukemia or adult lymphomas. Furthermore, neither average income, education, nor TRI release data were associated with NHL or leukemia except in one exception, TRI release was shown to modify the effects of TCE and high-grade non-Burkett's lymphoma in females.

This ecological study is subject to known biases and confounding as introduced through its study design (NRC, 1997). Exposure estimates are crude (averages), do not consider individual differences in drinking water patterns, and assigns group exposure levels to all subjects without consideration of residential history. Potential for misclassification bias is likely great in this study as is the potential for bias. This study does attempt to examine three possible confounding exposures, although these are crudely defined, and some potential for residual confounding is possible given the study's use of aggregated data.

Cohn P, Klotz J, Bove F, Berkowitz M, Fagliano J. (1994b). Drinking water contamination and the incidence of leukemia and non-Hodgkin's lymphoma. Environ Health Perspect 102:556–561.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This study was designed to further examine drinking water contaminates and lymphoma; a previous study of TCE and perchloroethylene in drinking water found a statistically significant association with leukemia among females residing in a 27-town study area (Fagliano et al., 1990).
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Incident cases of various forms of leukemia (all leukemia, acute lymphocytic, chronic lymphocytic, acute myelogenous, chronic myelogenous, other specified and unspecified leukemia) and NHL (total, low-grade, intermediate-grade [total and diffuse large cell a B-cell lymphoma], high-grade including non-Burkett's lymphoma) from 1979 to 1987 are identified from New Jersey State Cancer Registry. Subjects grouped in lowest exposure category are referents.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Not identified in paper.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Average and maximum concentration of TCE and other chemicals were estimated by considering together, for the period prior to 1985, details of the distribution system size, well or surface water use, patterns of water purchases among systems, and significant changes in water supply, and for years after 1985, samples of finished water from the plant and samples taken from the distribution system under the assumption of homogeneous mixing. No difference in municipality ranking by average or maximum concentration. Three grouped categories of maximum concentration in statistical analysis are <0.1 (referent), 0.1–5, >5 ppb (U.S. EPA Maximum Contaminant Level for TCE and perchloroethylene).
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	1,190 leukemia cases (663 males, 527 females), 119 cases assigned >5.0 ppb TCE. 1,658 NHL cases (841 males, 817 females), 165 cases assigned >5.0 ppb TCE.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age and sex.
Statistical methods	Poisson regression fitted to the age-and sex-specific count of cases in towns grouped by exposure strata and weighted by the logarithm of the strata-specific population.
Exposure-response analysis presented in published paper	Yes.
Documentation of results	Yes.

B.3.3.4. Vartiainen et al. (1993)

B.3.3.4.1. Author's abstract.

Concentrations up to 212 μg/l of trichloroethene (TCE) and 180 μg/l of tetrachloroethene (TeCE) were found in the drinking water from two villages in Finland. To evaluate a possible exposure, urine sample from m95 and 21 inhabitants in these villages and from two control groups of 45 and 15 volunteers were collected. Dichloroacetic acid (DCA) and trichloroacetic acid (TCA), the metabolites of TCE and TeCE, were also analyzed. The individuals using contaminated water in one of the villages excreted TCE an average 19 μg/d (<1 – 110 μg/d) and in the other 7.9 μg/d (<1 – 50 μg/d), while the controls excreted an average 2.0 μg/d (<1 – 6.4 μg/d) or 4.0 μg/d (<1 – 13 μg/d). No increased incidence rates were found in the municipalities in question for total cancer, liver cancer, non-Hodgkin's lymphomas, Hodgkin's disease, multiple myeloma, or leukemia.

B.3.3.4.2. Study description and comment.

This published study of two separate analyses: (1) urinary biomonitoring of 106 subjects from two Finish municipalities, Hausjärvi and Hattula and (2) calculation of total cancer and site-specific cancer incidence between 1953 and 1991 in Hausjärvi and Hattula residents. Limited exposure monitoring data are presented in the paper. TCE concentrations in drinking water from Oitti are lacking other than noting TCE and perchloroethylene were 100–200 μg/L in 1992. TCE concentrations in drinking water from Hattula were <10 μg/L in December 1991; however, samples (number unknown) taken 6 months later contained 212 and 66 μg/L TCE. These two municipalities discontinued use of these sources for drinking water in August 1992.

Cancer incidence for six sites (all cancers, liver cancer, NHL, Hodgkin lymphoma, multiple myeloma, and leukemia) between 1953 and 1991 in Hausjärvi and Hattula residents was obtained from the Finnish Cancer Registry. A total of 1,934 cancers were observed during the study period. Standardized incidence ratios for each municipality were calculated using site-specific cancer incidence rates from the Finnish population for the entire time period and for three shorter periods, 1953–1971, 1972–1981, and 1982–1991. The paper does not identity the source for or size of Hausjärvi and Hattula population estimates and if temporal changes in population estimates were considered in the statistical analysis. This study, using record systems, did not include information obtained directly from subjects and lacks information on personal and lifestyle factors that may introduce bias or confounding.

This study provides little information in an overall weight-of-evidence analysis on cancer risks and TCE exposure. A major limitation is its lack of exposure assessment to TCE and perchloroethylene. While this study provides some information on cancer incidence in the two towns over a 40-year period, this study is not able to identify potential risk factors and exposures.

Vartiainen T, Pukkala E, Rienoja T, Strandman T, Kaksonen K. (1993). Population exposure to tri- and tetrachloroethene and cancer risk: two cases of drinking water pollution. Chemosphere 27:1171–1181.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Study aim was: (1) to determine if residents of two villages in Finland had exposure to TCE and perchloroethylene as indicated from urinary biomonitoring; (2) identify biomarker for low-level exposure; and (3) to determine cancer incidence in Hausjärvi and Hattula, two municipalities in Finland. This study could not identify potential risk factors.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Cancer incidence cases identified from Finnish Cancer Registry. Site-specific cancer rates for the Finnish population was used a referent.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Not identified in paper.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Residence in two municipalities is the exposure surrogate in this ecologic study. The paper lacks exposure assessment to TCE and perchloroethylene in drinking water in Hausjärvi and Hattula.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	3,846 cancer cases; 1,942 from Hausjärvi and 1,904 from Hattula.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age and sex.
Statistical methods	SIR with cancer incidence rates in Finnish population as referent.
Exposure-response analysis presented in published paper	No.
Documentation of results	Cancer incidence analysis is not well documented.

