Trichloroethylene and Cancer: Epidemiologic Evidence

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Trichloroethylene is an organic chemical that has been used in dry cleaning, for metal degreasing, and as a solvent for oils and resins. It has been shown to cause liver and kidney cancer in experimental animals. This article reviews over 80 published papers and letters on the cancer epidemiology of people exposed to trichloroethylene. Evidence of excess cancer incidence among occupational cohorts with the most rigorous exposure assessment is found for kidney cancer (relative risk [RR] = 1.7, 95% confidence interval [CI] 1.1–2.7), liver cancer (RR = 1.9, 95% CI 1.0–3.4), and non-Hodgkin's lymphoma (RR = 1.5, 95% CI 0.9–2.3) as well as for cervical cancer, Hodgkin's disease, and multiple myeloma. However, since few studies isolate trichloroethylene exposure, results are likely confounded by exposure to other solvents and other risk factors. Although we believe that solvent exposure causes cancer in humans and that trichloroethylene likely is one of the active agents, we recommend further study to better specify the specific agents that confer this risk and to estimate the magnitude of that risk. *Key words*: cancer, degreasers, dry cleaning, epidemiology, PERC, solvents, TCE, TCOH, tetrachloroethylene, trichloroethylene. — *Environ Health Perspect* 108(suppl 2):161–176 (2000).
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Introduction

This article is a review of the epidemiologic evidence regarding the possible carcinogenicity of trichloroethylene (TCE). The basic approach adopted uses as guidance Hill's (*1*) framework for assessing causality and is based on the substantial epidemiologic literature reporting possible exposure to TCE. This literature of over 80 published articles on TCE's carcinogenicity to humans includes more than 20 reports on worker cohorts, more than 40 case–control studies, more than a dozen community-based studies, and several commentaries and reviews. We begin with a brief consideration of the experimental (animal) evidence for context. Then we review the epidemiologic evidence, beginning with the cohort studies in which temporality is inherent, assessing strength, consistency, and exposure response (biologic gradient). We consider the case–control studies to determine if they provide supporting evidence. Then we consider the community-based studies, which have less accurate, less precise, and less specific exposure information. We conclude with a discussion of all of these data and the previous reviews and commentaries.

One of the biggest challenges in interpreting the studies involving exposure to TCE is that exposure rarely occurs in isolation. That is, most workers exposed to TCE also are exposed to other solvents. This compromises our ability to make solvent-specific response evaluations. While we attempt to focus on TCE-specific effects, we are limited by the quality and specificity of the exposure data developed for the studies reported.

Evidence from Animal Studies

Trichloroethylene is an organic chemical that has been used for dry cleaning, for metal degreasing, and as a solvent for oils and resins. Because of widespread occupational exposures, scientists have investigated its carcinogenicity in animal models. It has been found to be carcinogenic in both mice and rats, which suggests that it may also be carcinogenic to humans. A 1975 National Cancer Institute (NCI) cancer bioassay report shows increased liver cancer in both male and female mice that had been administered TCE by gavage (gastric intubation) (*2*). Although the TCE used in the NCI study was technical grade (containing a small amount of epoxybutane and epichlorohydrin), a later replication of this experiment using a pure solution of TCE has similar findings. Additional bioassays show evidence of malignant tumors of the liver in mice by either respiratory (*3,4*) or oral exposure (*5*), although rats treated in a similar manner show cancer rates comparable to those of untreated controls (*6*). The occurrence of these liver tumors in mice is limited to $B6C3F_1$ and Swiss strains; a number of studies in other strains do not show elevated incidences in liver tumors in treated versus control animals. There is some belief that the $B6C3F_1$ mouse is particularly prone to liver tumors, suggesting that it may be a particularly sensitive test animal. Besides liver tumors, lung tumors (*3,4,7*), and lymphomas (*5*) are found in mice inhalation studies.

Male and female rats exposed to TCE both orally by gavage and via inhalation develop renal tubular adenocarcinomas at low incidences (*3,4*). These tumors are very rare among rats, and their occurrence in the TCE bioassays is considered biologically significant, even though the increased incidences are not statistically significantly elevated above those of controls. Additionally, Leydig cell tumors of the testes (*3,8*) (inhalation) and leukemia (*4*) in rats are observed.

Methods

Identification of Relevant Studies

To conduct this review of the epidemiologic evidence on the carcinogenicity of TCE exposures, we identified epidemiologic studies of populations with known, suspected, and possible TCE exposure. Starting with the most recent reviews, we followed back the literature and obtained more than 80 published articles or letters, and several unpublished reports. This was followed by a MEDLINE search (*9*), which turned up a few additional articles. The majority of studies available are occupational studies. There are 28 cohort studies (of 20 cohorts) that summarize outcomes in groups of exposed workers compared to those not exposed (often the general population), 43 case–control studies (mainly at 15 anatomical sites) in most of which the occupational or exposure history of workers with a particular cancer compared to that of others without that specific cancer (sometimes workers, sometimes the general population), 15 reports of community-based studies of disease rates in communities with contaminated water supplies, and 3 case series reports on cases without a comparison population. Note that the term cohort refers to groups of individuals followed from a disease-free state regardless of the measure of effect used (standardized incidence ratio [SIR]; standardized mortality ratio [SMR]; standardized mortality odds ratio [SMOR]; proportionate mortality ratio [PMR]).

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Three of the cohort studies we identified allegedly resulted from apparent clusters of disease (*10–12*). An argument can be made that studies initiated by a cluster report, even though the studies are traditional and rigorous cohort designs, should be excluded from summaries such as this simply because it was the observation of an apparent cluster that generated the interest. Implicit in those investigators' arguments is the assumption that inclusion of these cohorts somehow biases the overall assessment. We disagree, provided the study is a well-conducted study. We include all studies that we have been able to identify in which the population had documented or even plausible exposure to TCE regardless of why the study was undertaken. We did not include cluster studies per se but only the cohort studies that ensued. By examining all published cohort studies in conjunction with the case–control- and community-based studies, we believe we can provide useful insight into the possible association between TCE exposure and the site-specific risk of cancer.

Exposure Assessment

To study TCE as a cause of cancer, it is necessary to document that the people more likely to have disease are also the people more likely to have been exposed to TCE and ideally more highly exposed to TCE. In a few of the studies, exposures are determined quantitatively from chemical measures of the TCE metabolite trichloroacetic acid (TCA) in the workers' urine (U-TCA), which is considered a biomarker. This provides a quantitative measure of exposure that, in many ways, is preferable to qualitative or descriptive exposure metrics. One limitation of this approach is that it is a short-term measure reflective of exposures received over the past day and does not capture the long-term nature of exposure including variation in an individual's job history. In addition, variation caused by sampling frame and changes in industrial process are not accounted for in short-term biomarker studies and may lead to misclassification. Further, this biomarker does not provide information about possible exposure to other risk factors including other solvents that may confound the association under study.

For example, TCA is also a metabolite of tetrachloroethylene (PERC), another commonly used solvent in the workplace. Urine samples for which TCA is measured are not specific to TCE when exposure to TCE and PERC occur jointly, which can lead to misclassification. Only one study addressed this limitiation by using separate biologic measures, one each to estimate TCE, PERC, and 1,1,1-trichloroethane exposures.

More generally, even though U-TCA can quantify TCE exposure, it does not quantify total solvent exposures. If one sees an exposure–response gradient with TCE exposure, that would provide supporting evidence of a causal association. However, if exposure to another solvent is correlated with TCE exposure, it is not possible to completely separate their effects (i.e., there can be confounding). In short, without comprehensive exposure information, one's ability to make robust inferences about TCE is more limited.

In studies not using biomarkers, researchers often infer exposure by using an individual's employment history, sometimes combining the title of each job held by the worker with the length of employment in that job. Data for each job can be summarized in quantitative measures such as the number of years worked in a particular job and the specific period of years worked. If job title information is limited to a single job (e.g., dry cleaners), exposure may be summarized as a binary variable (exposed or not exposed). If a variety of job titles are reported (e.g., several different jobs all involving degreasing, such as in aircraft maintenance), then a categorical quantitative measure of job-specific exposure may be developed, such as one contrasting low, medium, and high exposures for different job titles. These categories can be derived using information from a variety of sources including interviews with long-time workers, walkthroughs by trained industrial hygienists, and more rarely, monitoring data. When such a classification is combined with an individual's job history information, it is called a job exposure matrix (JEM). Most often, exposure to TCE is inferred from ancillary information, such as job title and industrial process, rather than direct monitoring or measurement of biomarkers or air measurements. While this captures the time history of exposure, it may result in misclassification of exposure because the actual exposures typically varied markedly among workers with the same job title and varied over time among those with the same job title; some study subjects may have had little to no exposure to any TCE, while others may have had substantial exposure. In summary, job history information can be used to develop very simplistic measures of exposure with much misclassification (e.g., some or no exposure; routine, intermittent, or frequent exposure) to more sophisticated measures that rank jobs and exposures on a continuous, quantitative scale. Few studies address the joint distribution of TCE with other solvents.

Studies of dry cleaner and laundry workers are included in this review, since these workers may have been exposed occupationally to TCE. TCE was commonly used in dry cleaning from 1930 until 1960, along with petroleum-based solvents such as Stoddard's solvent. From the mid-1950s on, a change in dry cleaning technology resulted in the substitution of PERC for TCE and some petroleum solvents. PERC is classified by the International Agency for Research on Cancer (IARC) as a *probable human carcinogen* (*13*). In the dry cleaning industry, TCE exposure was mainly pre-1960, and it was followed by exposure to PERC for general dry cleaning after the 1960s. Exposure to petroleum-based solvents and TCE for spot removal occurred throughout the time period (*13,14*). However, even when TCE was available for dry cleaning, its use was limited because it caused dyes (i.e., colors) to run. Petroleum solvents were generally preferred (*14*). Since TCE was used in the dry cleaning industry, studies assessing dry cleaning exposure are included in this review provided that they include workers exposed before 1960. None of the dry cleaner and laundry worker studies reviewed separates TCE exposures from other solvent exposures [except one study that provides data on both the entire cohort and a TCE-only exposed cohort (*15*)], once again raising questions about specificity of exposure.

We divide the cohort studies into three tiers based on the specificity of the exposure information. Tier I studies are those in which TCE exposure has been inferred for individual study subjects and in which it is best characterized. This includes studies that used biomarkers and JEMs, and studies that conducted other worksite exposure evaluations such as walkthroughs. Tier II studies are those in which there is putative TCE exposure, but individuals are not identified as uniquely exposed to TCE. Tier III studies are the studies of dry cleaner and laundry workers in which subjects are exposed to a variety of solvents including TCE. There are 11 Tier I studies describing seven cohorts, 8 Tier II studies describing seven cohorts, and 9 Tier III studies describing six cohorts. Characteristics of these studies are shown in Tables 1–3.

Case–control studies mainly use job titles to describe exposures. We do not subdivide these. Community-based studies are far fewer in number and use a variety of methods to describe exposures. Again, these are not subdivided.

