

# Exhibit 266

# Occupational Trichloroethylene Exposure and Kidney Cancer

## A Meta-analysis

Michael A. Kelsh,<sup>a</sup> Dominik D. Alexander,<sup>b</sup> Pamela J. Mink,<sup>c,d</sup> and Jeffrey H. Mandel<sup>e</sup>

**Background:** We conducted a meta-analysis of occupational studies of trichloroethylene-exposed workers to evaluate patterns of associations by study design, exposure assessment methods, and occupational groups.

**Methods:** Estimates of summary relative risk (RR) were calculated using inverse-variance weighting methods. Cohort studies were classified as group I or group II, depending on quality of the study design and exposure assessment procedures. We conducted sensitivity analyses to examine sources of heterogeneity.

**Results:** Across all studies meeting our inclusion criteria ( $n = 23$ ), the summary RR was 1.42 (95% confidence interval = 1.17–1.77), with heterogeneity present (test for heterogeneity:  $P = 0.001$ ). After removal of 3 outlier studies, the summary RR for the remaining studies was 1.24 (1.06–1.45 (test for heterogeneity:  $P = 0.616$ )). The summary RR for studies of workers who were identified as more likely exposed to trichloroethylene (group I studies) was 1.34 (1.06–1.68). With outlier studies removed, the group II summary RR estimates for the cohort studies was 0.88 (0.58–1.33) and for the case-control studies was 1.33 (1.02–1.73). The summary RR for studies that used biomarkers to classify exposure ( $n = 3$ ) was 1.02 (0.59–1.77) and for studies of aerospace/aircraft workers ( $n = 7$ ) was 1.14 (0.84–1.57).

**Conclusions:** Positive associations were observed across various study groups. However, considerations of unmeasured potential confounding, lack of quantitative exposure assessment and lack of exposure-response patterns limit epidemiologic insight into the role of trichloroethylene exposure and its potential causal association with kidney cancer.

(*Epidemiology* 2010;21: 95–102)

Submitted 13 January 2009; accepted 24 June 2009.

From the <sup>a</sup>Health Science Practice, Exponent, Inc, Menlo Park, CA; <sup>b</sup>Health Science Practice, Exponent, Inc, Chicago, IL; <sup>c</sup>Health Science Practice, Exponent, Inc, Washington, DC; <sup>d</sup>Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA; and <sup>e</sup>Division of Environmental Health Sciences, School of Public Health, University of Minnesota, Minneapolis, MN.

Supported by the TCE Issues Group and the Halogenated Solvents Industry Association.

**SDC** Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article ([www.epidem.com](http://www.epidem.com)).

Correspondence: Michael A. Kelsh, Exponent, Inc, 149 Commonwealth Dr, Menlo Park, CA 94025. E-mail: [mkelsh@exponent.com](mailto:mkelsh@exponent.com).

Copyright © 2009 by Lippincott Williams & Wilkins

ISSN: 1044-3983/10/2101-0095

DOI: 10.1097/EDE.0b013e3181c30e92

Cancer of the kidney and renal pelvis account for approximately 4% of all new cancer cases and 2% of cancer deaths among US men and women.<sup>1</sup> Worldwide, the incidence of kidney cancer in men is twice as high as in women.<sup>2</sup> Incidence and mortality rates for renal cell carcinoma have increased over the past 30 years.<sup>3,4</sup> Cigarette smoking, obesity, and hypertension are the most commonly reported risk factors.<sup>2,3,5,6</sup> Inconsistent associations have been reported for exposure to asbestos, polycyclic aromatic hydrocarbons, diesel exhaust, cadmium, and trichloroethylene.<sup>2–5,7</sup>

Trichloroethylene (also known as TCE) has been widely used as a solvent since the early 1900s.<sup>8</sup> It has been used primarily in industrial degreasing involved with metal fabricating and manufacturing, especially in the aircraft/aerospace industry.<sup>8</sup> Trichloroethylene is also used in dry cleaning, textiles, leather processing, electronics, health services, agriculture, and the food and chemical industry.<sup>8–10</sup> However, workers engaged in metal degreasing appear to be the most heavily exposed.<sup>8,11</sup>

Trichloroethylene has been shown in animals to produce higher rates of cancer of the kidney, liver, lung, and hematopoietic tissue.<sup>11–17</sup> However; these findings are not consistent, and some effects appear to be specific only to certain species or strains of animals.<sup>18,19</sup> Reviews of the epidemiologic evidence regarding the carcinogenicity of trichloroethylene have not produced a consensus.<sup>20–23</sup> In this meta-analysis, we included recently published cohort studies of Danish workers,<sup>24,25</sup> aerospace workers,<sup>26,27</sup> and electronics manufacturing workers,<sup>28</sup> and 3 case-control studies<sup>7,29,30</sup> not evaluated in previous reviews. Our objectives were as follows (1) to calculate summary relative risks and (2) to examine potential sources of heterogeneity across studies. We also conducted sensitivity and influence analyses, and assessed the potential role of confounding, information bias, selection bias, and publication bias.

## METHODS

### Literature Search

We searched Medline and EMBASE, specifying trichloroethylene and human studies (including occupational studies); trichloroethylene or organic solvents with case-

control or cohort studies; degreasers and cancer; hazardous waste sites and cancer outcomes; and trichloroethylene, organic solvents, or chlorinated solvents and kidney cancer or renal cell cancer. We also searched the bibliographies of recent review articles.<sup>20–23,31–34</sup>

### Study Inclusion Criteria

We included epidemiologic studies that (1) used a cohort or case-control study design; (2) examined occupational trichloroethylene exposure and kidney cancer among workers; (3) specifically identified trichloroethylene exposure by reference to industrial hygiene records, individual biomarkers, job exposure matrices, or industrial processes that involved the use of trichloroethylene (cohort studies), or included questions regarding trichloroethylene exposure (case-control studies); (4) reported results specifically for kidney cancer or renal cell carcinoma; and (5) presented associations as relative risk estimates with corresponding measures of variability (eg, confidence intervals). Case-control studies included in this meta-analysis assessed trichloroethylene from self-reports of exposure or from job exposure matrices.<sup>7,29,30,35–38</sup> Case-control studies that collected nonspecific or general exposure information such as “solvents” or “chemicals,” or that analyzed findings by a single job title only that is, without a job exposure matrix were not included. Studies of dry cleaners and laundry workers were excluded because of exposure classification and study design limitations. Prior to the 1960s, dry cleaning work involved some exposure to trichloroethylene in addition to carbon tetrachloride and Stoddard solvent; however, perchloroethylene has been the predominant agent used in the dry cleaning industry since the early 1960s.<sup>8,39,40</sup> Dry cleaners did comprise a small proportion (<1%) of the study populations in 2 “multiple industry” studies included in this meta-analysis.<sup>24,25</sup> We identified a total of 25 peer-reviewed epidemiologic studies that assessed the relation between trichloroethylene exposure and kidney cancer and met our inclusion criteria. Two of those studies reported on largely overlapping cohorts<sup>26,27</sup> leaving 24 studies in our primary analyses.