B.3.3.5. Mallin (1990)

B.3.3.5.1. Author's abstract.

Cancer maps from 1950 through 1979 revealed areas of high mortality from bladder cancer for both males and females in several northwestern Illinois counties. In order to further explore this excess, a bladder cancer incidence study was conducted in the eight counties comprising this region. Eligible cases were those first diagnosed with bladder cancer between 1978 and 1985. Age adjusted standardized incidence ratios were calculated for each county and for 97 zip codes within these counties. County results revealed no excesses. Zip code results indicated elevated risks in a few areas, but only two zip codes had significantly elevated results. One of these zip codes had a significant excess in males (standardized incidence ratio = 1.5) and females (standardized incidence ratio = 1.9). This excess was primarily confined to one town in this zip code, in which standardized incidence ratios were significantly elevated in males (1.7) and females (2.6). Further investigation revealed that one of four public drinking water wells in this town had been closed due to contamination; two wells were within a half mile (0.8 km) of a landfill site that had ceased operating in 1972. Tests of these two wells revealed traces of trichloroethylene, tetrachloroethylene, and other solvents. Further investigation of this cluster is discussed.

B.3.3.5.2. Study description and comment.

This ecologic study of bladder cancer incidence and mortality among white residents in nine Illinois counties between 1978 and 1985 was carried out to further investigate a previous finding of elevated bladder cancer mortality rates in some counties. The study lacks exposure assessment to subjects and potential sources of exposure was examined in a post hoc manner in one case only, for a community with an observed elevated bladder cancer incidence. The limited exposure examination focused on groundwater contamination and proximity of Superfund sites to the community, lacked assignment of exposure surrogates to individual study subjects, and findings are difficult to interpret given the lack of exposure assessment for the other eight counties.

Histologically-confirmed incident bladder cancer cases were identified from hospital records in eight of the nine counties. Since the nine-county area bordered on neighboring states of Wisconsin and Iowa, incident bladder cancer cases were also ascertained from the Wisconsin Cancer Reporting System and Iowa's State Health Registry. No information is provided in the paper on completeness of ascertainment of bladder cancer cases among residents or on the source for identifying bladder cancer deaths. Expected numbers of incident cancers calculated using age-specific rates for white males and females from the SEER program (incidence) or the U.S. population (mortality), and the census data on population estimates for the nine-county area. Statistical analyses adopt indirect standardization methods to calculate SMR and SIRs for a community and SIRs for individual postal zip codes. The use of records and absence of

information collected from subject personal interviews precluded examination of possible confounders other than age and race.

This ecological study is subject to known biases and confounding as introduced through its study design (NRC, 1997). Ecological studies like this study are subject to bias known as "ecological fallacy" since variables of exposure and outcome measured on an aggregate level may not represent association at the individual level. Consideration of this bias is important for diseases with more than one risk factor, such as the site-specific cancers evaluated in this assessment. Lack of information on smoking is another uncertainty. While this study provides insight on bladder cancer rates in the studied communities, it does not provide any evidence on cancer and TCE exposure. For this reason, this study provides little weight in an overall weight-of-evidence analysis.

Mallin K. (1990). Investigation of a bladder cancer cluster in Northwestern Illinois. Amer J Epidemiol 132:S96–S106.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	The hypothesis of study was to "further exposure a previous finding of bladder cancer excess in several northwestern Illinois counties." (from abstract).
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Incident cancer cases diagnosed between 1978 and 1985 were identified in residents in nine northwestern Illinois counties from the Illinois Cancer Registry, the Wisconsin Cancer Reporting System or the Iowa State Health Registry. Source for deaths in subjects residing at the time of death in the 9 counties was not identified in the published paper. Expected number of bladder cancer derived using: (1) SEER age-race-sex specific incidence rates and (2) age-race-sex specific mortality rates of the U.S. population for 1978–1981 and for 1982–1985 and census estimates of population for each county or postal zip code area.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence and mortality.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Not identified in paper.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	This is a health survey and lacks exposure assessment to communities and to individual subjects. Monitoring of volatile organic chemicals including TCE in two municipal drinking water wells for 1982–1988 in a community with elevated bladder cancer rates was identified in paper; TCE concentrations were <15 ppb. It is not known whether monitoring data are representative of exposure to study subjects.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	712 bladder cancer incident cases and 222 bladder cancer deaths among white males and female residents in nine northwestern Illinois counties.

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age and sex.
Statistical methods	SIR with cancer incidence rates from SEER program and mortality rates of U.S. population as referents.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.3.6. Isacson et al. (1985)

B.3.3.6.1. Author's abstract.

> With data from the Iowa Cancer Registry, age-adjusted sex-specific cancer incidence rates for the years 1969-1981 were determined for towns with a population of 1,000–10,000 and a public water supply from a single stable ground source. These rates were related to levels of volatile organic compounds and metals found in the finished drinking water of these towns in the spring of 1979. Results showed association between 1,2 dichloroethane and cancers of the colon and rectum and between nickel and cancers of the bladder and lung. The effects were most clearly seen in males. These associations were independent of other water quality and treatment variables and were not explained by occupational or other sociodemographic features including smoking. Because of the low levels of the metals and organics, the authors suggest that they are not causal factors, but rather indicators of possible anthropogenic contamination of other types. The data suggest that water quality variables other than chlorination and trihalomethanes deserve further consideration as to their role in the development of human cancer.

B.3.3.6.2. Study description and comment.

This ecologic study of cancer incidence at six sites (bladder, breast, colon, lung, prostate, rectum) and chlorinated drinking water uses monitoring data from finished public drinking water supplies to infer exposure to residents of Iowa towns of 1,000–10,000 population sizes. Towns were included if they received water from a single major source (surface water, wells of <150 feet depth, or wells ≥50 feet depth) prior to 1965. Water monitoring for VOCs, trace elements, and heavy metals was carried in Spring, 1979, as part of a larger nationwide collaborative study of bladder cancer and artificial sweeteners (Hoover and Strasser, 1980), and samples analyzed using proton-induced x-ray emission for trihalomethanes, TCE, perchloroethylene, 1,2-dichloroethane, 1,1,1-trichloroethane, carbon tetrachloride, 1,2-DCE, and 43 inorganic elements. 1,1,1-Trichloroethane was the most frequently detected VOC in both surface and groundwater; TCE, perchloroethylene, and 1,2-dichloroethane were more frequently detected in shallow wells than in deep (>150 feet) wells.