Study Summary Methods

Given the large number of studies to assess, we use an ad hoc system to summarize the data. First, we consider cohort studies as most reliable design of the studies reviewed. To avoid undue heterogeneity among the tiers, we summarize the studies separately for each tier, providing an estimate of the average risk

across studies. Then, we consider the case–control studies, which we evaluate for all anatomical sites reported in the cohort studies. Exposure characterization varies widely among studies, usually reflecting job title. Rather than summarizing disparate exposures in a single average risk summary, a descriptive summary of the studies is presented for the cancer sites, with the most compelling results in the cohort studies. The community-based studies represent the set of studies in which TCE is identified as a possible or likely contaminant in the drinking water. Again, since exposures (and exposure characterizations) vary widely, as do outcomes reported, we present a summary result for each study rather than averaging them together.

Average risk calculation. To summarize the results of cohort studies within the same tier, we calculate an average relative risk using a meta-analysis–type approach. To do so, we calculate a weighted average of the individual measures of effect (i.e., SMRs, SMORs, SIRs, or PMRs), where the weights are the inverse of the variance of the individual measures (*16*). For those studies not reporting the variance, we calculated it using the formulas presented by Rothman and Boice (*17*). In situations where the reported confidence interval was not symmetric about the reported odds ratio (on a log scale), we recalculate the individual lower confidence limit based on the reported upper confidence limit, for consistency in the average.

Results

Cohort Studies

Tier I cohort studies. This set of studies (Table 1) determines exposures using urinary biomarkers (*18*), job exposure matrices (*19–23*), and job histories (*10,24*). The studies using urinary biomarkers represent the most direct assessment of exposure, although we have no way to gauge their accuracy. In one cohort, Axelson et al. (*18,25*) examine the incidence and mortality experience of Swedish TCE production workers. Workers themselves were able to request urine tests from a program designed to determine their TCE exposure using U-TCA only. The authors emphasize that exposures tend to be relatively low, with over 80% of the cases exposed to an average of less than 20 ppm. In the other biomarker study (*24,26*) of Finnish workers with known TCE exposure as identified through records of the Finnish Institute of Occupational Health (Helsinki, Finland), three different biomarkers are were used: urinary TCA (for the period 1965–1982), blood perchloroethylene (1974–1983), and blood 1,1,1-trichloroethane (1974–1983). Using these three measures, researchers were able to distinguish among exposures to TCE, PERC, and 1,1,1-trichloroethane, which often are intermingled in other studies. Again, exposures are relatively low, with over 90% of the exposures below 40 ppm.

The studies using JEMs to determine exposure employed various combinations of industrial hygiene evaluations, walkthroughs, interviews with employees, and monitoring data combined with work histories. Some characterize exposures by intensity, frequency, and duration, while others use overall assessments. Generally, three or more categories of exposure are used for each type of assessment. Again, these studies are limited by the absence of information on the joint distribution of the variety solvents (and other agents) in each workplace. Three of these are studies of aerospace workers, one is a study of cardboard manufacturers, and one is of uranium processers. The aerospace and cardboard workers use TCE for degreasing, whereas the uranium processers use it for chemical processing.

Overall, these are high-quality studies. They have moderately long follow-up periods (17–38 years) but do not adjust for many confounders. In general, the total mortality and cancer mortality SMRs are close to 1.0. No table deviations are seen for total mortality in Henschler et al. (*10*), Boice et al. (*21*), and Ritz (*23*) and for cancer mortality in Axelson et al. (*18*), all exhibiting a moderate healthy-worker effect.

Tier II cohort studies. Several studies (Table 2) evaluate the mortality experience of workers using job titles and other general information to assess potential exposure to TCE and other chemicals. These include studies of the U.S. Coast Guard inspectors (*27*), workers in the metal polishing and plating industry (*28*), jewelry workers (*29*),

Table 1. Tier I: a summary of cohort study characteristics.

Reference	Exposure assessment	Outcome	Follow-up, years	% Ascertainment	Exposed workers, no.	Total mortality	Total cancer mortality	Total cancer incidence	Exposure–response data
Anttila et al. (*24*) Tola et al. (*25*)	Urinary biomarkers: U-TCA, B-Per, B-TC	I, SIR	26	100	3,089	0.9 (0.8,1.0)	1.0 (0.8,1.2)	1.1 (0.9–1.2)	Years since measured; U-TCA (each site)
Axelson et al. (*18,25*)	Urinary biomarker: U-TCA	I, SIR	32	100	1,727	1.0 (0.9–1.1)	0.7 (0.5–0.9)	1.0 (0.8–1.2)	Exposure time; U-TCA (liver, prostate, skin)
Spirtas et al. (*19*) Blair et al. (*20*)	Occupation: aircraft maintenance; JEM (IH walk throughs, interviews, monitoring)	I, RR D, SMR	17 17		7,204	1.0 (1.0–1.1)	1.1 (1.0–1.3)	1.2 (1.0–1.6)	Cumulative unit-years (each site)
Boice et al. (*21*)	Occupation: aircraft manufacturing; JEM (IH files, walk throughs, interviews)	D, SMR	36		2,267	0.8 (0.8–0.9)	0.9 (0.8–1.0)	–	Number of years exposed
Henschler et al. (*10*)	Occupation: cardboard workers; walk throughs, interviews, and company use records (all exposed)	D, SMR	34	97	259	0.7 (0.5–0.9)	1.0 (0.5–1.7)		Exposed vs unexposed
Morgan et al. (*22*) Wong and Morgan (*104*)	Occupation: aerospace (degreaser); JEM (worker interviews only)	D, SMR	36	96	4,733	0.9 (0.8–1.0)	0.9 (0.8–1.0)	–	Cumulative exposure (high vs low; all sites); peak high vs low (liver, kidney, bladder, prostate, ovarian)
Ritz (*23*)	Occupation: nuclear worker (uranium); JEM (worker interviews only)	D, SMR	38		2,971	0.8 (0.8–0.9)	1.1 (1.0–1.2)	–	Number of years exposed

Abbreviations: B-Per, perchloroethylene in the blood; B-TC, 1,1,1-trichloroethane in the blood; D, mortality (death); I, incidence; IH, industrial hygiene assessment; JEM, job exposure matrix; O/E, observed/expected.

workers in aircraft manufacturing (*30*), workers in lamp manufacturing (*11*), workers at a plant using TCE as a degreasing agent (*31*), and workers in paperboard printing (*12,32*). These studies are very heterogeneous and few have any exposure data.

Implicit in the analysis of these data is the assumption that all members of the cohort have greater exposure to TCE than the comparison population; however, much uncertainty attends this assumption. Exposures among individuals with the same job title likely vary considerably. Patterns of disease may be suggestive but cannot be conclusive in light of the possible unadjusted confounding and lack of individual TCE exposure estimates. Overall, total mortality and total cancer mortality SMRs are near 1.0, suggesting a weak or nonexistent healthy worker effect.

In the study of Coast Guard inspectors, exposure to chemicals including organic solvents is categorized into three classes by reviewing job duties, recognizing that various solvents were used on the job (*27*). Several of the other studies characterize exposures by job title only, even though exposures were far more complex. For example, metal polishing and plating workers are exposed to heavy metals, acids, alkaline solutions, and solvents (*28*), jewelry workers are exposed to heavy metals and solvents (*29*), and aircraft manufacturing workers are exposed to metals, oils, paints, solvents, and other chemicals (including an estimate based on a case–control study of 70 subjects in which 37% of the jobs had TCE exposure (*30*). In all of these studies, all workers are considered exposed and compared to a putatively unexposed reference population. In several of the studies, exposure–response analyses were conducted using years of exposure as a proxy. The study of lamp manufacturing included review of reported amounts of chemicals used in the facility including methylene chloride and TCE (*11*).

The final study in this tier reported on paperboard printing in which TCE was used in the finishing department. Exposure can be inferred from the identification of a materials safety data sheet (MSDS) listing TCE as a possible chemical exposure, and from a letter from a National Institute of Occupational Safety and Health (Cincinnati, OH) investigation, in which the specific TCE-containing product is identified for use in the finishing department (*33*).

One study is not included in the analyses because mortality outcomes are only broadly grouped, e.g., respiratory system, and not presented for specific sites such as the kidney or liver (*31*).

Tier III cohort studies. Several studies (Table 3) of cancer mortality among dry cleaner and laundry workers have been conducted (*15,34–41*). Exposures are assessed through job title only. As noted above, the solvents used in dry cleaning changed over time. TCE was mainly used prior to 1960, after which it was replaced by PERC. Thereafter, its use was primarily for spot removal, but dry cleaners often preferred Stoddard's solvent. The studies included in this tier all report on workers initially employed prior to 1960 to ensure that there

Table 2. Tier II: summary of cohort study characteristics.

Reference	Exposure assessment	Outcome	Follow-up, years	% Ascertainment	Workers, no.	Total mortality	Total cancer	Exposure–response data
Blair et al. (*27*)	U.S. Coast Guard inspectors; chemical exposures on inspection of cargo tanks and other shipboard locations	D, SMR	38	–	1,292	0.8 (0.7–0.9)	0.9 (0.7–1.1)	Cumulative exposure
Blair et al. (*28*)	Occupation: metal polishing, plating; possible exposure to solvents	D, PMR	19	85	1,767	1.0 (0.9–1.1)	1.1 (1.0–1.2)	–
Dubrow and Gute (*29*)	Occupation as jewelry worker; possible exposure to solvents	D, PMR	11	–	3,141	–	1.0 (0.9–1.1) f 1.0 (0.9–1.1) m	–
Garabrant et al. (*30*)	Occupation: aircraft worker; exposure based on 70 subjects in a case control study; only 37% jobs had TCE exposure	D, SMR	25	95	14,067	0.8 (0.7–0.8)	0.8 (0.8-0.9)	Duration of employment (esophagus, pancreas, bladder)
Shannon et al. (*11*)	Occupation: lamp manufacturing; TCE listed on engineering instruction sheet	I, SIR	23	90	1,870	–	0.9 (0.6–1.2) m 1.1 (0.8–1.3) f	Years exposed (breast and gynecological together)
Shindell and Ulrich (*31*)	Occupation: brake manufacturing	D, observed vs exposed	26.5	98	–	0.8 (0.6–0.9)	0.7 (0.1–1.0)	–
Sinks et al. (*12,32*)	Occupation: paperboard workers; MSDS lists TCE containing product for use in finishing department	I, SIR D, SMR	53	99	2,086	1.0 (0.9–1.2)	0.6 (0.3–0.9)	–

Abbreviations: f, females; m, males.

Table 3. Tier III: dry cleaners and laundry workers—summary of cohort study characteristics.

Reference	Outcome	Follow-up, years	% Ascertainment	Workers, no.	Total mortality	Total cancer	Exposure years	Exposure–response data (site)
Blair et al. (*34,39*)	D, PMR D, SMR	30 32	–		1.0 (0.9–1.1) 0.9 (0.9–1.0)	1.3 (1.1–1.5) 1.2 (0.4–1.1)	1948–1979 1948–1979	Low, medium, high (esophagus, cervix, bladder, lymph/hematopoietic)
Duh and Asal (*36*)	D, SMOR	–	–	5,365	1.0 (0.9–1.1)	0.9 (0.7–1.2)	< 1980	–
Katz and Jowett (*35*)	D, PMR	–	–		–	1.0 (0.8–1.1)	< 1977	–
Lynge and Thygesen (*40*)	I, O/E	10	–	10,600	–	1.3 (1.1–1.4) m 1.0 (0.9–1.1) f	1946–1970	–
Lynge (*41*)								
McLaughlin et al. (*38*)	I, SIR	–	–		–	–	–	–
Ruder (*15*) Brown and Kaplan (*37*)	D, SMR	> 31	93		1.0 (0.9–1.1) m 1.1 (1.0–1.2) f	1.2 (1.0–1.5) m 1.3 (1.0–1.5) f	1940–1990	Latency, length of employment (intestine, bladder)

was an opportunity for exposure to TCE. Laundry workers are often included in dry cleaner cohorts even though they likely do not have any TCE or PERC exposure; this results in further misclassification (*35,36,40,41*). Only the studies of Ruder et al. (*15*), Brown and Kaplan (*37*), and Blair et al. (*39*) limited their study populations to dry cleaners.