### Classification of Studies and Data Extraction

Cohort studies were categorized into 2 groups. Group I studies (n = 10) specifically identified trichloroethylene as a workplace exposure through biomonitoring, industrial hygiene data, identified work practices, or job titles that involved trichloroethylene. Group I studies also demonstrated sufficiently complete enumeration of the workforce.<sup>24–27,41–46</sup> Three cohort studies<sup>24,45,46</sup> obtained urinary trichloroacetate measurements from workers, whereas other studies<sup>25–27,41–44</sup> assessed exposure to trichloroethylene through chemical inventory, industrial hygiene, or other records (eTable, <http://links.lww.com/EDE/A354>). Group II cohort studies (n = 7) were more limited in that they lacked specific, detailed trichloroethylene exposure information. For the group II studies,<sup>28,47–52</sup> the reports mentioned trichloroethylene but provided

little or no documentation of actual exposure<sup>28,47,50</sup> or identified trichloroethylene but did not specify an exposed subcohort<sup>51,52</sup>; alternatively, the cohort consisted of aerospace or aircraft workers who were presumed to be exposed to trichloroethylene (eTable, <http://links.lww.com/EDE/A354>).<sup>48,49</sup>

Relative risk (RR) estimates and associated 95% confidence intervals (CIs) were abstracted from each publication for (1) analyses that reflected the entire cohort under study (“total cohort”), or the exposure category that included all trichloroethylene exposed workers; (2) the “Subcohort” of workers in the group I cohort studies that were identified specifically as more likely exposed to trichloroethylene; and (3) exposure-response results (cumulative exposure or duration of exposure/employment). For studies based on urinary trichloroacetate monitoring,<sup>24,45,46</sup> the same data were used in both the total cohort and subcohort analyses. One group I cohort study did not specifically report data for an exposed subcohort and kidney cancer,<sup>44</sup> and was included only in the total cohort analyses. Two studies<sup>26,27</sup> analyzed largely overlapping populations from the same occupational cohort in Southern California (Rocketdyne): Zhao et al<sup>27</sup> evaluated kidney cancer incidence whereas Boice et al<sup>26</sup> evaluated kidney cancer mortality among the total cohort and a smaller group of workers identified as being more likely to have been exposed. The Boice et al study cohort was larger (n = 8372) and included more follow-up time (1948–1999) than the Zhao et al study (n = 5049 male workers follow-up from 1988–2000). Data from Boice et al were used in our primary meta-analysis, and we conducted sensitivity analyses using Zhao et al results were used in the separate analyses of kidney cancer incidence. For cohort studies that had been updated, we used the most recently published findings.<sup>43,45</sup> Results for men and women were combined.

Most studies reported results for malignant neoplasms of the kidney and renal pelvis together (ICD versions 8 and 9 codes 189.0 and 189.1, respectively). In 2 group II cohort studies, cancer of the kidney was combined with cancer of other urinary organs.<sup>48,49</sup> Excluding these studies from the meta-analyses, however, did not materially change summary estimates.

### Statistical Analysis

We conducted separate meta-analyses for group I cohort studies (total cohort and subcohort), group II cohort studies, group I and II cohort studies combined, case-control studies, and all types of studies combined. In addition, we conducted separate analyses of studies of (1) cancer incidence studies, (2) workers who were biomonitored for trichloroethylene exposure, (3) workers in the aircraft/aerospace industry, (4) workers from multiple industrial groups that used trichloroethylene, (5) duration of exposure/employment, and (6) cumulative exposure. Random effects meta-analysis methods were used to calculate summary estimates of relative risk and 95% CIs, with estimates of individual studies weighted by the inverse of their variance. We also conducted univariate meta-

regression analyses by study classification and study design. The relative influence of each study on the summary RR was examined by calculating a summary RR that included all studies, followed by recalculation of the summary RR after removing each study one at a time. Publication bias was assessed by evaluation of funnel plots and use of the Begg and Matzundar test and Egger regression method.<sup>53</sup>

All analyses were performed using Comprehensive Meta-Analysis version 2.2.046<sup>54</sup> and verified by Episheet.<sup>55</sup>

## RESULTS

A table in the electronic appendix summarizes characteristics of the studies, including the size of the study population, type of industrial/occupational group, follow-up time or enrollment periods, exposure assessment methods, and approximate trichloroethylene exposure levels (eTable, <http://links.lww.com/EDE/A354>). Study-specific kidney cancer results are also summarized in this table. The group I

cohort studies consisted of 5 US studies of aerospace manufacturing or aircraft maintenance workers, 1 study of uranium processing workers, and 4 European studies of workers from various industries using trichloroethylene. Three of the European studies used urinary trichloroacetic acid measurements to identify trichloroethylene-exposed workers. The 7 group II cohort studies consisted of aircraft, electronics, Coast Guard, military, and cardboard manufacturing workers. Of the 7 case-control studies, one was nested within a cohort of transformer assembly workers<sup>37</sup> and one analyzed French workers from a region where trichloroethylene was used in a screw cutting industry.<sup>30</sup> Three case-control studies were hospital-based and one identified cases from a statewide cancer surveillance system.

## All Studies Combined

The summary RR for all studies combined (group I [total cohort data], group II cohort, and case-control studies) was 1.30 (95% CI = 1.04–1.61). Strong heterogeneity was

**TABLE.** Summary of Meta-analysis Results of Occupational Trichloroethylene Exposure and Kidney Cancer

Studies/Study Groups Included in Analysis	No. Studies	SRRE (95% CI)	Test for Heterogeneity P
<b>All studies</b>			
All studies: total cohort data	23	1.30 (1.04–1.61)	<0.001
All studies: subcohort data from group I studies <sup>a</sup>	23	1.42 (1.13–1.77)	0.001
All studies <sup>a</sup> : data from outlier studies removed <sup>b</sup>	20	1.24 (1.06–1.45)	0.616
<b>Cohort studies</b>			
Group I cohort studies: subcohort data <sup>c</sup>	8	1.34 (1.07–1.67)	0.854
Group II cohort studies	7	1.58 (0.75–3.32)	<0.0001
Group II studies: data from outlier studies removed <sup>d</sup>	5	0.88 (0.58–1.33)	0.985
Cohort studies—cancer incidence findings summarized			
All cohort studies <sup>a</sup>	16	1.34 (1.00–1.81)	0.011
All cohort studies <sup>a</sup> : data from outlier studies removed <sup>d</sup>	14	1.19 (0.98–1.44)	0.826
Group I and group II cohort studies <sup>a</sup> : aircraft/aerospace worker cohorts	7	1.14 (0.84–1.57)	0.588
Group I cohort studies <sup>a</sup> : aircraft/aerospace worker cohorts (note: mortality studies conducted in the United States)	4	1.44 (0.94–2.21)	0.579
Group I cohort studies <sup>a</sup> : worker from various industries (note: incidence studies conducted in Europe)	4	1.31 (1.01–1.69)	0.754
Group I cohort studies: workers biomonitored for TCE exposure (all conducted in Europe)	3	1.02 (0.59–1.77)	0.899
<b>Case control studies</b>			
All case-control studies	7	1.57 (1.06–2.30)	0.003
Case-control studies: data from outlier studies removed <sup>e</sup>	6	1.33 (1.02–1.73)	0.143
<b>Exposure response</b>			
Duration of exposure/employment: shortest	7	1.50 (0.96–2.36)	0.272
Duration of exposure/employment: longest	7	1.24 (0.69–2.23)	0.085
Cumulative exposure: low	3	1.29 (0.68–2.47)	0.330
Cumulative exposure: high	3	1.39 (0.75–2.59)	0.331

<sup>a</sup>TCE-exposed subcohort data used for the group I cohort studies.

<sup>b</sup>Vamvakas et al.<sup>36</sup> Henschler et al.<sup>52</sup> and Sinks et al.<sup>47</sup> removed.

<sup>c</sup>Ritz<sup>44</sup> included in the group I total cohort analysis but not the subcohort analysis, as these data were not reported.

<sup>d</sup>Henschler et al.<sup>52</sup> and Sinks et al.<sup>47</sup> removed.

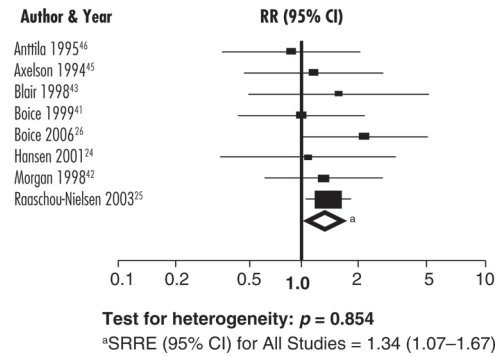
<sup>e</sup>Vamvakas et al.<sup>36</sup> removed.

SRRE indicates summary relative risk estimate.

present (test for heterogeneity:  $P < 0.001$ ). This heterogeneity remained when analysis was restricted to the trichloroethylene-exposed subcohorts from group I and all other studies (1.42 [1.13–1.77; test for heterogeneity:  $P = 0.001$ ]) (Table, Fig. 1). Three studies were limited in study design, exposure assessment, or control selection procedures.<sup>36,47,52</sup> After excluding these 3 studies, the summary RR was 1.24 (1.06–1.45 [test for heterogeneity:  $P = 0.62$ ]).