Cancer incidence was obtained for the period 1969 and 1981 with age-adjusted site-specific cancer incidence rates for males and females calculated separately for four VOCs (1,2-dichloroethane, TCE, perchloroethylene, and 1,1,1-trichloroethane) in finished groundwater supplies using the direct standardization method. Using the address at the time of diagnosis, each cancer patient was classified into one of two groups: (1) residing within the city limits and, thus, drinking the municipality's water; or (2) residing outside the city limits and consuming water from a private source. Age-adjusted incidence rates are reported by group study town into two TCE water concentrations categories of <0.15 and ≥0.15 μg/L.

This ecological study on drinking water exposure and cancer provides little information in a weight-of-evidence analysis of TCE and cancer. Exposure estimates are crude (averages),

do not consider individual differences in drinking water patterns or other sources of exposure, and assigns group exposure levels to all subjects. Potential for misclassification bias is likely great in this study, likely of a nondifferential nature, and dampen observations.

Isacson P, Bean JA, Splinter R, Olson DB, Kohler J. (1985). Drinking water and cancer incidence in Iowa. III. Association of cancer with indices of contamination. Amer J Epidemiol 121:856–869.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This ecological study was designed to examine consistency with the hypothesis of an association between cancer and chlorinated water through examination of other water contaminants besides water chlorination byproducts and trihalomethanes.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Subjects are incident cases of cancer of the bladder, breast, prostate, lung rectum, and stomach reported to the Iowa Cancer Registry between 1969 and 1981 and, who resided in towns with a 1970 population of 1,000–10,000 and a public drinking water supply coming solely from a single major source (wells) prior to 1965. Age-adjusted site-specific incidence rates are calculated using the direct method and the 1970 Iowa population.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	Not identified in paper.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	As part of another epidemiologic study on water chlorination and bladder cancer, finished drinking water samples from treatment plant were collected in Iowa municipalities with populations of 1,000 or larger in Spring 1979 and analyzed using proton induced x-ray emission for 4 trihalomethanes (chloroform, chlorodibromomethane, bromoform, dibromochloromethane), 7 VOCs (TCE, perchloroethylene, 1,1,1-trichloroethane, carbon tetrachloride, 1,2-dichloroethane, and cis- and trans-1,2-DCE) and 43 inorganic elements, including metals. The predominant contaminant was 1,1,1-tri-chloroethane; detectable levels of TCE were found in approximately 20% of sampled municipalities. Study towns were ranked into two categories of TCE in finished water, <0.15 µg/L and ≥0.15 µg/L in the statistical analysis.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	11,091 cancer cases of which ~20% of cases resided in municipality with finished water TCE concentration of ≥0.15 µg/L. Bladder, 852 cases Breast (female), 1,866 cases Colon, 2,032 cases Lung 1,828 cases Prostate, 1,823 cases Rectum, 824 cases
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age and sex.
Statistical methods	Age-adjusted site-specific mortality rates calculated using direct standardization method and 1970 Iowa population.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.3.7. Studies in the Endicott Area of New York

A series of health statistics reviews and exposure studies have been conducted in an area with a history of VOCs, including TCE, detected in municipal wells used to supply drinking water to residents of Endicott, Broome County, New York. These studies were carried out by staff the NYS DOH with support from the ATSDR. Early health surveys examined cancer incidence among Broome County residents between 1976 and 1980 or 1981 and 1990, with focused analyses of cancer incidence among residents of Endicott Village and other nearby towns, childhood leukemia in the Town of Union and possible etiologic factors, and adult leukemia deaths and employment in the shoe and boot manufacturing industry (NYSDOH, 2005; Forand, 2004). Two recent studies focused on cancer incidence or birth outcomes among Village of Endicott residents living in a geographically defined area with VOC exposure potential as documented from indoor and soil vapor monitoring (ATSDR, 2008b, 2006a).

The Village of Endicott is a mixed residential, commercial, and industrial community with a rich industrial heritage, and a number of VOCs were used at industrial locations in and around Endicott, as well as been disposed at area landfills (ATSDR, 2006b). Three wells provide drinking water to the Village of Endicott: Ranney, which supplied most of the water used by the Endicott Municipal Water Works since it was first placed in service in 1950; and, South Street, where two wells resided. The Endicott Municipal Water Supply operates on a grid-water system, neighborhoods closest to the wells are usually supplied at a greater rate from nearby wells as compared to wells farther away (ATSDR, 2006b).

Routine monitoring of the Ranney well in the early 1980s detected VOCs at levels above New York State drinking water guidelines (ATSDR, 2006b). A groundwater-contaminated plume northwest of the Ranney Well was found in a lower aquifer from which the municipal drinking supply is drawn. Several sources were initially recognized as contributing to contamination of the wellfield with a supplemental remedial investigation concluding that the Endicott Village Landfill was the source of the VOCs in the Endicott Wellfield water supply (ATSDR, 2006b). Groundwater samples collected from monitoring wells installed during previous investigations, wells installed as part of the supplemental remedial investigation, the Purge well, and the Ranney well contained many VOCs. Remediation efforts starting in the 1980s have reduced contamination in this well to current maximum contaminant levels. Water monitoring of the South Street wells (wells 5 and 28) has been carried out for VOCs since 1980 and 1981, respectively (ATSDR, 2006b). Detection limits for VOCs from the South Street wells varied from 0.5 to 1.0 µg/L; 1,1-dichloroethane had the highest detection frequency, in 44% of all samples, and TCE was detected in 3 of 116 samples obtained between 1980 and 2004 (ATSDR, 2006b).

An upper aquifer with a contaminant plume containing VOCs was also identified and sampling data indicated that there were multiple sources of vapor contamination, including a former IBM facility located in the Village (NYSDEC, 2008; U.S. EPA, 2005d). This

groundwater contaminant plume flows directly beneath the center of the Village of Endicott and serves as a source of soil vapor contamination. Findings of a 2002 investigation indicated that vapor migration had resulted in detectable levels of contaminants in indoor air structures, including locations in the Village of Endicott and Town of Union. Of soil gas and indoor air monitoring at >300 properties in an area south of the IBM Endicott facility, TCE was the most commonly found contaminant in indoor air, at levels ranging from 0.18 to 140 $\mu g/m^3$ (NYSDEC, 2008). This area is identified as the Eastern study area in the health statistics review of ATSDR (2008b, 2006a). Other contaminants besides TCE detected in soil gas and indoor air less frequently and at lower levels included tetrachloroethylene, cis-1,2-dichloroethene, 1,1,1-trichloroethane, 1,1-DCE, 1,1-dichloroethane, and Freon 113. Vapor-intrusion contamination was also identified in a neighborhood adjacent to the Eastern area, call the Western study in the health statistic review, and perchloroethylene and its degradation byproducts were detected by vapor monitoring. Perchloroethylene levels generally ranged from 0.1 to 3.5 $\mu g/m^3$ of air (ATSDR, 2006a).