Overall, total mortality rates generally are close to 1.0 but slightly elevated more often than not. Some total cancer mortality rates exceed 1.0, suggesting excess risk of cancer overall. Unfortunately, for the specific-site analyses, many different effect measures are used (i.e., PMR, SMR, SMOR, SIR), making quantitative comparisons difficult to interpret. These cohort studies are the least specific to TCE exposure.

Exposure–response evaluation. The identification of exposure–response gradients, or trends, provides particularly compelling evidence supporting a hypothesis of causation. Studies using U-TCA as a biomarker for TCE exposure provide data stratified by specific exposure levels that are amenable to trend analysis. Other studies provide information about the number of years worked or cumulative exposure (from a job exposure matrix), which can be used for indirect exposure–response analysis. Both Anttila et al. (*24*) and Axelson et al. (*18*) report SIR results stratified by level of exposure (above or below 100 μmol/L U-TCA) and duration [years since first measurement in Anttila et al. (*24*) and exposure time in Axelson et al. (*18*)]. Blair (*20*) provides TCE exposure–response data for mortality and incidence compared to those with no chemical exposure, stratifying results jointly by gender and four levels of TCE exposure (none, < 5 units/year, 5–25 units/year, > 25 units/year). The relative exposure scores are based on the exposure intensity, frequency, and duration of peak exposures from vapor degreasing and on low-level exposures at the workbench and surveys during the 1960s and 1970s of work practices at degreasers. Morgan (*22*) reports mortality results for dichotomous exposure categories separately for peak and cumulative exposure metrics based on analyses with the Cox proportional hazards model. Ritz (*23*) presents data cross-classified by two levels of exposure, two lag periods (0 and 15 years), and two periods of exposure duration (> 2 years, > 5 years). Boice (*21*) reports data for TCE-exposed workers stratified by years exposed. Specific patterns of exposure response will be discussed below.

Case–Control Studies

Several case–control studies were conducted for situations of likely TCE exposure. These include studies of bladder cancer (*12,42–45*), brain cancer (*46,47*), buccal and oral cancers (*48,49*), childhood brain cancer (*47*), childhood leukemia (*50*), childhood cancers (*51*), colon cancer (*52*), esophageal cancer (*49,53*), Hodgkin's disease (*54–56*), kidney cancer (*12,57–68*), laryngeal cancer (*49*), leukemia (*50*), liver cancer (*59,69–75*) lung cancer (*76*), melanoma (*77*), non-Hodgkin's lymphoma (*54,55, 78–80*), and pancreatic cancer (*81,82*). Most kidney cancer studies examine renal cell carcinoma, although a few also assess cancer of the renal pelvis. We group these studies together as reporting kidney cancer.

Two investigators each report a series of nested case–control analyses conducted within their own cohort. In one, Greenland et al. (*83*), studying a cohort of transformer assembly workers, evaluates the risks to white males from specific exposure (e.g., pyranol, benzene, TCE, solvents, machining fluids, asbestos, resin systems). In the other, Siemiatycki reports on a study of 3,730 men 35–70 years of age in Montreal, Canada, during 1979–1985 with cancer at 21 anatomical sites and 533 population controls of similar ages (*84*). Subjects were interviewed about their occupations, and exposures to 293 agents or mixtures were estimated by a group of chemists. The estimated prevalence of TCE exposure was 2%.

In general, the case–control studies do not provide the same specificity for TCE exposure as the cohort studies. That is, TCE is identified as a specific exposure in only a few studies. More often, it is captured as part of a more general class of exposures, such as organic solvents. This likely leads to substantial misclassification. Many of these studies did identify dry cleaning and laundry work as a specific exposure classification. However, even with this categorization, there is likely misclassification because many dry cleaners typically had exposure to PERC, whereas other dry cleaners and most (or all) laundry workers were not likely to be exposed to TCE or PERC.

In light of these exposure specification issues, we rely most heavily on studies that identify TCE exposure. Those listing organic solvent exposure are less relevant, as exposure likely included multiple solvents, some of which are known or suspected carcinogens. Those listing pre-1960 dry cleaning and laundries as an occupation or industry are subject to the exposure concerns discussed above for the Tier III cohort studies.

Community-Based Studies

Community-based studies of TCE exposure are a set of investigations in which group exposure is determined by place of residence or water supply and in which there is limited or no information on possible confounding variables. In general, these are cross-sectional studies of cancers, often childhood cancers, and drinking water contamination (*85–99*). The study with the most sophisticated exposure assessment, conducted in Finland, used U-TCA, a biomarker of TCE exposure in residents, to assess the possible association of drinking TCE-contaminated water and cancer (*87*). In all the other studies, exposures are inferred from measurements of contaminants in the drinking water source (*85,89,90*) and/or numerical models providing estimates of contaminants in the water (*86,99*), or proximity to hazardous waste sites containing TCE (*88,91–98*)

These studies are of particular interest for at least two reasons. First, these studies have relatively high statistical power (i.e., the ability to detect an effect if one exists) even though exposure levels are relatively low because of the large number of subjects consuming the TCE-contaminated water. Additionally, exposure in the drinking water studies occurs by the oral route, in contrast to the occupational studies in which inhalation exposure is the primary route. It should be noted, however, that a potential exists for inhalation exposure in studies with contaminated drinking water due to the volatilization of TCE during showering and other uses. Dermal absorption is a likely exposure route in both these drinking water and the occupational studies but typically of less importance quantitatively.

These studies have a number of limitations. Like a number of the cohort studies identified above, exposures typically are to multiple solvents in community-based studies, making it difficult to attribute observed results to only one agent. Exposure generally is assessed at a community level rather than the individual. Contemporaneous or retrospective assessment of disease relative to exposure compromises their interpretability. Adjustments for confounding typically were limited, if conducted at all. Finally, aggregation bias may be present in the analyses in which groups are the unit of analysis.

Case Series

Finally, there are three reports in which authors present data on cases without formal analysis. Malek et al. (*100*) followed up 57 men who worked as dry cleaners in Prague since the 1950s. Exposures assessed by U-TCA were high (60% over 100 mg/L, some near 1,000 mg/L). Three of the subjects had lung cancer, one had tongue cancer, one had rectal cancer, and one had both bladder cancer and two rectal cancers. No information about expected rates, confounders, or other risks was provided.

Novotna et al. (*101*) reports a review of the 63 liver cancer cases reported in Prague

between 1972 and 1974. None had been employed in workshops using TCE. Similarly, Paddle (*102*) reports on 95 cases of liver cancer in workers who live near a facility manufacturing TCE , but none of them were employed there.

These studies do not provide useful information regarding the possible carcinogenicity of TCE , since it is not known whether these cases represent the entire population at risk or whether other risk factors differed among the populations.

Site by Site Results

Results for the cohort studies are shown in Tables 4–9, for the case–control studies in Tables 10–12, and for the community-based studies in Table 13. We summarize the overall evidence in Table 14. Below we focus our discussion on those cancer sites for which there is the strongest evidence and those that have been suggested by other studies.

Kidney cancer/renal cell carcinoma. The evidence supporting a hypothesis of an association between TCE exposure and cancer is as strong or stronger for the kidney than for any other anatomical site. For kidney cancer, one sees elevated risks across all study types except community based, suggesting that kidney cancer is associated with both TCE and dry cleaning and laundry exposures. Most individual study results are elevated for both incidence and mortality across all tiers. In Tier I, three of five SIRs and three of five SMRs are elevated. The combined risk across Tier I studies is elevated (for incidence RR = 1.7, 95% CI 1.1–2.7; for mortality RR = 1.2, 95% CI 0.8–1.7) and represents a substantial number of individuals (21 cases and 37 deaths). Since 5-year survival is over 50% (*103*) and many cases may die of other causes, the incidence data are more relevant than the mortality data. Exposure–response patterns among the Tier I studies are observed only in the studies of Morgan et al. (*22*) and Wong and Morgan (*104*) with cumulative exposure to TCE (although the number of cases is small), and not in those of Blair et al. (*20*), Boice et al. (*21*), or Anttila et al. (*24*), which are the only other studies to provide adequate information for exposure–response consideration. All kidney cancers are grouped in these studies, so that differentiation between renal cell carcinoma and cancer of the renal pelvis is not possible. Incidence and mortality findings in the Tier II (RR = 3.7; 95% CI 1.7–8.1; RR = 1.3, 95% CI 1.0–1.7) and Tier III (RR = 0.9, 95% CI 0.7–1.2; RR = 2.3, 95% CI 1.5–3.5) studies are elevated, also are based on substantial numbers of cases and thus are supportive of the Tier I study results.

The case–control studies provide support, showing elevated risks for TCE, solvent, and dry cleaning exposures, but inferences about causation are less robust than the Tier 1 cohort studies due to limited exposure definition and potential biases (Table 10). Asal et al. (*60*), Auperin et al. (*67*), Sharpe et al. (*61*), and Vamvakas et al. (*66*) conducted hospital-based case–control studies. Greenland et al. (*83*), Lynge et al. (*59*), and Sinks et al. (*12*) conducted case–control studies nested within an occupational cohort. Dosemeci et al. (*68*), Harrington et al. (*57*), Mandel et al. (*64*), McCredie and Stewart (*63*), Mellemgaard et al. (*65*), Partanen et al. (*62*), Schlehofer et al. (*58*), and Siemiatycki (*84*) conducted population-based case–control studies. In all of these studies, there are concerns about selection bias, blinding of investigators or interviewers, and particularly exposure characterization. Some studies use job titles to infer exposure (*60,63,67*), one compares dry cleaning workers to laundry workers (*59*), others assess risk to subjects exposed to general classes of solvents (*57,63*), and still other studies ask about exposure to specific agents or used more sophisticated exposure characterizations (*58,61,62,64,66,68,83*).

Table 4. Tier I cohort SIRs: incidence.