### Cohort Studies

The summary RR for the group I cohort studies was 1.34 (1.07–1.67; test for heterogeneity:  $P = 0.85$ ) (Table, Fig. 2). The Raaschou-Nielsen et al study<sup>25</sup> contributed the greatest relative weight (57%) and other studies each contributed a relative weight of 9% or less. Removal of this large study slightly reduced the estimate to 1.27 (0.90–1.78; test for heterogeneity:  $P = 0.79$ ). The result for the 3 studies with biomonitoring was 1.02 (0.59–1.77; test for heterogeneity:  $P = 0.90$ ) (Table). Among aerospace/aircraft worker cohorts, the estimate was 1.44 (0.94–2.21) for group I studies and



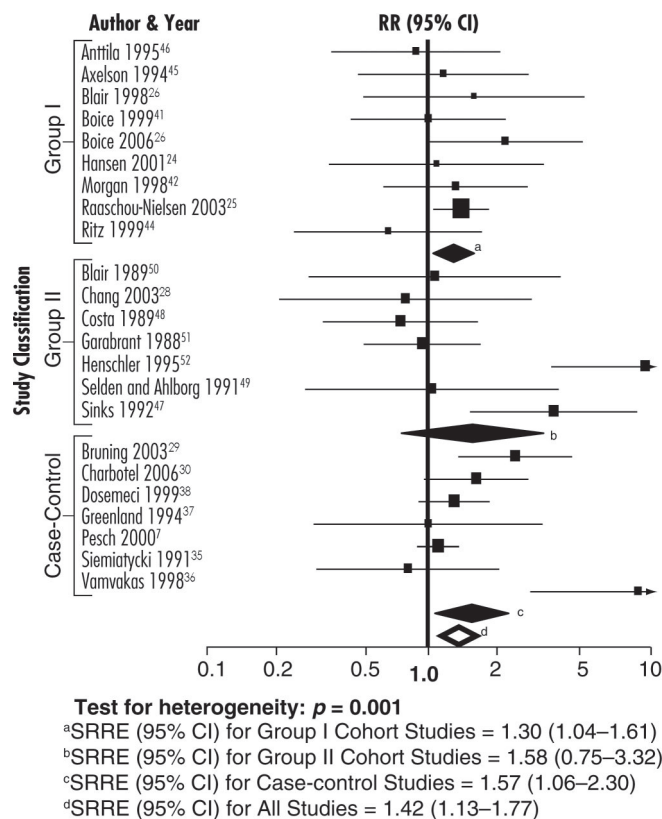
**FIGURE 2.** Meta-analysis of occupational trichloroethylene exposure and kidney cancer: Individual study results and summary relative risks for trichloroethylene-exposed subcohorts in group I studies.

1.14 (0.84–1.57) for group I and II studies combined (Table). Among workers from various industries (all European studies), the summary RR was 1.31 (1.01–1.69, test for heterogeneity:  $P = 0.75$ ) (Table).

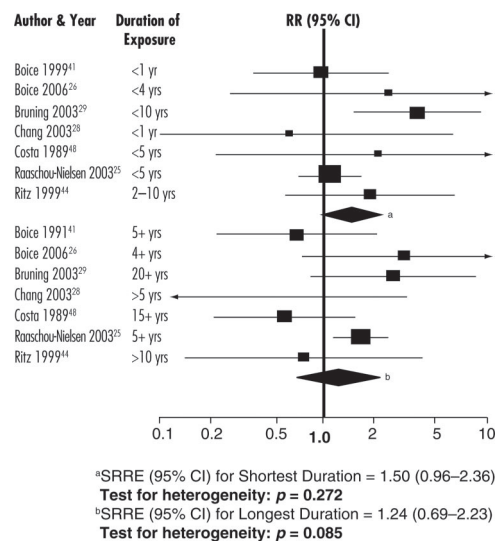
Meta-analysis of the 7 group II cohort studies resulted in a summary RR of 1.58 (0.75–3.32); (test for heterogeneity:  $P < 0.001$ ) (Table, Fig. 1). After excluding the 2 potential outlier studies, the estimate was 0.88 (0.58–1.33) with no heterogeneity ( $P = 0.99$ ) (Table).

### Case-Control Studies

The summary RR for the 7 case-control studies was 1.57 (1.06–2.30), test for heterogeneity:  $P = 0.003$  (Table, Fig. 1). Excluding one study with many limitations<sup>36</sup> lowered



**FIGURE 1.** Meta-analysis of occupational trichloroethylene exposure and kidney cancer: Individual study results and summary relative risk for all studies (with studies that followed-up cluster investigations removed: Henschler et al,<sup>52</sup> Vamvakas et al,<sup>36</sup> Sinks et al<sup>47</sup>) summary RR = 1.42 (1.06–1.45);  $P$  value for heterogeneity = 0.616. For group I cohort studies, TCE-exposed subcohort data used when available.



**FIGURE 3.** Meta-analysis of occupational trichloroethylene exposure and kidney cancer: Individual study results and summary relative risk estimates for duration of exposure/employment (Data for Ritz<sup>44</sup> included kidney and bladder cancer cases; data for Costa et al<sup>48</sup> included urinary system cases.)

the summary odds ratio and decreased heterogeneity (1.33 [1.02–1.73, test for heterogeneity:  $P = 0.14$ ]). Six studies adjusted for smoking, 3 studies adjusted for BMI, and 2 studies adjusted for hypertension.

### Analysis of Exposure Response and Publication Bias

Analysis of 10 studies with data on exposure categories showed no apparent exposure response patterns by duration or cumulative exposure (Table, Figs. 3, 4). Using funnel plots to assess potential publication bias, we observed slight asymmetry and identified 3 outlier studies<sup>36,47,52</sup> (Fig. 5). We conducted meta-analyses including and excluding these studies. Overall, statistical evaluations did not confirm publication bias, although the power to demonstrate this bias is generally low.<sup>53</sup>

## DISCUSSION

A recent committee review by the National Research Council recommended that meta-analysis of trichloroethylene and cancer should (1) identify and include all relevant studies and if studies are excluded, provide objective criteria for exclusion, (2) avoid use of subjective quality scoring, (3) assess heterogeneity, (4) analyze all studies combined (unless this introduces heterogeneity), and (5) conduct sensitivity analyses.<sup>56</sup> All of these standard procedures for meta-analysis have been applied in this review.<sup>57</sup> In addition, this meta-analysis included (1) recently published studies; (2) evaluated

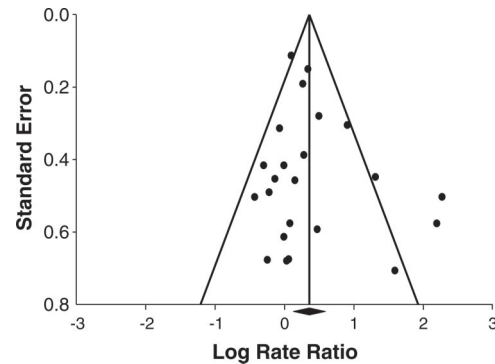


FIGURE 5. Funnel plot of standard error by log relative risk: occupational studies of kidney cancer.

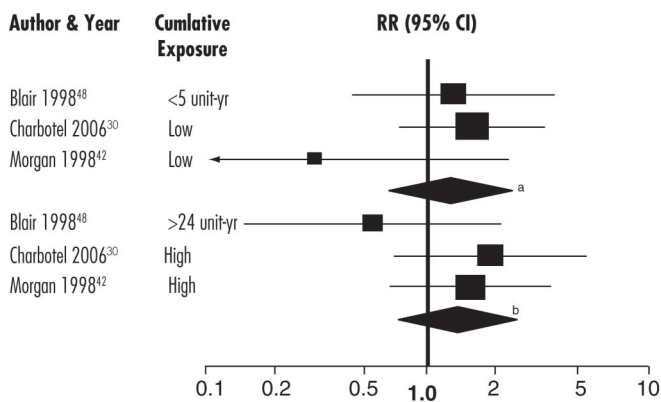
subgroups of studies defined by type of work, exposure assessment methods, and study design; (3) assessed exposure-response patterns; and (4) evaluated potential biases.