B.3.3.7.1. ATSDR (2008b, 2006a)

B.3.3.7.1.1. ATSDR (2006a) executive summary.

> ***Background*** The New York State Department of Health (NYS DOH) conducted this Health Statistics Review because of concerns about health issues associated with environmental contamination in the Endicott area. Residents in the Endicott area may have been exposed to volatile organic compounds (VOCs) through a pathway known as soil vapor intrusion. Groundwater in the Endicott area is contaminated with VOCs as a result of leaks and spills associated with local industry and commercial businesses. In some areas of Endicott, VOC contamination from the groundwater has contaminated the adjacent soil vapor which has migrated through the soil into structures through cracks in building foundations (soil vapor intrusion). Trichloroethene (TCE), tetrachloroethene (PCE) and several other VOCs have been found in the soil vapor and in the indoor air of some structures.
>
> ***Conclusions*** This health statistics review was conducted because of concerns that exposure to VOCs through vapor intrusion may lead to adverse health effects. Although this type of study cannot prove whether there is a causal relationship between VOC exposure in the study area and the increased risk of several health outcomes observed, it does serve as a first step in providing guidance for further health studies and interventions. The elevated rates of several cancers and birth outcomes observed will be evaluated further to try to identify additional risk factors which may have contributed to these adverse health outcomes.
>
> Limitations in the current study included limited information about the levels of VOCs in individual homes, the duration of the exposure, the amount of time residents spent in the home each day and the multiple exposures and exposure pathways that likely existed among long term residents of the Endicott area. In addition, personal information such as medical history; dietary and lifestyle choices such as smoking and drinking; and occupational exposures to chemicals

were not examined. Future evaluations of cancer and birth defects and VOC exposures in the area should take these factors into account. The small population size of the study area also limited the ability to detect meaningful elevations or deficits in disease rates, especially for certain rare cancers and birth outcomes.

This study represents the first step in a step-wise approach to addressing health outcome concerns related to environmental contamination in Endicott, NY. Follow-up will consist of further reviewing of the cancer and birth outcome data already collected. Additional efforts will include reviewing individual case records of kidney and testicular cancers, heart defects, Down syndrome and term low birth weight births. In addition, we will review spontaneous fetal deaths among residents of the area. The information gained, along with the results of this Health Statistics Review, will be used to assess if a follow up epidemiologic study is feasible. Any follow-up study should be capable of accomplishing one of two goals: either to advance the scientific knowledge about the relationship between VOC exposure and health outcomes; or as part of a response plan to address community concerns. While not mutually exclusive, the distinction between these goals must be considered when developing a follow-up approach. Any plans for additional study will need to address other risk factors for these health outcomes such as smoking, occupation and additional information on environmental exposures. As in the past, NYS DOH will solicit input from the community.

B.3.3.7.1.2. ATSDR (2008b) executive summary.

This follow-up investigation was conducted to address concerns and to provide more information related to elevated cancers and adverse birth outcomes identified in the initial health statistics review entitled "Health Statistics Review: Cancer and Birth Outcome Analysis, Endicott Area, Town of Union, Broome County, New York" (2006a).

The initial health statistics review was carried out to address concerns about health issues among residents in the Endicott area who may have been exposed to volatile organic compounds (VOCs) through a pathway known as soil vapor intrusion. The initial health statistics review reported a significantly elevated incidence of kidney and testicular cancer among residents in the Endicott area. In addition, elevated rates of heart defects and low birth weight births were observed. The number of term low birth weight births, a subset of low birth weight births, and the number of small for gestational age (SGA) births were also significantly higher than expected.

The purpose of this follow-up investigation was to gather more information and conduct a qualitative examination of medical and other records of individuals identified with adverse birth outcomes and cancers found to be significantly elevated. Quantitative analyses were also carried out for two additional birth outcomes, conotruncal heart defects (specific defects of the heart's outflow region), and spontaneous fetal deaths (stillbirths), and for cancer incidence accounting for race.

Cancer Incidence Adjusting for Race: Because a higher percentage of the population in the study area was white compared to the comparison population, we examined the incidence of cancer among whites in the study area compared to

the incidence in the white population of New York State, excluding New York City. Cancer incidence among whites was evaluated for the years 1980-2001. Results: Limiting the analysis of cancer to only white individuals had little effect on overall cancer rates or standardized incidence ratios compared to those of the entire study area population analyzed previously. The only difference was the lung cancer which had been borderline non-significantly elevated was not borderline significantly elevated.

Cancer Case Record Review: We reviewed medical and other records of individuals with kidney and testicular cancers to try to determine smoking, occupational and residential histories. A number of preexisting data sources were used including: hospital medical records; cancer registry records; death certificates; newspaper obituaries; Motor Vehicle records; and city and telephone directories. Results: The case record review did not reveal any unusual patterns in terms of age, gender, year of diagnosis, cell type, or mortality rate among individuals with kidney or testicular cancer. There was some evidence of an increased prevalence of smoking among those with kidney cancer and some indication that several individuals diagnosed with testicular and kidney cancer may have been recent arrivals to the study area.

Conclusions/Recommendations: The purpose of the additional analyses reported in the draft for public comment follow-up report was to provide information on certain cancers and reproductive outcomes which were elevated in the initial health statistics review. Although these additional analyses could not determine whether there was a causal relationship between VOC exposures in the study area and the increased risk of several health outcomes that were observed, they did provide more information to help guide additional follow-up. The March 2007 public comment report provided a list of follow-up options for consideration and stated, "Although an analytical (case-control) epidemiologic study of cancer or birth defects within this community is not recommended at this time, we describe several follow up options for discussion with the Endicott community. A case-control study would be the preferable method for progressing with this type of investigation, but the potentially exposed population in the Endicott area is too small for conducting a study that would be likely to be able to draw strong conclusions about potential health risks.