	Anttila et al. (*24*)	Axelson et al. (*25*)	Blair et al. (*20*) Male	Blair et al. (*20*) Female	Henschler et al. (*10*)	Average risk
Bladder	0.8 (5) (0.4–1.9)	1.0 (8) (0.5–2.0)	1.4 (9) (0.5–4.1)	1.0 (1) (0.1–9.1)	– –	1.0 (23) (0.6–1.6)
Brain	1.1 (9) (0.6–2.1)	– –	0.8 (1) (0.0 -13.2)	– –	– –	1.1 (10) (0.6–2.0)
Breast	– –	– –	– –	0.4 (3) (0.1–1.2)	– –	0.4 (3) (0.1–1.2)
Buccal	– –	– –	0.8 (7) (0.3–2.2)	– –	– –	0.8 (7) (0.3–2.2)
Cervix	2.4 (8) (1.2–4.8)	– –	– –	– –	– –	2.4 (8) (1.2–4.8)
Colon	0.8 (8) (0.4–1.7)	1.0 (8) (0.5–2.0)	5.7 (23) (1.9 -16.7)	0.9 (3) (0.3–3.2)	– –	1.2 (42) (0.8–1.8)
Esophagus	– –	– –	– –	– –	– –	0.0 (0) (0.0–0.0)
Hodgkin's disease	1.7 (3) (0.6–5.0)	1.0 (1) (0.5–6.0)	– –	– –	– –	1.5 (4) (0.6–3.7)
Kidney	0.9 (6) (0.4–1.9)	1.2 (6) (0.5–2.5)	0.4 (2) (0.1–2.3)	3.6 (2) (0.5–25.6)	8.0 (5) (3.4–18.6)	1.7 (21) (1.1–2.7)
Larynx	– –	1.4 (2) (0.4–5.0)	– –	– –	– –	1.4 (2) (0.4–5.0)
Leukemia	1.1 (5) (0.5–2.5)	– –	0.9 (4) (0.2–3.7)	– –	– –	1.0 (9) (0.5–2.1)
Liver	2.3 (5) (1.0–5.3)	1.4 (4) (0.6–3.6)	2.6 (3) (0.3–25.0)	– –	– –	1.9 (12) (1.0–3.4)
Liver/biliary	– –	– –	1.1 (4) (0.3–4.8)	– –	– –	1.1 (4) (0.3–4.8)
Lung	0.9 (25) (0.6–1.4)	0.7 (9) (0.4–1.3)	0.8 (15) (0.4–1.7)	– –	– –	0.8 (49) (0.6–1.1)
Lympho-hematopoietic	1.5 (20) (1.0–2.3)	– –	1.4 (17) (0.7–2.9)	0.9 (3) (0.2–3.3)	– –	1.4 (40) (1.0–2.0)
Melanoma	– –	– –	– –	– –	– –	0.0 (0) (0.0–0.0)
Multiple myeloma	1.6 (4) (0.6–4.2)	0.6 (1) (0.1–3.2)	5.1 (5) (0.6–43.7)	– –	– –	1.5 (10) (0.7–3.3)
Non-Hodgkin's lymphoma	1.8 (8) (0.9–3.6)	1.6 (5) (0.7–3.6)	1.0 (7) (0.3–2.9)	0.9 (2) (0.2–4.5)	– –	1.5 (22) (0.9–2.3)
Pancreas	1.6 (11) (0.9–2.9)	0.3 (1) (0.0–1.4)	0.7 (51) (0.2–2.4)	– –	– –	1.2 (63) (0.7–2.0)
Prostate	1.4 (13) (0.8–2.4)	1.3 (26) (0.8–1.8)	1.2 (56) (0.8–1.8)	– –	– –	1.3 (95) (1.0–1.6)
Rectum	1.7 (12) (1.0–3.0)	– –	– –	– –	– –	1.7 (12) (1.0–3.0)
Skin	– –	2.4 (8) (1.2–4.7)	– –	– –	– –	2.4 (8) (1.2–4.7)
Stomach	1.3 (17) (0.8–2.0)	0.7 (5) (0.3–1.6)	2.0 (6) (0.5–8.1)	1.0 (1) (0.1–10.9)	– –	1.2 (29) (0.8–1.7)

Table 5. Tier I cohort SMRs: mortality.

	Blair et al. (*20*)	Boice et al. (*21*)	Henschler et al. (*10*)	Morgan et al. (*22*)	Ritz (*23*)	Average risk
Bladder	1.2 (17) (0.5–2.9)	0.6 (5) (0.2–1.3)	– –	1.4 (8) (0.7–2.7)	1.2 (8) (0.6–2.3)	1.1 (38) (0.7–1.5)
Brain	0.8 (11) (0.3–2.2)	0.5 (4) (0.2–1.4)	3.7 (1) (0.7–20.6)	0.6 (4) (0.2–1.4)	1.3 (12) (0.7–2.2)	0.9 (32) (0.6–1.4)
Breast	1.8 (20) (1.0–3.3)	1.3 (7) (0.6–2.7)	– –	0.8 (16) (0.5–1.2)	– –	1.1 (43) (0.8–1.5)
Buccal	1.4 (9) (0.4–5.2)	0.6 (5) (0.3–1.4)	– –	– –	1.0 (9) (0.6–2.0)	0.9 (23) (0.6–1.5)
Cervix	1.8 (5) (0.5–6.5)	– –	– –	– –	– –	1.8 (5) (0.5–6.5)
Colon	1.4 (54) (0.8–2.4)	1.1 (30) (0.8–1.5)	– –	– –	1.0 (26) (0.7–1.5)	1.1 (110) (0.9–1.4)
Esophagus	5.6 (10) (0.7–44.5)	0.8 (7) (0.4–1.7)	– –	– –	1.2 (9) (0.6–2.3)	1.1 (26) (0.7–1.8)
Hodgkin's disease	1.4 (5) (0.2–12.0)	2.8 (4) (1.1–7.1)	– –	0.6 (1) (0.1–3.4)	2.1 (6) (1.0–4.5)	2.0 (16) (1.1–3.4)
Kidney	1.6 (15) (0.5–5.1)	1.0 (7) (0.5–2.0)	3.3 (2) (0.9–11.8)	1.3 (8) (0.7–2.6)	0.7 (5) (0.3–1.5)	1.2 (37) (0.8–1.7)
Larynx	– –	1.1 (4) (0.4–2.8)	– –	– –	1.2 (5) (0.5–2.8)	1.2 (9) (0.6–2.2)
Leukemia	0.6 (16) (0.3–1.2)	1.0 (12) (0.6–1.8)	– –	1.0 (10) (0.6–1.9)	1.1 (12) (0.6–1.9)	1.0 (50) (0.7–1.3)
Liver	1.7 (4) (0.2–16.2)	– –	– –	– –	– –	1.7 (4) (0.2–16.2)
Liver/biliary	1.3 (15) (0.5–3.4)	0.5 (4) (0.2–1.4)	– –	1.0 (6) (0.5–2.1)	1.7 (8) (0.8–3.3)	1.1 (33) (0.7–1.7)
Lung	0.9 (109) (0.6–1.3)	0.8 (78) (0.6–1.0)	1.4 (7) (0.7–2.9)	1.1 (97) (0.9–1.3)	1.0 (112) (0.9–1.2)	1.0 (403) (0.9–1.1)
Lympho-hematopoietic	1.1 (66) (0.7–1.8)	– –	1.1 (1) (0.2–6.1)	1.0 (25) (0.7–1.5)	1.3 (37) (0.9–1.8)	1.1 (129) (0.9–1.4)
Melanoma	1.0 (9) (0.3–3.1)	0.5 (2) (0.1–1.7)	– –	– –	– –	0.7 (11) (0.3–1.7)
Multiple myeloma	1.3 (14) (0.5–3.4)	2.8 (4) (1.1–7.1)	– –	– –	– –	1.9 (18) (1.0–3.7)
Non-Hodgkin's lymphoma	2.0 (28) (0.9–4.6)	1.2 (14) (0.7–2.0)	– –	1.0 (14) (0.5–1.7)	– –	1.2 (56) (0.9–1.7)
Pancreas	1.2 (33) (0.6–2.3)	0.4 (7) (0.2–0.9)	– –	0.8 (11) (0.4–1.4)	1.2 (18) (0.8–1.9)	0.9 (69) (0.7–1.2)
Prostate	1.1 (54) (0.7–1.8)	1.0 (32) (0.7–1.5)	– –	1.2 (21) (0.8–1.8)	1.4 (24) (0.9–2.1)	1.2 (131) (1.0–1.4)
Rectum	0.4 (5) (0.1–1.5)	1.3 (9) (0.7–2.5)	– –	1.1 (6) (0.5–2.3)	1.1 (7) (0.5–2.2)	1.0 (27) (0.7–1.6)
Skin	– –	– –	– –	– –	0.6 (4) (0.3–1.6)	0.6 (4) (0.3–1.6)
Stomach	0.9 (23) (0.4–1.9)	0.8 (7) (0.4–1.7)	– –	– –	1.4 (15) (0.8–2.3)	1.1 (45) (0.8–1.6)

Elevated odds ratios for kidney cancer are found for four different exposure classifications: degreasing agents (including TCE) (*60,61,66*), solvents (*61,63,65*), the iron/steel industry (likely including exposure to degreasing agents or solvents) (*58,62–65*), and dry cleaners/laundry workers (*60,64,65*). A few studies assesses TCE exposure specifically (*66,68,84*). The Sinks et al. study (*12*) characterizes renal cancer incidence by department (or work process) for those employed for 5 years or more. The finishing department, where the TCE was most likely to have been used, has three of the six reported cases or renal cell carcinoma and a highly elevated odds ratio (RR = 16.6, 95% CI 1.7–453.1).

The most recent and most striking renal cell carcinoma case–control study, by Vamvakas and colleagues (*66*), is hospital-based using accident victims as controls. The study was conducted in an area of Germany containing a large number of metal-working shops using TCE for degreasing purposes. The authors report that exposure is principally to TCE rather than to complex mixtures found in many other studies. This investigation reports a large and a statistically significant (but relatively imprecise) elevated adjusted odds ratio (OR) = 10.8, 95% CI 3.4–34.8) with 19 exposed cases. Limitations include the fact that the controls are not matched and substantial demographic and behavioral differences may exist between cases and controls, raising questions of control selection bias, and the source of the population is a hospital (i.e., Berkson's bias). The exposure data are collected by personal interview conducted by physicians, with possible recall bias and reporting bias. Nonetheless, the difference between this reported OR and the average risk in the Tier I cohort studies is striking. It may, in part, reflect differences in exposures between biomarker studies (generally < 40 ppm) (*18,24*) and subjects in this study (*66*) who experienced narcotic symptoms, which can occur only at much higher exposure levels [e.g., 200 mL/m^3, Stopps and McLaughlin (*105*) and Torkelson and Rowe (*106*)]. These findings are also supported by the results of Dosemeci et al. (*68*).

Confounding and effect modification may be important in interpreting these studies. Devesa et al. report that cigarette smoking is associated with higher risks for renal and bladder cancers (*107*). However, consideration of other smoking related sites (e.g., lung) does not reveal a strong smoking effect. Brownson reports that cigarette smoking is an independent risk factor for renal cancer, but alcohol consumption is not (*108*). Potential confounding or modifying agents are not considered in most of the studies we review. None of the community-based studies report on kidney cancer incidence.

In summary, the cohort studies provide strong evidence and the case–control studies provide supporting evidence of an association between the incidence of kidney cancer among workers exposed to degreasing agents and solvents and to those in both the iron and steel and dry cleaning and laundry work industries. However, since most often exposures are not measured, direct causality cannot be assessed. Exposure–response data do not add to this assessment. Failure to adjust for confounding and effect modification also may affect the results.

Liver and biliary cancers. Studies of liver and biliary cancers also offer strong data in support of the carcinogenicity of TCE. Some reports list liver and biliary cancers separately and some combine them. Since we do not have access to the raw data, we tabulate the study results as published. Of the 16 cohort studies reporting liver cancer, 3 report only primary liver cancer, 5 report only liver and biliary cancers combined, and 8 report liver and biliary cancers separately. Nearly all the case–control studies used only primary liver

cancer cases. Therefore, for this discussion, we use only primary liver cancer, where available, and combined liver and biliary otherwise. Elevated liver cancer risks are found across all study types except community-based, and this finding supports the hypothesis of an increased liver cancer risk due to TCE exposure.