### Group I Cohort Studies

The group I cohort studies used better exposure assessment methods compared with group II studies and had potentially more homogeneous trichloroethylene exposure compared with the case-control studies. However, the number of kidney cancer cases in most group I cohort studies was low. The 3 European cohort studies with biomonitoring had 4–7 cases each; the US aerospace/aircraft workers studies had 7–15 cases in the exposed subcohorts and 30–125 cases in the total cohorts. The Danish study<sup>25</sup> had a total of 103 kidney cancer cases; the standardized incidence ratio was 1.2 (95% CI = 0.9–1.5) among all blue-collar workers (76 cases) and 1.4 (1.0–1.8) among the subcohort of blue-collar workers who were potentially more highly exposed (53 cases) (eTable, <http://links.lww.com/EDE/A354>). One of the aircraft-maintenance-worker studies<sup>43</sup> appeared to have some of the highest trichloroethylene exposures and reported no overall excess risk or exposure-response pattern (eTable). This study was recently updated with follow-up through the year 2000, with similar results.<sup>58</sup> The group I cohort studies had summary relative risk estimates ranging from 1.0 (biomonitoring) to 1.44 (aerospace workers), with an overall estimate of 1.34 (1.07–1.64).

### Group II Cohort Studies

The group II cohort studies had less-specific trichloroethylene exposure information. Some of those studies had other design limitations including short latency,<sup>28</sup> lack of individual exposure data, and limited exposure information (eg, material safety data sheets information only<sup>47</sup>). Henschler et al<sup>52</sup> conducted a small cohort study of 169 workers exposed to trichloroethylene at a cardboard factory in Germany, where exposures are reported to be relatively high (eTable). Numerous limitations of this study have been discussed in previous reviews.<sup>20,21,23</sup> After excluding 2 studies



<sup>a</sup>SRRE (95% CI) for Low Cumulative Exposure = 1.29 (0.68–2.47)  
**Test for heterogeneity:  $p = 0.330$**

<sup>b</sup>SRRE (95% CI) for High Cumulative Exposure = 1.39 (0.75–2.59)  
**Test for heterogeneity:  $p = 0.331$**

FIGURE 4. Meta-analysis of occupational trichloroethylene exposure and kidney cancer: All studies: Individual study results and summary relative risk estimate for cumulative exposure (Morgan et al<sup>42</sup>: TCE categorization of high and low based on months of exposure multiplied by potential exposure score. Charbotel et al<sup>30</sup>: Cumulative exposure categorization calculated based on total exposure doses for each job period and duration in each job period.)

that introduced considerable heterogeneity and had serious design limitations, the group II studies do not indicate excess kidney cancer risk among workers potentially exposed to trichloroethylene (Table).

### Case-Control Studies

The findings of the case-control studies were mixed—some reported positive associations and others reported equivocal or no associations. Two studies in one region of Germany identified an increased risk of kidney cancer related to self-reported trichloroethylene exposure or work history.<sup>29,36</sup> Vamvakas et al conducted a case-control study using cases defined as all renal cell cancer patients from the Urology Department of a specific hospital in Germany. However, shortcomings in case identification procedures, selection of controls, potential interview bias, and problems with matching may have led to biased results.<sup>20,21</sup> The Bruning et al study<sup>29</sup> improved upon several study design aspects of the Vamvakas et al study; however, hospital referral patterns in the region and the use of hospital-based controls may have introduced bias. All other studies collected data on work histories and job titles that were incorporated into a job-exposure matrix for trichloroethylene. Studies of self-reported trichloroethylene exposure reported higher relative risks than those based on a matrix, which could either indicate a cancer effect or reflect potential recall bias. A more recent investigation of occupational exposures in a wider region of Germany did not find substantial increases in renal cell cancer risk among men with “high exposure” to trichloroethylene.<sup>7</sup> Among French workers there was an exposure-response trend, with an odds ratio of 2.2 in the high cumulative-exposure group.<sup>30</sup> Greenland et al<sup>37</sup> reported no increased risk of kidney cancer among workers from a US transformer assembly plant. Similarly, Siemiatycki<sup>35</sup> evaluated self-reported trichloroethylene exposure as well as specific occupations and industries, and did not find elevated odds ratios for kidney cancer. In summary, the interpretation of the case-control studies depends largely on the weight given to, and the validity of, the 2 German studies. If these are included, the estimate is 1.59 (1.00–2.54; test for heterogeneity:  $P = 0.002$ ); if excluded, the estimate is 1.14 (0.93–1.76; test for heterogeneity:  $P = 0.80$ ).

### Exposure Assessment

A recent comprehensive review of trichloroethylene exposure in the United States reported several general trends relevant to this meta-analysis (1) exposures are higher in degreasing and vapor degreasing activities; (2) metal workers will likely have higher exposures; (3) trichloroethylene use was very limited in the dry-cleaning industry; (4) trichloroethylene use dropped dramatically in the 1980s; and (5) for many industries, trichloroethylene is reported as “having been used,” but there are only limited data available that quantify the potential exposures to workers. Many job groups

that have often been listed as “trichloroethylene-exposed” (eg, electric components, rubber industry, paints, and lacquers) likely have had very limited trichloroethylene exposures, which suggests the possibility that case-control studies overestimate exposure.<sup>8</sup>

Exposure assessment has been a critical limitation among epidemiologic studies of trichloroethylene-exposed workers. Most studies have relied on some type of qualitative job exposure matrix, often with a dichotomous yes/no classification. Three European studies used biomonitoring data to establish their study cohorts, but the number of observed cancers was small, thus limiting the opportunity to use the more quantitative exposure information.<sup>24,45,46,59</sup> In addition, the use of the urinary trichloroacetate biomarker may be limited in assessing long term/historical trichloroethylene exposure because the half-life of urinary trichloroacetate is relatively short (ie, days)<sup>46</sup> and because, for nearly all participants, only a few biomarker measurements were available to represent an entire work history. The recent case-control study in France integrated more semi-quantitative exposure data, thus representing an improvement over most previous case-control studies.

Although based on limited data, there were no overall exposure-response patterns for duration of employment or cumulative exposure (Table, Figs. 3, 4). Similarly, study-specific exposure estimates did not show a consistent pattern of exposure response (eTable, <http://links.lww.com/EDE/A354>).

Several studies relied on job exposure or facility exposure matrices to assign individual worker exposure, which can be limited by unaccounted-for within-worker variability. For example the largest study<sup>25</sup> classified all workers at trichloroethylene companies with 200 or fewer employees as “high trichloroethylene” assuming that a high proportion of workers at such facilities were exposed. In fact, the percentage of workers actually exposed at these smaller facilities varied from 1% to 100%.<sup>59,60</sup>

Thus it appears that exposure classification protocols in the Danish and perhaps US studies labeled more workers as exposed to trichloroethylene than were truly exposed. If this exposure misclassification was nondifferential it could lead to underestimating the summary relative risks; if differential, it could lead to either over- or underestimation of summary relative risks.

### Confounding and Other Potential Biases

Smoking has been consistently identified as a risk factor for kidney cancer, with an average 2-fold relative risk and increasing risk with duration of smoking and total pack-years.<sup>6,61</sup> Although data on smoking were not available in the trichloroethylene cohort studies, general surveys of smoking prevalence by industries labeled as “metal industries,” “machinery,” and occupational categories such as “fabrication,” “crafts workers,” “machine operators,” and “extraction-precision production” indicate that smoking prevalence is higher

among these groups as compared with other occupational groups and the general population.<sup>62,63</sup> The Danish investigators also noted that smoking was likely higher among blue collar workers compared with the general population.<sup>25</sup> Thus, lack of control for smoking may have upwardly biased the relative risk estimates in the cohort studies that used external comparisons, but may not have affected case-control studies or cohort studies using internal comparison groups.

The impact of uncontrolled confounders (such as obesity) on meta-analysis results remains unknown. Diagnostic bias among employed populations, who may have better access to health care and thus may be more likely to have cancer diagnosed, may contribute to upwardly biased risk estimates, especially in areas such as the United States where most health insurance coverage depends on employment. Conversely, potential nondifferential disease misclassification when relying on mortality data could bias risk estimates towards the null value.