Alternative follow-up options were discussed at meetings with Endicott stakeholders and were the subject of responses to comments on the draft report. From these discussions and written responses, NYS DOH has noted community interest in two possible options for future activities: a health statistics review based on historic outdoor air emissions modeling, and a multi-site epidemiologic study examining cancer outcomes in communities across the state with VOC exposures similar to Endicott. NYS DOH has considered these comments and examined whether these options would be able to accomplish one of two goals: either to advance the scientific knowledge about the relationship between VOC exposure and health outcomes or to be part of a response plan to address community concerns.

An additional health statistics review using historic outdoor air emission modeling results to identify and study a larger population of residents potentially exposed to TCE is not likely to meet either of these goals at this time. Because of

the limitations of the health statistics review for drawing conclusions about cause and effect, conducting an additional health statistics review is not likely to increase our understanding of whether exposures in the Endicott area are linked to health outcomes. Limitations with the available historic outdoor air data also would make it difficult to accurately define the appropriate boundaries for the exposure area. ATSDR historic outdoor air emissions modeling activity was unable to model TCE due to a lack of available records.

A multi-site epidemiologic study of health outcomes in communities across the state with VOC exposures similar to Endicott offers some promise of meeting the goal of advancing the scientific knowledge about the relationship between VOC exposures and health outcomes. The community has indicated its preference that such a study focus on cancer outcomes. Given the complex issues involved in conducting such a study (e.g., tracking down cases or their next of kin after many years, participants' difficulty in accurately remembering possible risk factors from many years ago, and the long time period between exposure to a carcinogen and the onset of cancer), we do not consider a multisite case-control study of cancer as the best option at this time. An occupational cancer study is a better option than a community-based study because it can better incorporate information about past workplace exposures and could use corporate records to assist in finding individual employees many years after exposure.

Heart defects have been associated with TCE exposure in other studies. Given the shorter latency period, and thus the shorter time period in which other risk factors could come into play, a multi-site study of heart defects has some merit as a possible option. Currently, NYS DEC and NYS DOH are investigating many communities around New York State which could have VOC exposure patterns similar to Endicott, and thus could be included in such a multi-site epidemiologic study. However, in most of these communities exposure information sufficient to identify a study population is not yet available. NYS DOH will continue to evaluate these areas as additional exposure information becomes available, with the goal of identifying other communities for possible inclusion in a multi-site epidemiologic study of heart defects.

NYS DOH will continue to keep the Endicott community and stakeholders informed about additional information regarding other communities with exposures similar to those that occurred in the Endicott area. NYS DOH staff will be available as needed to keep interested Endicott area residents up-to-date on the feasibility of conducting a multi-site study that includes the Endicott area.

B.3.3.7.1.3. Study description and comment.

Health statistics review conducted by NYS DOH because of concerns about possible exposures to VOCs in Endicott area groundwater and vapor intrusion into residences examined cancer incidence between 1980 and 2001 and birth outcomes among residents living in a study area defined by soil vapor sampling and exposure modeling. The reviews were supported by ATSDR and conclusions presented in final reports (ATSDR, 2008b, 2006a) have received external comment, but the studies have not been published in the open peer-reviewed literature. Testing of soil gas and indoor air of >300 properties, including 176 residences (location not identified) for VOCs detected TCE levels ranging from 0.18 to 140 $\mu g/m^3$; other VOCs less

commonly detected included perchloroethylene, 1,1-dichloroethane, 1,1-DCE, 1,2-DCE, vinyl chloride, 1,1,1-trichloroethane, methylene chloride, and Freon 113. A model was developed to predict VOC presence in soil vapor based on measured results ("Groupwater Vapor Project, Endicott, New York: Summary of findings, working draft. Cited in ATSDR," 2006). Subsequent sampling and data collection verified this model. Initial study area boundaries were determined based on the extent of the probable soil vapor contamination >10 $\mu g/m^3$ of VOCs as defined by the model. Contour lines of modeled VOC soil vapor contamination levels, known as isopleths, were mapped using a GIS. This study area is referred to as the Eastern study area in ATSDR (2008b, 2006a). Additional sampling west of the initial study area identified further contamination with the contaminant in this area primarily identified as perchloroethylene at levels ranging from 0.1 to 3.5 $\mu g/m^3$ in an area referred to as the Western study area (ATSDR, 2008b, 2006a). The source of perchloroethylene contamination was not known. A digital map of the 2000 Census block boundaries was overlaid on these areas of contamination. The study areas were then composed of a series of blocks combined to conform as closely to the areas of soil vapor contamination as possible.

Incident cancer cases for 18 sites, including cancer in children ≤19 years, between 1980 and 2001 and obtained from the New York State Cancer Registry and addresses were geocoded to identify cases residing in the study area. The observed numbers of site-specific cancers were compared to that expected calculated using age-, sex-, and year-specific cancer incidence rates for New York State exclusive of New York City and population estimates from 1980, 1990, and 2000 Censuses. Expected numbers of site-specific cancer did not include adjustment for race in (ATSDR, 2006a); however, race was examined in the 2008 follow-up, study which compared cancer incidence among the white residents in the study area to that of whites in New York State (ATSDR, 2008b). Over the 22-year period, a total of 347 incident cancers were observed among residents in the study area, 339 of these were in white residents. Less than six cases of cancers in children ≤19 years old were identified and ATSDR (2006a) did not present a SIR for this grouping, similar to their treatment of other site-specific cancers with less than six observed cases.

The follow-up analysis by ATSDR (2008b) reviewed medical records of kidney and testicular cancer cases for smoking and occupational and residential histories, and restricted the statistical analysis to white residents, given the few numbers of observed cancers in the small population of nonwhite residents. Limiting the analysis to only white individuals in the study area had little effect on overall cancer rates or SIR estimates (ATSDR, 2006a). As observed in ATSDR (2006a), statistically significant excess risks were observed for kidney cancer in both sexes and testicular cancer in males. In addition, lung cancer estimate risks in males and in males and females were of the same magnitude in both analyses, but CIs excluded a risk of 1.0 in the ATSDR (2008b) analyses, which adjusted for race. Review of medical records for the 15 kidney and 6 testicular cancer cases provided limited information about personal exposures

and potential risk factors because of incomplete reporting in records. The record review did not reveal any unusual patterns in either kidney or testicular cancer in terms of age, year of diagnosis, anatomical site, cell type, or mortality rate. Occupational history suggested possible workplace chemical exposure for roughly half of the 13 kidney cancer cases and none of the testicular cancer cases whose medical records included occupational history. For smoking, half of the nine kidney cancer cases and some (number not identified) of the three testicular cancer cases with such information in medical records were current or former smokers; smoking habits were not reported for the other cases. Last, examination of city and phone directories revealed that while half the kidney cancer cases as long term Endicott residents, several cases of testicular cancer were among residents who recently moved into the Endicott area.