In the Tier I cohort studies, incidence is elevated in all three studies reporting, none statistically significantly, and mortality is elevated in one of two studies reporting. The average relative risk for the incidence of liver cancer is elevated (RR = 1.9, 95% CI 1.0–3.4), although only exposed 12 cases were reported. The average relative risk of dying from liver and biliary cancer is slightly elevated (RR = 1.1, 95% CI 0.7–1.7) for 33 deaths. Evidence is strongest for an association in the cohort biomarker study by Anttila et al. (*24*) that isolated TCE, where a statistically significantly elevated liver cancer risk is observed among individuals with the longest time since first exposure. This may be due to higher historical exposure or to allowance for latency. Additional support for an association is provided by the positive exposure response gradients with both cumulative exposure and with time since first exposure in the Anttila study. Ritz shows data indicating an increased risk of mortaity for increased exposure and increased duration of exposure (*23*). Data from Boice et al. do not show an exposure–response relationship (*21*).

In the Tier II studies, 3 of 5 report that relative risks are greater than 1.0 for liver or biliary cancer. The average risk for liver cancer only, based on 15 exposed cases, is more elevated (RR = 2.0, 95% CI 1.3–3.3) than that for liver and biliary cancers combined (RR = 1.3, 95% CI 1.0–1.8), based on 34 cases. Findings from studies of dry cleaners and laundry workers (Tier III studies) are more ambiguous, showing elevated incidence for liver cancer alone and liver and biliary cancers but depressed mortality for liver and biliary cancers combined. These results may reflect lack of exposure specificity. Females in one study show elevated risks for liver and combined liver and biliary cancer incidence (*40*), while four other studies show slightly depressed risk of mortality. The study with the elevated rates among females had more cases (i.e., 14 incident cases) than the other four studies combined (i.e., 11 deaths). The relationship between work as a dry cleaner or laundry worker and liver cancer is not clear, although this observation is limited by the statistically small number of liver cancer cases and deaths.

The results of the case–control data are reported in Table 11. Most studies assess organic solvents generically or dry cleaning and laundries, limiting interpretability with respect to TCE exposure. Results are mixed for each of these exposures.

Table 6. Tier II cohort SIRs: incidence.

	Shannon et al. (*11*) Male	Shannon et al. (*11*) Female	Sinks et al. (*12*)	Average risk
Bladder	0.9 (3)	–	1.1 (3)	1.0 (6)
	(0.3–2.7)	–	(0.4–3.1)	(0.5–2.1)
Breast	–	2.0 (8)	–	2.0 (8)
	–	(1.0–4.0)	–	(1.0–4.0)
Cervix	–	1.1	–	1.1 (1)
	–	(0.2–5.9)	–	(0.2–5.9)
Kidney	–	–	3.7 (6)	3.7 (6)
	–	–	(1.7–8.1)	(1.7–8.1)
Lung	0.6 (6)	–	–	0.6 (6)
	(0.3–1.3)	–	–	(0.3–1.3)
Prostate	1.6 (7)	–	–	1.6 (7)
	(0.8–3.2)	–	–	(0.8–3.2)

Few of the studies reviewed provide information about confounding variables or effect modifiers. Interactions in the metabolic system have been found between TCE and alcohol consumption (*109,110*). Hernberg et al. (*73*), however, found alcohol consumption to be a negative confounder in a study of liver cancer and solvent exposure. Failure to adjust for these and similar effects could affect inferences. However, data availability precluded adjustments for this evaluation.

One community-based study reports results for liver cancer (*87*). That study, conducted in Finland, reports lower rates of liver cancer in both municipalities' studies from 1953 to 1991 than expected based on national data.

In summary, results suggest that workers with solvent exposure are likely to be at excess risk of liver cancer, although specific exposure information and exposure–response gradients are wanting.

Non-Hodgkin's lymphoma. Elevated non-Hodgkin's lymphoma risks are found in the Tier I, case–control, and community-based studies supporting the hypothesis that TCE exposure is associated with cancer at this site. Two of four Tier I reports have elevated incidence of non-Hodgkin's lymphoma (although the two for which it was not elevated were the gender-specific rates from the same study). The average incidence rate is elevated (RR = 1.5, 95% CI 0.9–2.3) and is based on 22 cases. Mortality is elevated in two of three reports, with an average of RR = 1.2, 95% CI 0.9–1.7 based on 56 deaths. Risks appear to increase with increasing latency (time since first exposure) in the biomarker study of Anttila et al. (*24*) and with mean exposure in Axelson et al. (*18*). There is no clear exposure–response pattern in the Boice et al. data (*21*).

Results of Tier II and Tier III studies are considered null in that there was only weak evidence for an association and results are based on 8 incident cases and 20 deaths. Again, this may be due in part to the less robust definition of exposure in these studies compared to that in the Tier I studies.

The findings from the case–control studies (*54–56,78–80,83,84*) shown in Table 12 add further support for an association between solvents, specifically TCE, and non-Hodgkin's lymphoma. Six of seven studies showed elevated ORs, two were statistically significant, and several reported TCE (rather than general solvent) exposure.

Similarly, findings from two community-based studies support an association between non-Hodgkin's lymphoma and drinking water exposure although the mixed solvent exposures in these studies make this result difficult to interpret.

Hodgkin's disease. Elevated risks for Hodgkin's disease are found for incidence and mortality in the Tier I studies, mortality in Tier III studies, and case–control studies, with solvent exposures supporting a possible TCE-related etiology. In Tier I, both biomarker studies report excess incidence, although case numbers are very low, and three of four mortality studies report excess risk. In Tier II, only one of five studies shows excess mortality risk, although again, case numbers are very small. In Tier III, only one study reports on Hodgkin's disease, but it shows excess mortality risk. The three case–control studies (Table 12), all with substantial numbers of cases, show risks between 2.8 and 6.8. Only one community-based study reports on Hodgkin's disease, with mixed results for two communities (*87*). Overall, these results are suggestive.

Cervical cancer. Cervical cancer, although sparsely reported, is elevated in Tier I, Tier II, and Tier III studies. The average risk in Tier III mortality studies, the only tier with more than one study with the same type of outcome, is depressed for incidence (RR = 0.8, 95% CI 0.6–1.2) and elevated for

Table 7. Tier II cohort SMRs—mortality.

	Blair et al. (27)	Blair et al. (28)	Dubrow and Gute (29)		Garabrant et al. (30)	Sinks et al. (12)	Average risk
			Male	Female			
Bladder	0.5 (2)	1.0 (8)	1.0 (13)	0.9 (3)	1.3 (17)	2.6 (1)	1.1 (44)
	(0.1–1.8)	(0.4–2.0)	(0.6–1.8)	(0.2–2.6)	(0.8–2.0)	(0.5–14.7)	(0.8–1.5)
Brain	1.7 (5)	1.1 (7)	1.0 (9)	1.5 (17)	0.8 (13)	–	1.2 (51)
	(0.7–4.0)	(0.4–2.2)	(0.5–1.9)	(1.0–2.4)	(0.5–1.3)	–	(0.9–1.5)
Breast	–	–	–	0.9 (66)	0.9 (16)	–	0.9 (82)
	–	–	–	(0.7–1.1)	(0.6–1.5)	–	(0.7–1.1)
Buccal	0.8 (3)	1.5 (11)	0.6 (7)	1.3 (6)	0.6 (10)	–	0.9 (37)
	(0.3–2.4)	(0.7–2.6)	(0.3–1.3)	(0.5–2.9)	(0.3–1.1)	–	(0.7–1.3)
Cervix	–	–	–	1.2 (13)	–	–	1.2 (13)
	–	–	–	(0.7–2.0)	–	–	(0.7–2.0)
Colon	1.4 (16)	1.1 (23)	1.3 (43)	0.9 (39)	0.9 (47)	–	1.1 (168)
	(0.9–2.3)	(0.7–1.7)	(1.0–1.8)	(0.6–1.2)	(0.6–1.3)	–	(0.9–1.3)
Esophagus	0.7 (2)	1.9 (10)	0.4 (3)	0.8 (3)	1.1 (14)	–	1.1 (32)
	(0.2–2.6)	(0.9–3.4)	(0.1–1.1)	(0.2–2.3)	(0.7–1.9)	–	(0.8–1.6)
Hodgkin's disease	0.8 (1)	1.4 (5)	0.6 (2)	0.3 (1)	0.7 (4)	–	0.8 (13)
	(0.1–4.6)	(0.5–3.3)	(0.1–2.1)	(0.0–1.7)	(0.3–1.9)	–	(0.5–1.4)
Kidney	1.1 (3)	1.1 (6)	1.6 (11)	1.8 (8)	0.9 (12)	1.4 (1)	1.3 (41)
	(0.4–3.1)	(0.4–2.4)	(0.9–2.8)	(0.8–3.4)	(0.5–1.6)	(0.3–7.7)	(0.9–1.7)
Larynx	0.6 (1)	1.4 (5)	1.1 (6)	–	–	–	1.2 (12)
	(0.1–3.2)	(0.5–3.3)	(0.5–2.4)	–	–	–	(0.7–2.0)
Leukemia	1.5 (7)	0.6 (6)	1.0 (10)	1.0 (9)	0.8 (16)	–	0.9 (48)
	(0.8–3.2)	(0.2–1.3)	(0.5–1.8)	(0.5–1.9)	(0.5–1.3)	–	(0.7–1.2)
Liver	1.1 (3)	2.8 (5)	3.0 (6)	0.4 (1)	–	–	2.0 (15)
	(0.4–3.3)	(0.9–6.5)	(1.1–6.5)	(0.0–2.4)	–	–	(1.3–3.3)
Liver/biliary	–	1.6 (10)	2.0 (10)	0.8 (6)	0.9 (8)	–	1.3 (34)
	–	(0.8–3.0)	(1.0–3.7)	(0.3–1.7)	(0.5–1.9)	–	(1.0–1.8)
Lung	0.5 (18)	1.1 (62)	1.0 (89)	1.3 (46)	0.8 (138)	–	0.9 (353)
	(0.3–0.8)	(0.8–1.4)	(0.8–1.2)	(1.0–1.7)	(0.7–1.0)	–	(0.8–1.0)
Lympho-hematopoietic	1.6 (17)	–	–	–	0.8 (38)	–	1.0 (55)
	(1.0–2.5)	–	–	–	(0.6–1.1)	–	(0.7–1.3)
Melanoma	–	–	–	–	–	–	0.0 (0)
	–	–	–	–	–	–	(0.0–0.0)
Multiple myeloma	–	–	1.1 (4)	1.0 (4)	–	–	1.1 (8)
	–	–	(0.3–2.9)	(0.3–2.6)	–	–	(0.6–2.1)
Non-Hodgkin's lymphoma	–	1.4 (8)	1.0 (8)	0.4 (4)	–	–	0.9 (20)
	–	(0.6–2.7)	(0.5–1.9)	(0.2–1.1)	–	–	(0.6–1.4)
Pancreas	0.6 (4)	1.3 (17)	0.8 (12)	1.0 (15)	1.2 (34)	–	1.1 (82)
	(0.2–1.6)	(0.8–2.1)	(0.5–1.4)	(0.6–1.7)	(0.8–1.7)	–	(0.9–1.3)
Prostate	1.1 (10)	1.1 (19)	0.7 (18)	–	0.9 (25)	–	0.9 (72)
	(0.6–2.0)	(0.7–1.7)	(0.4–1.1)	–	(0.6–1.4)	–	(0.7–1.2)
Rectum	1.2 (5)	1.2 (11)	0.7 (8)	1.1 (11)	1.0 (15)	–	1.0 (50)
	(0.5–2.8)	(0.6–2.2)	(0.3–1.3)	(0.6–1.9)	(0.6–1.7)	–	(0.8–1.3)
Skin	1.6 (3)	–	–	–	0.7 (7)	–	0.9 (10)
	(0.5–4.6)	–	–	–	(0.3–1.5)	–	(0.5–1.7)
Stomach	0.5 (4)	0.8 (14)	1.2 (20)	1.7 (20)	0.4 (9)	–	1.0 (67)
	(0.2–1.4)	(0.5–1.4)	(0.8–1.8)	(1.1–2.7)	(0.2–0.8)	–	(0.8–1.3)

mortality (RR = 1.7, 95% CI 1.5–2.0) based on 34 and 43 cases, respectively. In the Anttila et al. study (*24*), there is an exposure–response relationship. Most case–control studies on cervical cancer do not address relationships with solvent exposure or dry cleaning. The association observed in the cohort studies may be explained by confounding from socioeconomic status or other lifestyle factors. In addition, there is good evidence from other studies of a viral etiology (*111*). However, the data in this review are sufficiently compelling in implicating solvent exposure that they warrant further study.