We found no consistent indication of publication bias based on various assessments, although removal of 3 studies (all reporting positive results) reduced heterogeneity considerably. All 3 studies were apparently initiated in response to reported disease clusters, and although researchers attempted to conduct a full epidemiologic investigation, the results will be predictably elevated given that the cohort was defined (or cases and controls were selected) after identification of the cluster.

## CONCLUSIONS

While a simple summary meta-analysis of occupational exposure to trichloroethylene suggests an association with kidney cancer, more careful analyses of subgroups of studies indicate no association or, at best, moderately elevated associations. Exposure response analysis, although limited, did not show a pattern of higher risk with higher exposure. In addition, sources of systematic bias, such as confounding due to smoking and diagnostic bias, could plausibly explain the modest association between trichloroethylene and kidney cancer. Despite modest elevations in some summary relative risk estimates, insight into the role of trichloroethylene exposure and its association with kidney cancer is limited by the consideration of unmeasured confounding, the general lack of quantitative exposure assessment, and the absence of clear exposure-response trends.

## ACKNOWLEDGMENTS

We thank Betty Dowd for graphical assistance.

## REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58:71–96.
2. Janout V, Janoutova G. Epidemiology and risk factors of kidney cancer. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2004;148:95–101.
3. McLaughlin JK, Lipworth L, Tarone RE, Blot WJ. Renal cancer. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. New York: Oxford University Press; 2006:1087–1100.
4. Moore LE, Wilson RT, Campleman SL. Lifestyle factors, exposures, genetic susceptibility, and renal cell cancer risk: a review. *Cancer Invest*. 2005;23:240–255.
5. Lindblad P, Adami HO. Kidney cancer. In: Adami HO, Hunter D, Trichopoulos D, eds. *Textbook of Cancer Epidemiology*. New York: Oxford University Press; 2002:467–485.
6. Kuper H, Boffetta P, Adami HO. Tobacco use and cancer causation: association by tumour type. *J Intern Med*. 2002;252:206–224.
7. Pesch B, Haerting J, Ranft U, et al; MURC Study Group. Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. Multicenter urothelial and renal cancer study. *Int J Epidemiol*. 2000;29:1014–1024.
8. Bakke B, Stewart PA, Waters MA. Uses of and exposure to trichloroethylene in U.S. industry: a systematic literature review. *J Occup Environ Hyg*. 2007;4:375–390.
9. Wong O. Carcinogenicity of trichloroethylene: an epidemiologic assessment. *Clin Occup Environ Med*. 2004;4:557–589.
10. Blair A. Mortality among workers in the metal polishing and plating industry, 1951–1969. *J Occup Med*. 1980;22:158–162.
11. International Agency for Research on Cancer. *Trichloroethylene: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Vol 63. Lyon, France: World Health Organization; 1995.
12. US Department of Health and Human Services, Public Health Service, National Toxicology Program. *Report on Carcinogens, Eleventh Edition*. Research Triangle Park, NC: National Institute of Environmental Health Sciences, 2005.
13. Maltoni C, Lefemine G, Cotti G, Perino G. Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice. *Ann NY Acad Sci*. 1988;534:316–342.
14. Fukuda K, Takemoto K, Tsuruta H. Inhalation carcinogenicity of trichloroethylene in mice and rats. *Ind Health*. 1983;21:243–254.
15. National Toxicology Program. NTP carcinogenesis studies of trichloroethylene (without epichlorohydrin) (CAS No. 79–01–6) in F344/N rats and B6C3F1 mice (Gavage studies). *Natl Toxicol Program Tech Rep Ser*. 1990;243:1–174.
16. Rhomberg LR. Dose-response analyses of the carcinogenic effects of trichloroethylene in experimental animals. *Environ Health Perspect*. 2000;108(suppl 2):343–358.
17. National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of Trichloroethylene (CAS No. 79–01–6) in Four Strains of Rats (ACI, August, Marshall, Osborne-Mendel) (Gavage Studies). *Natl Toxicol Program Tech Rep Ser*. 1988;273:1–299.
18. Henschler D, Elsasser H, Romen W, Eder E. Carcinogenicity study of trichloroethylene, with and without epoxide stabilizers, in mice. *J Cancer Res Clin Oncol*. 1984;107:149–156.
19. Henschler D, Romen W, Elsasser HM, et al. Carcinogenicity study of trichloroethylene by longterm inhalation in three animal species. *Arch Toxicol*. 1980;43:237–248.
20. Mandel JS, Kesh MA. A review of the epidemiology of trichloroethylene and kidney cancer. *Hum Ecol Risk Assessment*. 2001;7:727–735.
21. McLaughlin JK, Blot WJ. A critical review of epidemiology studies of trichloroethylene and perchloroethylene and risk of renal-cell cancer. *Int Arch Occup Environ Health*. 1997;70:222–231.
22. Wartenberg D, Reyner D, Scott CS. Trichloroethylene and cancer: epidemiologic evidence. *Environ Health Perspect*. 2000;108(suppl 2):161–176.
23. Weiss NS. Cancer in relation to occupational exposure to trichloroethylene. *Occup Environ Med*. 1996;53:1–5.
24. Hansen J, Raaschou-Nielsen O, Christensen JM, et al. Cancer incidence among Danish workers exposed to trichloroethylene. *J Occup Environ Med*. 2001;43:133–139.
25. Raaschou-Nielsen O, Hansen J, McLaughlin JK, et al. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. *Am J Epidemiol*. 2003;158:1182–1192.
26. Boice JD Jr, Marano DE, Cohen SS, et al. Mortality among Rocketdyne workers who tested rocket engines, 1948–1999. *J Occup Environ Med*. 2006;48:1070–1092.
27. Zhao Y, Krishnadasan A, Kennedy N, Morgenstern H, Ritz B. Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers. *Am J Ind Med*. 2005;48:249–258.