These health surveys are descriptive; they provide evidence of cancer rates in a geographical area with some documented exposures to several VOCs including TCE, but are unable to identify possible etiologic factors for the observed elevations in kidney, testicular, or lung cancers. The largest deficiency is the lack of exposure assessment, notably historical exposure, to individual subjects. Review of city and phone directories suggests some kidney and testicular cancer cases were among recently-arrived residents, a finding inconsistent with a cancer latent period; however, of greater importance is the finding of cancers among subjects with long residential history. On the other hand, the population in the study areas has declined over the past 20 years (ATSDR, 2006a) and residents who may have moved from the study area were not included, introducing potential bias if cancer risks differed in these individuals. The medical history review suggests several risk factors, including smoking and occupational exposure, as important to kidney and testicular cancer observations. Lacking information for all subjects, there is uncertainty regarding the additive effect of other potential risk factors such as smoking to residential exposures. For this reason, while excesses in several incident cancers are observed in these reports, potential etiological risk factors are ill-defined, and the weight these studies contribute in the overall weight-of-evidence analysis is limited.

ATSDR (Agency for Toxic Substances and Disease Registry). (2006a). Health Consultation. Cancer and Birth Outcome Analysis, Endicott Area, Town of Union, Broome County, New York. Health Statistics Review. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. May 26, 2006.

ATSDR (Agency for Toxic Substances and Disease Registry). (2008b). Health Consultation. Cancer and Birth Outcome Analysis, Endicott Area, Town of Union, Broome County, New York. Health Statistics Review Follow-Up. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. May 15, 2008.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	This health statistics review examined incidence for 18 types of cancer in residents living in the Village of Endicott at the time of diagnosis. This study was not designed to identify possible etiologic factors.
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Subjects are incident cases of cancer of the 18 types of cancers including childhood cancer (all cancers in children ≤19 yrs of age) reported to the New York Cancer Registry between 1980 and 2001 among residents in two areas of the Village of Endicott, New York. The expected number of cancer cases for the period was calculated using cancer incidence rates for New York State exclusion of New York City and population estimates from 1980, 1990, and 2000 Censuses.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD 9th Revision.

CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	This geographic-based study does not develop quantitative estimates of exposure, rather study boundaries are defined using soil gas and indoor air monitoring data and computer modeling. Testing of soil gas and indoor air of >300 properties, including 176 residences (location not identified) in the Eastern study area for VOCs detected TCE levels ranging from 0.18 to 140 µg/m^3; other VOCs less commonly detected included perchloroethylene, 1,1-dichloroethane, 1,1-DCE, 1,2-DCE, vinyl chloride, 1,1,1-trichloroethane, methylene chloride, and Freon 113. A model was developed to predict VOC presence in soil vapor based on measured results (["Groupwater Vapor Project, Endicott, New York: Summary of findings, working draft. Cited in ATSDR," 2006]). Subsequent sampling and data collection verified this model. Initial study area boundaries were determined based on the extent of the probable soil vapor contamination >10 µg/m^3 of VOCs as defined by the model. Additional sampling west of the initial study area identified further contamination with the contaminant in this area primarily identified as perchloroethylene at levels ranging from 0.1 to 3.5 µg/m^3 in an area referred to as the Western study area. The study areas were then composed of a series of blocks combined to conform as closely to the areas of soil vapor contamination as possible. Cancer incident cases in residents at the time of diagnosis in the two areas were included in the study.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	No information.
>50% cohort with full latency	No information.
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Record study.
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	Record study.
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	347 total cancers in males and females among an estimated population size of 3,540 (1980)–3,002 (2000).

CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age and sex (ATSDR, 2006a). Age, sex, and race (ATSDR, 2008b). Medical record review of 15 kidney and 6 testicular cancer cases provided limited information on smoking, work history, and residential history for a small percentage of these cases (ATSDR, 2008b).
Statistical methods	
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.3.8. Studies in Arizona

B.3.3.8.1. Studies of West Central Phoenix Area, Maricopa County, Arizona.

B.3.3.8.1.1. Aickin et al. (1992), Aickin (2004).

B.3.3.8.1.1.1. Aickin et al. (1992) author's abstract.

Reports of a suspected cluster of childhood leukemia cases in West Central Phoenix have led to a number of epidemiological studies in the geographical area. We report here on a death certificate-based mortality study, which indicated an elevated rate ratio of 1.95 during 1966-1986, using the remainder of the Phoenix standard metropolitan statistical area (SMSA) as a comparison region. In the process of analyzing the data from this study, a methodology for dealing with denominator variability in a standardized mortality ratio was developed using a simple linear Poisson model. This new approach is seen as being of general use in the analysis of standardized rate ratios (SRR), as well as being particularly appropriate for cluster investigations.

B.3.3.8.1.1.2. Aickin (2004) author's abstract.

BACKGROUND AND OBJECTIVES: Classical statistical inference has attained a dominant position in the expression and interpretation of empirical results in biomedicine. Although there have been critics of the methods of hypothesis testing, significance testing (P-values), and confidence intervals, these methods are used to the exclusion of all others. METHODS: An alternative metaphor and inferential computation based on credibility is offered here. RESULTS: It is illustrated in three datasets involving incidence rates, and its advantages over both classical frequentist inference and Bayesian inference, are detailed. CONCLUSION: The message is that for those who are unsatisfied with classical methods but cannot make the transition to Bayesianism, there is an alternative path.

B.3.3.8.1.1.3. Study description and comment.

This study by staff of Arizona Department of Health Services of leukemia mortality or incidence rates among children ≤19 years old living at the time a death in West Central Phoenix in Maricopa County assume residence in the defined geographical area as a surrogate of undefined exposures. Aickin et al. (2004) adopted a classical statistical approach, linear Poisson regression, to estimate age-, sex- and calendar year adjusted RRs for leukemia mortality between 1966 and 1986 among children ≤19 years old living in the study area at the time of death. Leukemia mortality rates for the rest of Maricopa County, excluding the study area and three additional geographic areas previously identified with hazardous waste contamination, were selected as the referent (Aickin et al., 1992). Aickin (2004) adopted inferential or Bayesian approaches to test whether childhood leukemia incidence between 1966 and 1986 would confirm the mortality analysis observation.