Pancreatic cancer. Pancreatic cancer results are mixed in the Tier I and II studies but more consistent and stronger in the dry cleaning and laundry worker (Tier III) studies. The average RRs in the Tier III studies for incidence (RR = 1.7, 95% CI 1.2–2.6) and mortality (RR = 1.3, 95% CI 1.0–1.7) are both elevated based on 22 and 42 cases, respectively. Since the average 5-year survival for people with pancreatic cancer is below 5% (*103*), incidence and mortality are of comparable validity as measures of effect. There is evidence for a protective effect from the case–control studies with solvent exposure (*82,83*), evidence for cancer risk with TCE exposure (*83*), and evidence for cancer risk with dry cleaning and laundry work including an exposure–response relationship (*81*). Since the effect is strongest in Tier III studies and also seen in dry cleaner and laundry worker studies, this outcome is likely to be linked to dry cleaner exposures. However, the lack of more defined exposure assessments in the dry cleaner studies precludes drawing conclusions about a specific solvent. Random variation is another possible but unlikely explanation for the observed results. The evidence for an association between TCE exposure and pancreatic cancer is null to weak for TCE but moderate for dry cleaner exposures.

Other cancers. The cohort studies provide weak supportive data of an association between TCE exposure and multiple myeloma, and prostate and ski cancers. Further data and study are needed to be able to make any inferences.

The leukemia results of the case–control and community-based studies are intriguing. The studies conducted of children in Woburn, Massachusetts, provide particularly thorough evaluation, with the most recent studies explaining the leukemias in children born after the contaminated wells were closed by documenting *in utero* exposures (*86,99,112*). Of the community-based studies conducted in six different regions, all but one of the regions have an excess incidence of leukemia in at least one gender. Unfortunately, inferences regarding TCE and leukemia are limited because these drinking water/hazardous waste site studies are not sufficiently specific to a single causative agent and generally do not adjust for confounding factors. The results are not supported by the cohort studies that show little evidence of leukemia risk from TCE exposure. However, we suggest that in light of the preponderance of excess leukemia in these drinking water/hazardous waste site studies, it is important to determine the likely risk factor for this disease, be it TCE, some other compound in the drinking water (e.g., trihalomethanes), some other factor, or some combination of factors.

Two sites that show strong associations with dry cleaning and laundry work but not TCE exposure are bladder and esophageal cancers. Bladder cancer is elevated in the most well-designed cohort studies of dry cleaners (*15,39*) and in only one of the three studies reporting on dry cleaners and laundry workers together. On average, the risk was statistically significantly elevated. This increased risk of bladder cancer is also supported in the case–control studies (*42–45*). Esophageal cancer is elevated in the two dry cleaner

cohorts reporting this outcome (*15,39*) and elevated in one case–control study (*49*). An excess of esophageal cancer is not found among laundry workers, a population similar to dry cleaners but without exposure to PERC (*53*). These observations suggest that PERC is the likely etiologic agent for both of these outcomes but warrant further investigation for confirmation and to adjust for other known risk factors for cancer at these sites.

Summary of Results

A summary of results is provided in Table 14. The cancer sites are ordered by those showing evidence in animal studies, followed by those showing evidence in Tier I cohort studies, followed by the other sites examined. Sites showing statistically significant average risks are denoted with "+++"; those with average risks above 1.2, with "+"; those within the range from 0.8 to 1.2, by "0", and those below 0.8, by "–". "H" is used to signify substantial variation among the studies. Sites that show the most consistent and compelling results with respect to TCE exposure and cancer are the kidney and liver. The next most compelling results with respect to TCE exposure are for Hodgkin's disease, non-Hodgkin's lymphoma, and cervical cancer. For dry cleaners and laundry workers, presumably due to PERC exposure, the most compelling results are found for kidney, liver, cervical, lung, esophageal, and pancreatic cancers and multiple myeloma. Weaker results were found for laryngeal, colon, and prostate cancer with TCE exposure, and for bladder cancer among TCE-exposed dry cleaners and laundry workers.

In general, exposure–response gradients are observed in two or more studies for cancers of the kidney, liver, and specific lymphatic tissues. The overall effects are moderate but consistent across studies.

Table 8. Tier III cohort SIRs: incidence.

	Lynge and Thygesen (*40*) Male	Lynge and Thygesen (*40*) Female	McLaughlin et al. (*38*) Male	McLaughlin et al. (*38*) Female	Average risk
Bladder	0.6 (6)	0.9 (8)	–	–	0.8 (14)
	(0.2–1.3)	(0.4–1.7)	–	–	(0.5–1.3)
Brain	1.5 (5)	1.0 (12)	–	–	1.1 (17)
	(0.5–3.5)	(0.5–1.8)	–	–	(0.7–1.8)
Breast	–	0.8 (94)	–	–	0.8 (94)
	–	(0.7–1.0)	–	–	(0.7–1.0)
Buccal	–	–	–	–	0.0 (0)
	–	–	–	–	(0.0–0.0)
Cervix	–	0.8 (34)	–	–	0.8 (34)
	–	(0.6–1.2)	–	–	(0.6–1.2)
Colon	1.4 (10)	0.9 (25)	–	–	1.1 (35)
	(0.7–2.7)	(0.6–1.4)	–	–	(0.8–1.5)
Esophagus	–	–	–	–	0.0 (0)
	–	–	–	–	(0.0–0.0)
Hodgkin's disease	–	–	–	–	0.0 (0)
	–	–	–	–	(0.0–0.0)
Kidney	1.5 (6)	0.6 (5)	1.0 (18)	0.9 (25)	0.9 (54)
	(0.5–3.3)	(0.2–1.4)	(0.6–1.6)	(0.6–1.3)	(0.7–1.2)
Larynx	–	–	–	–	0.0 (0)
	–	–	–	–	(0.0–0.0)
Leukemia	0.7 (2)	0.7 (5)	–	–	0.7 (7)
	(0.1–2.6)	(0.2–1.7)	–	–	(0.4–1.5)
Liver	–	3.3 (7)	–	–	3.3 (7)
	–	(1.3–6.9)	–	–	(1.6–6.90)
Liver/biliary	0.5 (1)	2.0 (14)	–	–	1.8 (15)
	(0.0–2.5)	(1.1–3.4)	–	–	(1.1–2.9)
Lung	1.1 (28)	1.3 (32)	–	–	1.2 (60)
	(0.8–1.7)	(0.9–1.8)	–	–	(0.9–1.6)
Lympho-hematopoietic	–	–	–	–	0.0 (0)
	–	–	–	–	(0.0–0.0)
Melanoma	1.0 (2)	0.7 (8)	–	–	0.7 (10)
	(0.1–3.6)	(0.3–1.3)	–	–	(0.4–1.3)
Multiple myeloma	3.3 (4)	1.1 (3)	–	–	2.0 (7)
	(0.9–8.5)	(0.2–3.1)	–	–	(1.0–4.1)
Non-Hodgkin's lymphoma	2.8 (5)	0.5 (3)	–	–	1.4 (8)
	(0.9–6.5)	(0.1–1.5)	–	–	(0.7–2.8)
Pancreas	2.4 (9)	1.4 (13)	–	–	1.7 (22)
	(1.1–4.5)	(0.7–2.4)	–	–	(1.2–2.6)
Prostate	1.4 (11)	–	–	–	1.4 (11)
	(0.7–2.6)	–	–	–	(0.8–2.6)
Rectum	1.4 (9)	0.7 (11)	–	–	1.0 (20)
	(0.6–2.6)	(0.4–1.3)	–	–	(0.6–1.5)
Skin	1.0 (14)	0.7 (31)	–	–	0.8 (45)
	(0.5–1.6)	(0.5–1.0)	–	–	(0.6–1.1)
Stomach	1.3 (7)	1.3 (11)	–	–	1.3 (18)
	(0.5–2.7)	(0.6–2.3)	–	–	(0.8–2.0)

Discussion

At the outset, it is important to note some of the limitations of our analysis. First, we recognize that the summary relative risks we report for each tier of cohort studies is highly dependent on the selection of cohorts for each tier. We do include in our analysis all cohorts that report data by anatomical site. The three-tier classification scheme we use is based on our assessment of the quality of the exposure data for TCE-exposed workers.

Second, as noted above, the exposure information available is rather crude and does not isolate TCE. The crude exposure information most likely biases results toward the null. The failure to isolate TCE from other occupational exposures, including other solvents, could bias the results in either direction. Of particular concern is the possibility that exposures from different solvents are correlated with one another and one of the others may be carcinogenic.

Third, we note that few of the more traditional confounding variables (e.g., smoking, alcohol consumption) are assessed in any study. We believe it unlikely that adjustment for these factors would result in substantial changes in the reported risks but cannot rule it out.

Fourth, there is only limited exposure–response data, which limits our ability to make inferences.

Fifth, the occurrences of the diseases studied are relatively rare, limiting the sensitivity of the studies reviewed. In short, there are many limitations to the set of studies that we consider in this review. Nonetheless, we believe that there is substantial consistency across studies, which suggests that it is unlikely that any of these concerns have a substantial effect on our analysis.

Others view the consideration of the possible carcinogenicity of TCE as a controversial topic. In addition to several reviews

Table 9. Tier IV cohort SMRs: mortality.