28. Chang YM, Tai CF, Yang SC, et al. A cohort mortality study of workers exposed to chlorinated organic solvents in Taiwan. *Ann Epidemiol*. 2003;13:652–660.
29. Bruning T, Pesch B, Wiesenhutter B, et al. Renal cell cancer risk and occupational exposure to trichloroethylene: results of a consecutive case-control study in Amsberg, Germany. *Am J Ind Med*. 2003;43:274–285.
30. Charbotel B, Fevotte J, Hours M, Martin JL, Bergeret A. Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: epidemiological aspects. *Ann Occup Hyg*. 2006;50:777–787.
31. Alexander DD, Mink PJ, Mandel JH, Kelsh MA. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukaemia. *Occup Med (Lond)*. 2006;56:485–493.
32. Mandel JH, Kelsh MA, Mink PJ, et al. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review. *Occup Environ Med*. 2006;63:597–607.
33. Lyng E, Anttila A, Hemminki K. Organic solvents and cancer. *Cancer Causes Control*. 1997;8:406–419.
34. Alexander DD, Kelsh MA, Mink PJ, et al. A meta-analysis of occupational trichloroethylene exposure and liver cancer. *Int Arch Occup Environ Health*. 2007;81:127–143.
35. Siemiatycki J. *Risk Factors for Cancer in the Workplace*. Boca Raton, FL: CRC Press; 1991.
36. Vamvakas S, Bruning T, Thomasson B, et al. Renal cell cancer correlated with occupational exposure to trichloroethene. *J Cancer Res Clin Oncol*. 1998;124:374–382.
37. Greenland S, Salvan A, Wegman DH, Hallock MF, Smith TJ. A case-control study of cancer mortality at a transformer-assembly facility. *Int Arch Occup Environ Health*. 1994;66:49–54.
38. Dosemeci M, Cocco P, Chow WH. Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons. *Am J Ind Med*. 1999;36:54–59.
39. Blair A, Petralia SA, Stewart PA. Extended mortality follow-up of a cohort of dry cleaners. *Ann Epidemiol*. 2003;13:50–56.
40. Travier N, Gridley G, De Roos AJ, et al. Cancer incidence of dry cleaning, laundry and ironing workers in Sweden. *Scand J Work Environ Health*. 2002;28:341–348.
41. Boice JD Jr, Marano DE, Fryzek JP, Sadler CJ, McLaughlin JK. Mortality among aircraft manufacturing workers. *Occup Environ Med*. 1999;56:581–597.
42. Morgan RW, Kelsh MA, Zhao K, Heringer S. Mortality of aerospace workers exposed to trichloroethylene. *Epidemiology*. 1998;9:424–431.
43. Blair A, Hartge P, Stewart PA, McAdams M, Lubin J. Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow up. *Occup Environ Med*. 1998;55:161–171.
44. Ritz B. Cancer mortality among workers exposed to chemicals during uranium processing. *J Occup Environ Med*. 1999;41:556–566.
45. Axelsson O, Selden A, Andersson K, Hogstedt C. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. *J Occup Med*. 1994;36:556–562.
46. Anttila A, Pukkala E, Sallmen M, Hernberg S, Hemminki K. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. *J Occup Environ Med*. 1995;37:797–806.
47. Sinks T, Lushniak B, Haussler BJ, et al. Renal cell cancer among paperboard printing workers. *Epidemiology*. 1992;3:483–489.
48. Costa G, Merletti F, Segnan N. A mortality cohort study in a north Italian aircraft factory. *Br J Ind Med*. 1989;46:738–743.
49. Selden A, Ahlborg G Jr. Mortality and cancer morbidity after exposure to military aircraft fuel. *Aviat Space Environ Med*. 1991;62:789–794.
50. Blair A, Haas T, Prosser R, et al. Mortality among United States Coast Guard marine inspectors. *Arch Environ Health*. 1989;44:150–156.
51. Garabrant DH, Held J, Langholz B, Bernstein L. Mortality of aircraft manufacturing workers in southern California. *Am J Ind Med*. 1988;13:683–693.
52. Henschler D, Vamvakas S, Lammert M, et al. Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. *Arch Toxicol*. 1995;69:291–299.
53. Rothstein H, Sutton A, Borenstein M. *Publication Bias in Meta-Analysis: Prevention, Assessment, and Adjustment*. Chichester, UK; John Wiley and Sons, Ltd; 2005.
54. *Comprehensive Meta-Analysis version 2.2.046*. Englewood, NJ: Biostat; 2007.
55. Andersson T, Ahlbom A. Episheet software: spreadsheets for the analysis of epidemiologic data. 2004. Rothman K. Available at: <http://members.aol.com/krothman/episheet.xls>.
56. National Research Council of the National Academies. *Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues*. Washington, DC: National Academies Press; 2006.
57. Blair A, Burg J, Foran J, et al. Guidelines for application of meta-analysis in environmental epidemiology. ISLI Risk Science Institute. *Regul Toxicol Pharmacol*. 1995;22:189–197.
58. Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: an extended follow-up. *J Occup Environ Med*. 2008;50:1306–1319.
59. Hansen J. Cohort studies of cancer risk among Danish workers exposed to TCE. In: Symposium on new scientific research related to the health effects of trichloroethylene; 2004; Washington, DC.
60. Raaschou-Nielsen O, Hansen J, Thomsen BL, et al. Exposure of Danish workers to trichloroethylene, 1947–1989. *Appl Occup Environ Hyg*. 2002;17:693–703.
61. Dhote R, Thiounn N, Debre B, Vidal-Trecan G. Risk factors for adult renal cell carcinoma. *Urol Clin North Am*. 2004;31:237–247.
62. Leigh JP. Occupations, cigarette smoking, and lung cancer in the epidemiological follow-up to the NHANES I and the California Occupational Mortality Study. *Bull NY Acad Med*. 1996;73:370–397.
63. Bang KM, Kim JH. Prevalence of cigarette smoking by occupation and industry in the United States. *Am J Ind Med*. 2001;40:233–239.
64. Fevotte J, Charbotel B, Muller-Beaute P, Martin J, Hours M, Bergeret A. Case-control study of renal cell cancer and occupational exposure to trichloroethylene. Part 1: Exposure Assessment. *Ann Occup Hyg*. 2006;50:777–787.

**Table 1. TCE Worker Studies: Description of Cohort and Case-Control Studies and Summary of Exposure Levels and Exposure Assessment Methods**

First Author, Year, (Ref no.)	Workforce Size (n)	Person-Years	Cohort Description	Quantitative or Semi-Quantitative Exposure Estimates <sup>1</sup>	Type of Work or Work Activity	TCE Exposure Method/Comments	Reported Relative Risks and 95% Confidence Intervals for Kidney Cancer
<b>Group I Cohort Studies</b>							
Axelsson 1994 (45)	1670	23,516	Male workers $\leq 79$ years, biomonitoring for TCE from 115 facilities in Sweden 1955-1975. Cancer incidence follow-up through 1987.	Majority (81%) uTCA < 50 mg/L, which corresponds to an average air exposure ~ 20 ppm 100 mg/m <sup>3</sup>	Facility where TCE was used. Free surveillance was offered to workers.	Urinary TCA biomonitoring: Exposure indices: 1) mean uTCA all urine samples 2) highest mean uTCA across for 3-year period	SIR = 1.16 (0.42-2.52) 6 cases among workers < 79 years old
Anttila 1995 (46)	3974 Total 3,089 (TCE)	71,800 Total 59,905 (TCE)	Finnish male (n = 2050) and female (n = 1924) solvent workers biomonitoring for TCE. Over 600 different worksite or sampling laboratory codes. Follow-up (cancer incidence) 1967-1992.	uTCA Before 1970 (median): Men: 80-90 $\mu$ mol/L ~ 40-50 ppm Wom: 60-80 $\mu$ mol/L ~ 30-40 ppm uTCA Overall: (median) Men 48 $\mu$ mol/L ~ 35 ppm Women 63 $\mu$ mol/L ~ 40 ppm	TCE used primarily in degreasing or cleaning of metal surfaces. Also used in rubber work, gluing, dry cleaning, and as a component in cleaning fluid.	Urinary TCA concentrations measured 1965-1982. An average of 2.5 measurements conducted per worker.	Yrs since first measurement: All yrs: SIR=0.87 (0.32-1.89) 0-9 yrs SIR=0.53 (0.01-2.95) 10-19 yrs SIR=1.39 (0.45-3.24) 20+ yrs (0 cases)
Morgan 1998 (42)	20,508 Total 4,733 (TCE)	461,617 Total 105,852 (TCE)	Worked at Aerospace manufacturing site (Arizona), 1950-1985. The total cohort consisted of 13,742 men and 6,766 women. Follow-up (mortality) from 1950-1993.	"Highest levels near 50 ppm" [Based on IH studies assume range of 30-50 ppm]	Most TCE exposure occurred in vapor degreasing between 1952 and 1977. Potential exposure from drinking water at the plant.	Job-exposure matrix (JEM) defined TCE subcohort (high/medium/low/none). High (9): work on degreaser, medium (4): near degreaser, Low (1): occasional contact or proximity to degreaser.	Standardized Mortality Analysis: Any TCE: SMR=1.32 (0.6-2.6) "Low" TCE: SMR=0.47 (0.01-2.62) "High" TCE: SMR=1.78 (0.7-3.7) Internal Cohort Analysis: Cumulative Low: RR=0.3 (0.04-2.4) Cumulative High: RR=1.6 (0.7-3.7) Peak High: RR=1.9 (0.8-4.2)
Blair 1998 (43)	14,457	NR	Update of Sprittas (1991). Male (n = 10,730) and female (n = 3727) workers, aircraft maintenance facility (Utah), with at least one year of work experience, 1952-1957. Follow-up (cancer mortality and incidence) through 1990.	Rough estimates: 600 ppm - 1934-54 400 ppm - 1955-67 200 ppm - 1968-78 15 ppm - desktop cleaning Note: "numbers should not be interpreted as ppm"	TCE used primarily in vapor degreasers to remove oils or other contaminants (large parts); cleaning small electrical parts with squeeze bottles. After 1978 "Cold state" TCE discontinued in degreasers.	Walk-through surveys, interviews, historical record review, chemical inventory, review of available industrial hygiene data.	Mortality Analyses: Overall RR=1.6 (0.5-5.1) Males (Cumulative TCE unit yrs) No TCE RR=2.5 (0.7-8.9) < 5 U-yrs RR=2.0 (0.5-7.6) 5-25 U-yrs RR=0.4 (0.1-4.0) 25+ U-yrs RR=1.2 (0.3-4.8)