Both studies use residence at time of diagnosis or death in the study area, West Central Phoenix, Arizona, as the exposure surrogate; specific exposures such as drinking water contaminants are not examined nor is information on parental factors considered in the analysis. Some information on potential exposures in the community-at-large may be obtained from reports prepared by the AZ DHS of epidemiologic investigations of cancer mortality rates among residents of this area. Aickin et al. (1992) is the published finding on childhood leukemia. Past exposure to the population of West Central Phoenix to environmental contaminants has been difficult to quantify because of a paucity of environmental monitoring data (ADHS, 1990). Community concerns about the environment focused on TCE found in drinking water in late 1981: air pollution, from benzene emission from a nearby major gasoline storage and distribution facility, and pesticide residues. Two wells that occasionally supplemented the water supply in West Central Phoenix were closed after TCE was detected at the wellhead. The levels of TCE measured at the time contamination was detected were 8.9 and 29.0 ppb (report does not identify the number of samples nor concentration ranges). The period over which contaminated water had been supplied from these wells was not known nor whether significant exposure to the population occurred after mixing with surface water. Other compounds identified in the contaminated plume besides TCE included 1,1-DCE, trans-1,2-DCE, chloroform, and chromium. The exposure assessment in the AZ DHS reports is inadequate to describe exposure potential to TCE to subjects of Aickin et al. (1992) and Aickin (2004). Moreover, potential etiologic factors for the observed elevated estimated RR for childhood leukemia bases are not examined. While these studies support an inference of elevated childhood leukemia rates in residents of West Central Phoenix, these studies provide little information on childhood leukemia and TCE exposure and contribute little weight in the overall weight-of-evidence analysis of cancer and TCE.

Aickin M, Chapin CA, Flood TJ, Englender SJ, Caldwell GG. (1992). Assessment of the spatial occurrence of childhood leukemia mortality using standardized rate ratios with a simple linear Poisson model. Int J Epidemiol 21:649–655.

Aickin M. (2004). Bayes without priors. J Clin Epidemiol 57:4–13.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Aickin et al. (1992) illustrated a methodologic approach to reduce variability in rate ratios from small-sized populations. Childhood leukemia mortality in a geographically-defined area in central Phoenix, Arizona, was the case study adopted to illustrate methodologic approach. The analysis was not designed to examine possible etiologic factors. The purpose of Aickin (2004) "was to determine whether a 1.95 standardized mortality ratio [19] for leukemia in West Central Phoenix (compared to the remainder of Maricopa County) would be confirmed in an incidence study" [p. 8].
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Leukemia deaths among children ≤19 yrs of age between the years 1966 and 1986 and with addresses on death certificates in the geographically-defined study area were identified from Arizona death tapes. Referent group is childhood leukemia mortality rate of all other Maricopa residents excluding the study area and three other areas with identified hazardous waste contamination (Aickin et al., 1992). Incident cases of childhood leukemia (≤19 yrs) among residents living in study area were identified from the Arizona Cancer Registry and from cancer registry and medical record reviews at 13 area hospitals (ADHS, 1990).
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer mortality (Aickin et al., 1992). Cancer incidence (Aickin, 2004).
Changes in diagnostic coding systems for lymphoma, particularly NHL	Mortality—ICD 7, ICDA 8, ICD 9 (Flood, 1988). Incidence—ICD-O.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Residence in geographical area is a surrogate of undefined exposures; possible exposures are not identified in the paper.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	

>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Record study.
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	
CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	38 childhood leukemia deaths over a period of 21 yrs. 49 childhood leukemia incident cases over a period of 21 yrs.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, and year (1966–1969, 1979–1981, 1982–1986).
Statistical methods	Poisson regression using 1970, 1980, and 1985 population estimates from U.S. Bureau of the Census.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.

B.3.3.8.2. Studies in Tucson, Pima County, Arizona.

B.3.3.8.2.1. Arizona Department of Health Services (1995, 1990).

B.3.3.8.2.1.1. Arizona Department of Health Services (1990) author's summary.

In 1986, responding to community concerns about possible past exposure to low levels of trichloroethylene in drinking water, a committee appointed by the Director of the Arizona Department of health Services recommended that the incidence of childhood leukemia and testicular cancer be studied in the population residing in the Tucson Airport Area (TAA). The study reported here was designed to count all cancer cases occurring in 0-19 year-old Pima County residents, and all testicular cancer cases in Pima County residents of all ages, during the 1970-1986 time period. Based on the incidence rates in the remainder of Pima County, approximately seven cases of childhood leukemia and approximately eight cases of testicular cancer would have been expected in the TAA. Eleven cases of leukemia (SIR = 1.50, 95% C.I. 0.76-2.70) and six cases of testicular cancer (SIR = 0.78, 95% C.I. 0.32-1.59) were observed. Statistical analyses showed that the incidence rates of these cancers were not significantly elevated. Additionally, it was determined that the rates of other childhood cancers in the TAA, grouped as lymphoma, brain/CNS and other, were not significantly elevated. The childhood leukemia, childhood cancer, and testicular cancer rates in Pima County were comparable to rates in other states and cities participating in the National Cancer Institute's Surveillance Epidemiology and End Results Program.

B.3.3.8.2.1.2. Arizona Department of Health Services (1995) author's summary.

In 1986, responding to community concerns about possible past exposure to low levels of trichloroethylene in drinking water, a committee appointed by the Director of the Arizona Department of health Services recommended that the incidence of childhood leukemia and testicular cancer be studied in the population residing in the Tucson Airport Area (TAA). The study reported here was designed to count all cancer cases occurring in 0-19 year-old Pima County residents, and all testicular cancer cases in Pima County residents of all ages, during the 1986-1991 time period. Based on the incidence rates in the remainder of Pima County, approximately 3 cases of childhood leukemia and 4 cases of testicular cancer would have been expected in the TAA. Three cases of leukemia (SIR = .80; 95% C.I. 0.31-2.05) and 4 cases of testicular cancer (SIR = .93; 95% C.I. 0.37-2.35) were observed. Statistical analyses showed that the incidence rates of these cancers were not significantly elevated. Additionally, results indicate no statistically elevated incidence rates of childhood lymphoma, brain/CNS, and other childhood cancers, for ages 0-19, in the TAA. No consistent pattern of disease occurrence was observed when comparing the past incidence and mortality studies conducted by ADHS in the TAA with this present study regarding disease categories.