	Blair et al. (*39*)	Duh and Asal (*36*)	Katz and Jowett (*35*)	Ruder et al. (*15*) Male	Ruder et al. (*15*) Female	Average risk
Bladder	1.7 (8) (0.9–3.3)	0.4 (1) (0.1–2.8)	1.9 (5) (0.6–4.4)	3.3 (7) (1.6–6.7)	1.4 (2) (0.4–5.1)	2.0 (23) (1.3–2.9)
Brain	0.2 (1) (0.0–1.2)	– –	– –	– –	– –	0.2 (1) (0.0–1.2)
Breast	1.0 (36) (0.7–1.4)	0.1 (1) (0.0–0.4)	0.7 (27) (0.5–1.0)	– –	1.1 (19) (0.7–1.7)	0.9 (83) (0.7–1.1)
Buccal	1.0 (5) (0.5–2.2)	0.5 (1) (0.1–3.4)	– –	2.1 (5) (0.9–5.0)	0.8 (1) (0.1–4.3)	1.2 (12) (0.7–2.1)
Cervix	1.7 (21) (1.4–2.0)	1.3 (2) (0.3–5.3)	2.0 (10) (0.9–3.6)	– –	1.8 (10) (1.0–3.3)	1.7 (43) (1.5–2.0)
Colon	1.0 (25) (0.7–1.4)	0.6 (7) (0.3–1.2)	1.0 (21) (0.6–1.6)	1.4 (9) (0.7–2.6)	1.7 (17) (1.1–2.7)	1.1 (79) (0.9–1.4)
Esophagus	2.1 (13) (1.2–3.6)	– –	– –	1.6 (5) (0.7–3.7)	3.2 (5) (1.4–7.6)	2.2 (23) (1.5–3.2)
Hodgkin's disease	2.1 (4) (0.8–5.3)	– –	– –	– –	– –	2.1 (4) (0.8–5.3)
Kidney	0.5 (2) (0.1–1.8)	3.8 (7) (1.9–7.6)	2.6 (7) (1.0–5.3)	0.7 (1) (0.1–3.7)	2.4 (3) (0.8–7.0)	2.3 (20) (1.5–3.5)
Larynx	1.6 (3) (0.5–4.7)	– –	– –	0.8 (1) (0.1–4.6)	2.9 (1) (0.5–16.3)	1.6 (5) (0.7–3.5)
Leukemia	0.9 (7) (0.4–1.8)	– –	0.7 (4) (0.2–1.7)	– –	0.8 (2) (0.2–2.7)	0.8 (13) (0.5–1.3)
Liver	– –	– –	– –	– –	– –	0.0 (0) (0.0–0.0)
Liver/biliary	0.7 (5) (0.3–1.7)	0.5 (1) (0.1–3.5)	0.9 (4) (0.2–2.3)	0.5 (1) (0.1–3.6)	– –	0.7 (11) (0.4–1.3)
Lung	1.3 (47) (1.0–1.7)	1.7 (37) (1.2–2.5)	1.0 (10) (0.5–1.8)	1.3 (31) (0.9–1.8)	1.0 (12) (0.6–1.8)	1.3 (137) (1.1–1.5)
Lympho-hematopoietic	1.2 (24) (0.8–1.8)	– –	– –	0.9 (5) (0.4–2.0)	0.6 (4) (0.2–1.4)	1.0 (33) (0.7–1.4)
Melanoma	– –	– –	– –	– –	– –	0.0 (0) (0.0–0.0)
Multiple myeloma	– –	– –	– –	– –	– –	0.0 (0) (0.0–0.0)
Non-Hodgkin's lymphoma	– –	– –	– –	– –	– –	0.0 (0) (0.0–0.0)
Pancreas	1.2 (15) (0.8–1.9)	0.5 (3) (0.1–1.7)	1.2 (9) (0.5–2.2)	1.7 (7) (0.8–3.5)	1.6 (8) (0.8–3.2)	1.3 (42) (1.0–1.7)
Prostate	0.7 (5) (0.3–1.7)	0.8 (4) (0.3–2.4)	– –	0.8 (7) (0.4–1.7)	– –	0.8 (16) (0.5–1.3)
Rectum	1.4 (10) (0.8–2.5)	0.9 (2) (0.2–3.5)	1.2 (6) (0.4–2.6)	1.0 (2) (0.3–3.8)	1.5 (3) (0.5–4.3)	1.3 (23) (0.9–1.9)
Skin	0.8 (2) (0.2–2.8)	1.5 (2) (0.4–6.1)	2.1 (4) (0.6–5.3)	– –	– –	1.5 (8) (0.8–2.9)
Stomach	0.8 (11) (0.5–1.4)	0.8 (3) (0.3–2.5)	0.3 (2) (0.0–1.2)	0.4 (2) (0.1–1.5)	0.9 (3) (0.3–2.5)	0.7 (21) (0.5–1.0)

that have been published in the peer-reviewed literature, two expert panels have reviewed TCE. In a 1992 report, the American Conference of Governmental Industrial Hygienists, examining animal and epidemiologic studies, concludes that the evidence indicated no carcinogenic risk, and places TCE in their category A5, not carcinogenic to humans (*113*). Several years later, IARC, looking at both occupational exposures and drinking water exposures, classifies TCE as probably carcinogenic to humans (Group 2A) based on "limited" human evidence and "sufficient" animal evidence (*13*).

Henschler and colleagues (*114*), in a letter responding to a vitriolic attack by Bloemen and Tomenson (*115*) and Swaen (*116*) about the design of their study (*10*), calculate the combined OR among six case–control studies (*60–64,83*) assessing the association between occupational risk factors and renal cell cancer. They find statistically significantly elevated average rates for those working in the iron and steel industry and related professions where TCE and PERC are used for metal degreasing (OR= 1.49, 95% CI = 1.19, 1.86) and for those exposed to PERC used as a dry cleaning solvent (OR=1.49, 95% CI = 1.24, 1.80). They conclude that TCE exposure does pose a risk of kidney cancer.

McLaughlin and Blot (*116*) subsequently review the epidemiology of TCE and kidney cancer in seven cohort studies (*10,18,19,24, 30,31,104*) and six case–control studies (*57,60–62,83,84*) In their discussion, they fail to distinguish results either between men and women or incidence and mortality, and argue that none of the cohort studies except "the methodologically questionable" Henschler et al. study (*10*) show a relationship between TCE and kidney cancer risk. We note that the updates of two of the studies were published after that review and, as noted above, show weakly positive associations, as does the study of Sinks et al. (*12,32*), which was omitted. McLaughlin and Blot also argue that the case–control studies do not show support for the hypothesized association.

Weiss (*6*) also reviews the occupational epidemiology of TCE exposure, concentrating on only four studies (all of which are Tier I studies): the Blair et al. NCI-based study of aircraft maintenance workers (*20*), the Axelson et al. Swedish worker study (*18*), the Anttila et al. Finnish worker study (*24*), and an early version of the Wong and Morgan study of the Hughes Aircraft employees (*104*). Weiss suggests that the data provide only weak support for carcinogenicity of TCE, and then only for liver and biliary tract cancers, kidney cancers, and non-Hodgkin's lymphoma. He argues that the rarity of disease among these cohorts (23 kidney cancer cases; 16 liver cancer cases; 12 biliary cancer cases; 33 non-Hodgkin's lymphoma cases), the relatively small relative risks, and the lack of clear exposure–response data are too limited to infer causality. Using the most recent reports in the Tier I studies, we found 51 cases of kidney cancer (21 incident; 37 deaths), 16 cases of liver cancers (12 incident; 4 deaths), 37 biliary cancers combined (4 incident; 33 deaths), and 78 cases of non-Hodgkin's lymphoma (22 incident; 56 deaths), a more than doubling of cases over those reported by Weiss except for liver cancer (for which no new studies were used).

Morgan and colleagues (*22*) in their report of their own study also combine their results with those of Anttila et al. (*24*), Axelson et al. (*18*), and Spirtas et al. (*19*). They note slightly elevated but not statistically significant SMRs for liver, prostate, kidney and bladder cancers and non-Hodgkin's lymphoma (SMRs 1.1–1.3). They, too, conclude that the interpretation of causality is compromised due to the small number of cases.

Table 10. Case control studies: kidney cancer.

Reference	Exposure assessment	Exposure classification	Number of subjects (cases/controls)	Participation rate (cases/controls), %	Odds ratio (95% CI)	Exposure response
Asal et al. (*60*)	Occupation	DC (male) DC (female) Metal degreasing	315/313+336 (hospital + population)	–	0.7 (0.2–2.3) 2.8 (0.8–9.8) 1.7 (0.7–3.8)	–
Auperin et al. (*67*)	Occupation	Dry cleaning	196/347	99/99	Too few exposed	–
Dosemeci et al. (*68*)	Occupation from interview to JEM	TCE (male) TCE (female) TCE (total)	273/462 165/225 438/687	86 86 86	1.0 (0.6–1.7) 2.0 (1.0–4.0) 1.3 (0.9–1.9)	
Greenland et al. (*83*)	JEM	TCE as degreaser	1,821/1,202	75/64	1.0 (0.3–3.3)	–
Harrington et al. (*57*)	Questionnaire	Solvent exposure	54/54	53/?	1.0 (0.2–4.9) No exposed cases	–
Lynge et al. (*59*)	Occupation	Dry cleaning	16/80	?	0.7 (0.2–3.6)	–
Mandel et al. (*64*)	Interview	DC industry (male) DC solvents (male) DC solvents (female) Iron/steel industry (male)	1,732/2,309	72/75	0.9 (0.3–2.4) 1.4 (1.1–1.7) 1.6 (1.0–2.7) 1.6 (1.2–2.2)	None
McCredie and Stewart (*63*)	Interview	DC industry Solvent exposure Iron/steel industry	489/523	91/74	2.7 (1.1–6.7) 1.5 (1.1–2.1) 1.2 (0.8–1.9)	Trend in years worked for iron/steel industry
Mellemgaard et al. (*65*)	Interview	DC (male) DC (female) Solvents (male) Solvents (female) Iron/steel industry (male)	368/396	86/78	2.3 (0.2–27.0) 2.9 (0.3–33.0) 1.5 (0.9–2.4) 6.4 (1.2–23.0) 1.4 (0.8–2.4)	–
Partanen et al. (*62*)	Mail survey	DC, solvents Iron/metalwork	338/338	69/68	Too few exposed 1.9 (0.9–3.8)	–
Schlehofer et al. (*58*)	Interview	PERC Metal industry	277/286	85/75	2.5 (1.2–5.2) 1.6 (1.1–2.5)	–
Sharpe et al. (*61*)	Mail survey	Organic solvents Degreasing solvents	164/161	97	1.7 (0.9–3.2) 3.4 (0.9–12.7)	–
Siemiatycki (*84*)		TCE (2% prevalence)	3,730/533	78	0.8 (0.4–2.0)	None
Sinks et al. (*12*)	Job history	TCE and solvents	6/48		21.7 (3.0–inf)	
Vamvakas (*66*)	Medical doctor interview	TCE and PERC (PERC in controls only)	58/84	79/75	10.8 (3.4–34.8)	Weak evidence

DC, dry cleaning.

Table 11. Case–control studies: liver cancer.