Ritz 1999 (44)	3,814 120,237	Male uranium processing workers (Ohio). Follow-up (mortality) from 1951 through 1989. Risk estimates only for bladder and kidney cancer combined.	Eighty percent of cohort had some TCE exposure, non classified as heavy. 2,792 workers: "light" TCE exp 179 workers; "moderate" TCE [Assume low exposure < 10 ppm]	Male uranium processing workers – used TCE and other chemicals, 1952-1977	IH classified TCE exposure categories: none (0), light (1), moderate (2), heavy (4).	All workers: SMR=0.65 (0.2-1.5) Lag 15 yrs by duration:* >2 yrs RR=1.03 (0.3-3.7) >5 yrs RR=1.02 (0.3-4.1) Duration, "Light" TCE Exp*: 2-10 yrs RR=1.9 (0.6-6.4) 10 yrs + RR=0.8 (0.1-40.0)
----------------------	------------------	---	--	---	--	---

First Author & Year	Workforce Size (n)	Person-Years	Cohort Description	Quantitative or Semi-Quantitative Exposure Estimates	Type of Work or Work Activity	TCE Exposure Method/Comments	Reported Relative Risks and 95% Confidence Intervals for Kidney Cancer
Boice 1999 (41)	77,965 Total 2,267 (routine TCE exposure)	1,889,795 Total 66,183 (TCE)	Aircraft manufacturing (Burbank, California) workers (men: n = 62,477; women: n = 15,488). Cancer (mortality) follow-up between 1960-1991.	~ 3,000 workers "intermittent" exposure ~ 2,075 workers "routine" exposure No air sampling prior to 1970s. [Based on IH data - assume range of 30-50 ppm for aerospace workers]	Aerospace workers mainly: - Process equip oper & helpers - Electrolaters - Metal band assemblers - Sheet metal formers TCE primary organic solvent used in vapor degreasers until 1966.	Walk-through surveys, interviews, review of available industrial hygiene data, and job descriptions. Toured similar facilities. Accounted for ventilation, respiratory protection.	Routine TCE Exposure: All Workers: SMR=0.99 (0.4-2.0) <1 yrs: SMR=0.97 (0.4-2.5) 1-4 yrs: SMR=0.19 (0.02-1.4) 5+ yrs: SMR=0.7 (0.2-2.1) SMRs less than 1.0 for: assembly, fabrication, processing, and maintenance workers
Hansen 2001 (24)	803	16,730	Danish male (n = 658) and female (n = 145) workers 275 companies. Follow-up (cancer incidence) was between 1969 - 1996.	uTCA: (Mean/median) $\mu$ mol/L 1947-89: 40/15 1947-64: 62/25 1965-73: 43/15 1974-79: 30/10 1980-89: 9/2	Air Monitoring (mg/m <sup>3</sup> ) 1947-89: 101 ~ 20 ppm 1974-79: 372 ~ 75 ppm 1980-89: 79 ~ 15 ppm Workers from 275 companies, uTCA or breathing zone air measurements, 1947-1989.	Urinary TCA or breathing zone TCE measurements. Average of 2.2 measurements per worker. The largest group: metal and iron industry.	Cancer incidence risk in 803 workers: Men: SIR=0.9 (0.2-2.6) Women: SIR=2.4 (0.03-14.0) Combined: SIR=1.1
Raascho u-Nielsen 2003 (25) [IH data from Raascho u-Nielsen 2002] (59)	40,049 Total 14,360 (TCE)	706,317 Total 339,486 (TCE)	Danish blue collar workers from 347 TCE-using companies. Men contributed 588,047 p-y and women contributed 118,270 p-y. Follow-up (cancer incidence) was between 1968-1997.	uTCA (means mg/L): 1947-53 78 ~ 50 ppm 1960-64 58 ~ 40 ppm 1970-74 49 ~ 35 ppm 1980-85 14 ~ 10 ppm TCE air measurements (total): 1950s: 586 mg/m <sup>3</sup> ~ 117 ppm 1960s 318 mg/m <sup>3</sup> ~ 63 ppm 1970s 198 mg/m <sup>3</sup> ~ 40 ppm 1980s 75 mg/m <sup>3</sup> ~ 15 ppm	Iron & metal workers: Air (mean/medians) mg/m <sup>3</sup> 1947-59: 693/323 ~ 138/65 ppm 1960-69: 322/261 ~ 65/52 ppm 1970-79: 302/104 ~ 60/21 ppm 1980-89: 70/27 ~ 14/1.4 ppm Electronics workers: Air (mean/medians) mg/m <sup>3</sup> 1947-59: 125/109 ~ 25/22 ppm 1960-69: 202/198 ~ 40/40 ppm 1980-89: 42/4 ~ 8.4/0.8 ppm	Historical IH measurement files. Predictor variables for TCE exposure: 1) size of company, 2) duration of exposure, 3) year of first exposure. Cohort restricted to workers from smaller companies (< 200) assuming increased likelihood of TCE-exposure. Most common types of workers: "metal work" (54%), electronics workers (11%).	Men: SIR=1.2 (0.97-1.48) Women: SIR=1.2 (0.56-2.11) Subcohort SIR=1.4 (1.0-1.8) # employees: < 50 SIR=0.7 (0.3-1.4) 50-100 SIR=1.6 (1.0-2.4) 101-200 SIR=1.2 (0.8-1.6) Duration of employment (mean): < 1 yr: SIR=0.8 (0.5-1.4) 1-4 yr: SIR=1.2 (0.8-1.7) 5+ yr: SIR=1.6 (1.1-2.3) Yr first employment (mean): < 1970: SIR=1.7 (1.2-2.3) 1970-79: SIR=0.7 (0.4-1.2) 1980+: SIR=0.9 (0.4-1.7)
Zhao 2005 (40)	5,049 (incidence cohort)	80,784 (estimated by mean duration of employment)	Male workers employed before 1980 in the aerospace division of SSSL (Rockwell/Rocketdyne facility). Follow-up (incidence cohort) started in 1988 and continued through 2000.	Mean cum exp score = 10.2 Median cum exp score = 8.0 [Based on IH data - assume range of 50-100 ppm]	TCE exposure occurred during cleaning of rocket engines, also used as a general degreasing solvent to clean metal parts.	Industrial hygiene review, walk-through visits, interviews with managers and workers, historical facility reports. JEM constructed: high, medium, low, none.	Mortality Analysis: Medium TCE: RR=1.4 (0.5-4.2) High TCE: RR=2.0 (0.5-8.3) Incidence Analysis: Medium TCE: RR=1.9 (0.6-6.2) High TCE: RR=4.9 (1.2-19.6)
Boice 2006 (39)	41,351 all Rocketdyne workers	56,286 Test stand mechanics 254,198 Santa Suzanna Facility 1,138,610 All Rocketdyne	Rocketdyne workers (men: n = 7083; women: n = 1289) employed at the Santa Susana Field Laboratory (SSFL) (California), a rocket engine testing facility. Cancer (mortality) follow-up was between 1948-1999.	[Based on IH data - assume range of 50-100 ppm]	Test stand mechanics had the greatest potential for TCE exposure. Others (maintenance, machinists) had much less exposure (different from Zhao et al assessment).	Job titles extracted from work and personnel listings (phone directories). Walk-through surveys and personnel interviews.	Mortality Analysis - Test Stand Mechanics: Test Stand Mech: SMR=1.8 (0.8-2.5) Any TCE: SMR=2.2 (0.9-4.6) Years as Test Stand Mechanic: < 1 yrs RR=1.3 (0.2-9.3) 1-4 yrs RR=2.1 (0.7-6.2) 5+ yrs RR=2.1 (0.6-7.1) Years Engine Flush: < 4 yrs RR=2.5 (0.3-4.4) 4+ yrs RR=3.1 (0.7-13.2)