B.3.3.8.2.1.3. Study description and comment.

These reports by staff of AZ DHS of cancer incidence among children ≤19 years old and of testicular cancer incidence among males living at the time a diagnosis in 1970–1986 or 1987–1991 in the Tucson International Airport Area (TAA) of southwest Tucson (ADHS, 1995, 1990) compared to incidence rates for the rest of Pima County were conducted in response to community concerns about cancer and possible past exposure to low levels of TCE in drinking water. In contrast to studies in West Central Phoenix, findings from the 1990 and 1995 AZ DHS studies in Tucson have not been published in the peer-reviewed literature. Childhood cancers included were leukemia, brain/CSN, lymphoma, and a broad category of all other cancers diagnosed in children ≤19 years old. The Arizona Cancer Registry and reviews of medical records of 10 Pima county hospitals served as sources for identifying incident cases. The study area was defined as a geographical area overlaying a plume of contaminated groundwater and was comprised of five census tracts. The approximate areas boundaries are Ajo Way (north), Los Reales Road (south), Country Club Road (east), and the Santa Cruz River (west). Adjacent census tracts in Pima County were aggregated into four separate study areas and incident cancer rates during the 1970–1986 time period (ADHS, 1990) or 1987–1991 (ADHS, 1995) of the aggregated four-area census tract, excluding the TAA area, were used to calculate expected numbers of cancers using the indirect standardization method and population estimates from 1960, 1970, 1975, 1980, and 1985 (ADHS, 1990) or 1990 (ADHS, 1995) of the U.S. Bureau of Census. A secondary analysis of AZ DHS (1990) compared the incidence rate of childhood leukemia and testicular cancer among Pima County residents to that reported to the SEER for a similar time period.

These studies assume residence in the defined geographical area as a surrogate of undefined exposures. The reports do not identify specific exposures for the individual subjects and some information on exposures in the community-at-large may be obtained from Public Health Assessments of the Tucson International Airport Area Superfund Site prepared by the AZ DHS for the ATSDR (2001, 2000). The TAA site includes one main contaminated groundwater plume with smaller areas of groundwater contamination located east of the main plume. Insufficient data existed to evaluate groundwater contamination prior to 1981. Studies conducted by AZ DHS in 1981–1982 showed TCE concentrations of >5 ppb, the maximum contaminant level, in the main groundwater plume with TCE detected in some municipal drinking water wells at concentrations of up to 239 ppb. An ATSDR health assessment conducted in 1988 indicated that soil and groundwater in the Main Plume had been contaminated by chromium and VOCs such as TCE and DCE (ATSDR, 2000). Sampling of private wells from 1981 through 1994 identified both drinking and irrigation private wells in and near the TAA with TCE concentrations ranging from nondetected to 120 ppb. Concentrations of other VOCs and chromium from the 1980s are not presented in the ATSDR reports. Besides groundwater, areas of contaminated soil and sediment have also been identified as part of the site. The “Three

Hangars" area of the airport was found to contain polychlorinated biphenyls in drainage areas with migration off-site into residential neighborhoods (ATSDR, 2001). The exposure assessment in these studies is inadequate to describe exposure to TCE. The studies provide little information on cancer risks and TCE exposure and carry little weight in the overall weight-of-evidence analysis.

AZ DHS (Arizona Department of Health Services). (1990). The incidence of childhood leukemia and testicular cancer in Pima County: 1970–1986. Prepared by the Arizona Department of Health Services, Division of Disease Prevention, Office of Risk Assessment and Investigation, Office of Chronic Disease Epidemiology. September 17, 1990.

AZ DHS (Arizona Department of Health Services). (1995). Update of the incidence of childhood leukemia and testicular cancer in Southwest Tucson, 1987–1991. Prepared by the Arizona Department of Health Services, Office of Risk Assessment and Investigation, Disease Prevention Services. June 6, 1995.

	Description
CATEGORY A: STUDY DESIGN	
Clear articulation of study objectives or hypothesis	Yes, from ADHS (1990), "1) To determine whether there was an elevated incidence of leukemia or other cancers among children residing in the Tucson Airport Area (TAA) and 2) To determine whether there was an elevated incidence of testicular cancer in males in the TAA." From ADHS (1995), "The objective of this study is to determine whether the incidence rates of childhood leukemia (ages 0–19) and testicular cancer in males of all ages were significantly elevated in the TAA when compared to the rest of Pima County for the years 1987 through 1991."
Selection and characterization in cohort studies of exposure and control groups and of cases and controls in case-control studies is adequate	Cases are identified from the Arizona Cancer Registry and review of medical records at 10 Pima County hospitals. The referent is incidence rates for the remaining population of Pima County, excluding the study area.
CATEGORY B: ENDPOINT MEASURED	
Levels of health outcome assessed	Cancer incidence.
Changes in diagnostic coding systems for lymphoma, particularly NHL	ICD-O and ICD-9 or equivalent codes from ICDA-8, ICD-7, HICDA, or SNODO.
CATEGORY C: TCE-EXPOSURE CRITERIA	
Exposure assessment approach, including adoption of JEM and quantitative exposure estimates	Residence in geographical area is a surrogate of undefined exposures; possible exposures are not identified in the paper.
CATEGORY D: FOLLOW-UP (COHORT)	
More than 10% loss to follow-up	
>50% cohort with full latency	
CATEGORY E: INTERVIEW TYPE	
<90% face-to-face	Record study.
Blinded interviewers	
CATEGORY F: PROXY RESPONDENTS	
>10% proxy respondents	

CATEGORY G: SAMPLE SIZE	
Number of deaths in cohort mortality studies; numbers of total cancer incidence studies; numbers of exposed cases and prevalence of exposure in case-control studies	ADHS (1990), 31 childhood cancers—11 leukemia cases, 2 lymphoma, 3 CNS/Brain, and 15 other, and 6 testicular cancers. ADHS (1995), 11 childhood cancers—3 leukemia, 1 lymphoma, 2 CNS/Brain, and 5 other, and 4 testicular cancers.
CATEGORY H: ANALYSIS	
Control for potential confounders in statistical analysis	Age, sex, and year.
Statistical methods	SIRs calculated using indirect standardization.
Exposure-response analysis presented in published paper	No.
Documentation of results	Yes.