Reference	Exposure assessment	Exposure classification	Number of subjects (cases/controls)	Participation rate (cases/controls), %	Odds ratio (95% CI)	Exposure response
Austin et al. (*74*)	Interview	DC	80/146	–	0 (only 4 exposed controls)	–
Greenland et al. (*83*)	JEM	TCE as degreaser	1,821/1,202	75/64	0.5 (0.1–2.6) LB	–
Hardell et al. (*71*)	Mail survey	Solvent exposure	102/200	99/97	1.8 (1.0–3.4) PLC 2.1 (1.1–4.0) HCC	–
Hernberg et al. (*73*)	Mail survey and IH	Solvent exposure (TCE, PERC, CCl_4)	377/385	72/71	0.6 (0.3–1.3) m, PLC 3.4 (1.3–8.6) f, PLC	
Hernberg et al. (*72*)	Mail survey and IH	Solvent exposure	126/175	/62%	2.3 (0.8–7.0) PLC	Mainly women
Houton and Sonnesso (*70*)	Interview	DC	102/	–	Too small to assess; 2 cases in DC	–
Lynge et al. (*59*)	Occupation	DC	17/85	100/97	No exposed cases	–
Stemhagen et al. (*69*)	Interview	DC	265/530	79/77	2.5 (1.0–6.1) PLC 2.3 (0.9-6.1) HCC	–
Suarez et al. (*75*)	Death certificate	DC	1,742/1,742	–	1.0 (0.4–2.2) PLC	–

Abbreviations: HCC, hepatocellular cancer; LB, liver and biliary cancer; PLC, primary liver cancer.

The newest data on kidney cancer suggest different interpretations, although Weiss (*6*) and McLaughlin and Blot (*117*) caution the reader on the interpretation of these results because the Tier I cohort studies they had available showed, at best, a weak response. They also suggest exclusion of the Henschler et al. study (*10*) because it was a follow-up from a cluster report, a judgment with which we disagree. We found that updates of two Tier I cohorts (*20,22*) show positive results as do some additional case–control results. With these additional data, the association is even more convincing to us, although we are still plagued by our inability to isolate TCE exposure from PERC exposure. One also must note the low exposures reported in most of the Tier I cohort studies, which may limit the resolving power of these studies but not the importance of the observed association.

Table 12. Case–control studies: lymphoma.

Reference	Exposure assessment	Exposure classification	Number of subjects (cases/controls)	Participation rate, cases/controls, %	Odds ratio (95% CI)	Exposure response
Hodgkin's Disease						
Hardell et al. (*54*) (Hodgkin's and non-Hodgkin's)	Survey	TCE, PERC, styrene, benzene	169/338	–	4.6 (1.9–11.4)	–
Olsson and Brandt (*56*)	Interview	Organic solvents (2 with TCE reported)	25/50	–	6.8 (1.8–23.8)	–
Persson et al. (*55*)	Survey	TCE	54/275 Hodgkin's	96/83	2.8 (1.1–7.2)	–
Non-Hodgkin's lymphoma						
Blair et al. (*80*)	Interview	Occupation/JEM Nonbenzene solvents	622/1245	87/80	1.1 (0.9–1.4)	Positive for intensity
Greenland et al. (*83*)	JEM	TCE as degreaser	1,821/1,202	75/64	0.8 (0.2–2.4)[a]	–
Figgs et al. (*79*)	Death certificate	Occupation: aircraft mechanics	23,890/119,450	–	2.5 (1.1–6.0)	–
Hardell et al. (*54*) (Hodgkin's and non-Hodgkin's)	Survey	TCE, PERC, styrene, benzene	169/338	–	4.6 (1.9–11.4)	–
Hardell et al. (*78*)	Survey	TCE	105/335	–	7.2 (1.3–42.0)	–
Persson et al. (*55*)	Survey	TCE	106/275 NHL	96/83	1.5 (0.6–3.7)	–
Siemiatycki (*84*)	TCE (2% prevalence)		3,730/533	78	1.1 (0.6–2.3)	No

[a]Lymphomas, lymphosarcomas, and reticulosarcomas.

Table 13. Community-based studies.

Outcome	Exposure assessment	Reference	Relative risk	Exposed cases	Comments
Bladder	Solvents in town water (including TCE)	Mallin (*98*)	1.7 m (1.1–2.6) 2.6 f (1.2–4.7)	21 10	
Hodgkin's disease	Residence in town	Vartiainen et al. (*87*)	0.8 (0.3–1.7) Hausjarvi, Finland 1.4 (0.7–2.5) Hattula, Finland	6 11	
Leukemia	VOCs other than THMs in town water	Fagliano et al. (*89*)	1.5 (1.0–2.2) f 1.0 (0.7–1.5) m	28 25	Exposure response for females
	TCE in town water	Cohn et al. (*90*)	1.4 (1.1–1.9) f 1.1 (0.8–1.4) m	56 63	Exposure response for females
	Residence in town; VOCs in water	Lagakos et al. (*86*) MDPH (*99*)	2.2 (1.5–2.9) 2.4 (0.5–10.6)	20 21	Exposure response not consistent
	Residence in town	Vartiainen et al. (*87*)	1.2 (0.8–1.7) Hausjarvi, Finland 0.7 (0.4–1.1) Hattula, Finland	33 19	
	Residence in county	Kioski et al. (*93,96*)	1.5 (0.8–2.7)	11	Low level of TCE in drinking water
	Residence in area F	Flood and Chapin (*94*) Flood et al. (*95*) Porter et al. (*97*)	0.9 (0.5–1.5)	9	Childhood leukemia mortality rates elevated in prior study
	Proximity to waste site with TCE	Turnbull et al. (*88*) Waller et al. (*91*) Waller and Turnbull (*92*)		592	Clustering statistically significant for some waste sites
Liver	Residence in village	Vartiainen et al. (*87*)	0.7 (0.3–1.4) Hausjarvi, Finland 0.6 (0.2–1.3) Hattula, Finland	7 6	
Multiple myeloma	Residence in town	Vartiainen et al. (*87*)	0.7 (0.3–1.3) Hausjarvi, Finland 0.6 (0.2–1.3) Hattula, Finland	7 6	
Non-Hodgkin's lymphoma	TCE in town water	Cohn et al. (*90*)	1.4 (1.1–1.7) f 1.2 (0.9–1.5) m	87 78	Hint of exposure response for females
	Residence in town	Vartiainen et al. (*87*)	0.6 (0.3–1.1) Hausjarvi, Finland 1.4 (1.0–2.0) Hattula, Finland	14 31	
Various	Residence in towns	Isacson et al. (*85*)			Various rate comparisons

Abbreviations: VOCs, volatile organic compounds; THMs, trihalomethanes.

Table 14. Summary of results.

Cancer	Animal	Cohort			Case–control	Community-based	Summary
		Tier I	Tier II	Tier III			
Kidney	+++	+++	+++	+++	+++solvents; +++DC		*TCE/DC
Liver	+++	+++	+++	+++	+++solvents; +DC	–	*TCE
Lung	+++	0	0	+++	+DC		*DC
Hodgkin's	+++	+++	H0	+	+++TCE; +++solvents	0	
Testes	+						ND
Leukemia	+	0	H0	–	+++TCE	+++	
Cervical		+++	0	+++			*TCE/DC
Non-Hodgkins lymphoma		+	H0	+	+++TCE; +++solvents	+	*TCE
Prostate		+++	0	H0	–TCE		*TCE
Multiple myeloma	+++	0	+++		–	*TRI	
Breast		0	H0	0			
Esophagus		0	H0	+++			*DC
Pancreas		H0	H0	+++	+DC		*DC
Skin		+++	H0	H0			
Brain		0	0	H0	+TCE; +DC		
Larynx		0	0	+			?TCE
Bladder		0	0	H+++	0 TRI; +DC	+	?DC
Buccal		0	0	H0			
Colon		0	0	0	+TCE; +DC		?TCE/DC
Rectum		0	0	+	–TCE		
Stomach		0	H0	0	–TCE		
Melanoma		0		–	+TCE		

Abbreviations: +++, statistically significantly positive; +, positive (RR ≥ 1.2); 0, neutral (1.2 ≥ RR ≥ 0.8); –, negative (RR ≤ 0.8); H, results heterogeneous across studies; H+, heterogeneous but positive on average; H–, heterogeneous but negative on average; H0, heterogeneous but neutral on average; *, evidence of risk; ?, weak suggestion of risk; ND, insufficient data.

For the liver data, Weiss (*6*) raises concerns with the possible mechanism of disease and appropriately criticizes that lack of more specific outcome data (i.e., the separation of the data on cancer of the biliary tract from that of liver cancer). Nonetheless, the data from Tier I, Tier II, and the case–control studies by and large support this association. Interestingly, the Tier III data are inconsistent, as are the case–control data on dry cleaners and laundry workers, suggesting that, in contrast to kidney, TCE is implicated although PERC is not.

Overall, our analysis is consistent with that of IARC (*13*) and Weiss (*6*) but suggests more strongly an association of TCE exposure with kidney and liver cancers and some support for Hodgkin's disease and non-Hodgkin's lymphoma. There is also a possible association of cervical cancer with TCE or PERC exposure. Some data suggest associations between TCE exposure and multiple myeloma and prostate, laryngeal, and colon cancers. There is support for an association between dry cleaning and laundry work (likely PERC exposure) and kidney, pancreatic, cervical, esophageal, and lung cancers, and some support for bladder and colon cancers. These data warrant follow-up and further study. Overall, the results are consistent despite the wide variety of studies and exposures, and we strongly urge further study of cancer risk from solvent exposures in general, and TCE and PERC in particular.

Finally, the data on community exposure to contaminated drinking water and leukemia are striking, although no particular agent has been identified adequately because exposures are all to complex mixtures of chemicals.

In terms of Hill's aspects of causation (*1*), we find moderate support. The strength of association for kidney and liver cancer and non-Hodgkin's lymphoma using our average risks from Tier I are 1.7, 1.9, and 1.5, respectively. These values are moderate but based on a substantial number of cases. There results are relatively consistent, with most studies reviewed showing elevated risks. TCE is not specific, as evidenced by the multiple cancers we study. Since we give the greatest weight to the cohort studies, we are emphasizing the cohort studies for which there is implicit temporality. There are limited data on biologic gradient (or exposure response), but these data tend to support an association. The paucity of such data limits our ability to assess this aspect. There is plausibility for several of the cancers mentioned, as noted in other articles in this monograph. There is coherence in that we do not believe the natural history and biology of the diseases conflict with TCE causing cancer. There is experimental evidence in the animal bioassay literature, as described in the introduction of this article. Finally, we do not know of any appropriate analogy for TCE, although this may reflect our lack of imagination more than the absence of the analogy. In short, although this is a subjective judgment, TCE scores quite high on Hill's aspects of causation.

Future Research Directions

There are two main areas in which we feel further research is needed. First, as the next step in the analysis of extant data, we recommend that a meta-analysis be conducted. The goal of this study would be to try to isolate factors that help explain the observed risks, as well as to better quantify the risk. One would have to focus carefully on the possible heterogeneity among studies, carefully considering which groups of studies to combine. When combining studies in an analysis, it would be useful to identify specific design and other study differences that might help explain the variation in results among studies. In addition, assessment of influence and publication bias could be helpful.

Second, further studies of workers exposed to solvents could be helpful in elucidating the observed cancer risks. Other reviews also have found excess cancer risk (*118,119*). In particular, biomarker studies, which enable researchers to isolate exposures to specific solvents, could be helpful in unraveling some of the apparently conflicting results reported herein. It would be important to separate exposures of TCE, PERC, 1,1,1-trichloroethane, methylene chloride, carbon tetrachloride, toluene, xylene, and benzene, among other solvents. Studies should include dry cleaner and laundry workers as a particularly at risk population. Special attention should be paid to possible confounding variables such as socioeconomic status in the reports of cervical cancer that may help explain the observed excesses. The most efficient approach would be to use a case–control study nested within an occupational cohort with known TCE exposure.

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