**Group II Cohort Studies**

First Author & Year	Workforce Size (n)	Person-Years	Cohort Description	Quantitative or Semi-Quantitative Exposure Estimates	Type of Work or Work Activity	TCE Exposure Method/Comments	Reported Relative Risk
Carabrant 1988 (51)	14,067	222,100	Aircraft manufacturing (San Diego County, California). Male (n = 11,898) and female (n = 2169) workers. Follow-up (cancer mortality) from 1958 through 1982.	[Based on IH studies assume range of 30-50 ppm]	Aircraft manufacturing: Assume degreasing/solvent exposures. TCE mentioned.	Estimated that 3.7% of cohort had TCE exposure, based on interviews of small sample of workers.	Total Cohort: SMR = 0.93 (0.5-1.6)
Blair 1989 (50)	1,767 (Inspectors)	36,720	Male U.S. Coast Guard marine inspectors (1942-1970). Follow-up (mortality) through 1979.	[Cannot be determined or estimated from IH data, highly variable given inspectors changing job sites]	Male U.S. Coast Guard marine various chemicals. TCE was not evaluated as a separate exposure.	Job title analyses only	Total Cohort (n=1,767) SMR = 1.06 (0.2-3.1)
Costa 1989 (48)	8,626	132,042	7676 men and 950 women. Follow-up (mortality) between 1954-1981 (urinary system cancers).	[Based on IH studies assume range of 30-50 ppm]	Aircraft manufacturing workers (Italy). Assume degreasing/solvent exposure, TCE..	Solvents listed among hazardous substances used; TCE not specifically mentioned.	Total Cohort All Yrs SMR = 0.7 (0.3-1.5) Hired < 1954 SMR=0.4 (0.1-1.3) Hired > 1954 SMR=1.6 (0.4-4.0)
Selden & Ahlborg 1991 (49)	2,176	21,463	Male Swedish Armed Forces (SAF). Follow-up (cancer incidence) between 1975-1983.	[Cannot be determined or estimated, very limited TCE exposure associated with degreasing activities]	Jet fuel exposure during three-year period 1972-1974.	TCE used for metal degreasing to a limited extent. No data on individual exposures.	Total Cohort (n=2,176) SMR = 1.03 (0.2-3.0)
Sinks et al. 1992 (47)	2,086	36,744	Workers from a paperboard manufacturing and processing plant (Georgia). Follow-up (cancer mortality and incidence) between 1957-1998.	[TCE exposure not demonstrated - may have had little opportunity for exposure]	Chemicals used in finishing department, ink mixing, storage rooms	TCE listed on MSDS forms, no exposure assessment.	Mortality Analyses: All workers: SMR=1.4 (0.0-7.7) Incidence Analyses: All workers: SIR=3.7 (1.4-8.1) Finishing Dept. SIR=16.6 (1.7-453.1)
Henschler et al. 1995 (52)	169 (Exposed) 190 (Unexposed)	5,188 (Exposed) 6,100 (Unexposed)	Male cardboard manufacturers, worked at least 1 year (Germany), 1956-1975. Follow-up (incidence) through 1992.	Favorite estimates: 135 ppm (range 60-270) Cherrie estimated levels: 10 - 225 ppm for hot degreasing peaks to 2000 ppm	TCE used in: 1) cardboard machine area (parts cleaned twice/week ~ 4-5 hours) 2) locksmith electrician shop - continuous exposures, lower concentrations, 3) cleaning floor and clothing, 1956 to 1975.	Walk-through surveys and interviews with long-term employees.	Cancer Incidence by Comparison Group: German Data: SIR=9.66 (3.1-22.6) Denmark Data: SIR=7.97 (2.6-8.7) Distribution of cases: board machining (2) locksmith (1) electricians (2)
Chang 2003 (26)	86,868	1,022,094	Workers (men: n = 16,133; women: n = 70,735). Follow-up (mortality) between 1985-1997	[Levels reported in electronics facility (Singapore) - 30ppm - however no TCE subcohort identified]	Electronics manufacturing factory (Taiwan). No job title or subgroup analyses.	TCE in wells near facility, assume worker exposures, no specific data.	Cohort Mortality Analyses: Males: SMR=0.0 (no cases obs) Females SMR=1.18 (0.2-3.4)

Case-control Studies							
First Author & Year	Source of Cases (n)	Source of Controls (n) <sup>2</sup>	Confounders Evaluated	Quantitative or Semi-Quantitative Exposure Estimates	Type of Work or Work Activity	TCE Exposure Method/Comments	Reported Relative Risk
Siemiatycki 1991 (33)	Metropolitan Montreal hospitals. (177 cases)	Hospital controls: metropolitan Montreal. Population controls: electoral lists & RDD. (533 population controls; 2481 other cancers – 2 <sup>nd</sup> control group)	Age, sex, smoking.	[“Any” and “substantial” categories - cannot be determined or estimated from IH data. Aircraft mfg and metal fabrication – can assume 30-50 ppm based on IH studies]	“Widely used in vapor degreasing since 1930s”. Solvent for adhesives and lubricants. Main Occupations: Machinist, aircraft mechanics, industrial equipment mechanics.	Self reported occupational history classified into TCE JEM - two categories “any exposure” and “substantial” exposure.	TCE Exposure classification: Any Exposure OR=0.8 (0.4-2.0) Substantial Exp OR=0.8 (0.2-2.6) Occupations/Industries: Aircraft Mfg (any) OR=1.0 (0.6-1.8) Aircraft Mfg (sub) OR=1.0 (0.4-2.7) Metal Fab & Mach (a) OR=1.0 (0.7-1.6) Metal Fab & Mach (s) OR=1.3 (0.8-2.3)
Greenland 1994 (35)	Nested case-control study transformer assembly workers (12)	Non-cancer deaths. (1202 total controls)	Age, year of death.	[Based on IH studies assume range of 30-50 ppm]	TCE was used from 1930 to 1977 as a degreaser in plant.	Work histories, TCE JEM: no exposure (0) or any exposure (1).	Mortality Analysis: Any TCE exp: OR=0.99 (0.3-3.32)
Vamvakas et al. 1998 (34)	Kidney cancer patients, nephrectomy in German hospital. (58 cases)	Accident wards from three hospitals < 20 km from case hospital, 1993. (84 controls)	Age, gender, obesity, high blood pressure, smoking, diuretic intake.	[Cannot be determined or estimated from IH data]	Occupational history questionnaire. Interview with patients or their colleagues/relatives regarding work history and conditions.	Odds ratios by exposure groups: +++ OR=11.4 (2.0-66.8) ++ OR=11.9 (2.6-55.6) + OR=6.6 (0.5-87.8) All age groups: OR=9.0 (2.9-27.8)	
Dosemeci et al. 1999 (36)	Minnesota Cancer Surveillance System. (438 cases)	Population based controls. (687 controls)	Age, smoking, hypertension, use of diuretics and or anti hypertension drugs, and BMI.	Overall 13% of cases exposed to TCE, 10% of control subjects exposed. [Cannot be determined or estimated from IH data]	Personal interviews with patients and next of kin, occupational history questionnaires, JEMs developed by NCI.	ORs for TCE exposure by sex: Males: OR=1.0 (0.6-1.7) Females: OR=1.96 (1.0-4.0) Both Sexes OR=1.3 (0.9-1.9)	

Results by job and job/task matrices: German	
<p>Pesch et al. 2000 (7)</p> <p>Kidney cancer patients from five German regions. (935 cases)</p> <p>Frequency matched controls by age, sex and area from local residency registry. (4298 controls)</p>	<p>JEM – Cannot estimate exposure levels. [Degreasing activities could range from 30-100 ppm based on European IH data (Raaschou-Nielsen, 2002)]</p> <p>Age, study center, smoking.</p> <p>Exposure indices incorporate duration, probability and intensity of TCE exposure</p> <p>Questionnaire ascertaining occupational history. Exposures defined according to British JEM, German JEM and job-task exposure matrix (JTEM).</p> <p>Job exposure matrix:                      High: OR=1.1 (0.7-1.8)                      Medium: OR=1.1 (0.9-1.4)                      Substantial: OR=1.3 (0.9-1.8)</p> <p>Job, Task Exposure Matrix:                      Medium: OR=1.3 (1.0-1.8)                      High: OR=1.1 (0.8-1.5)                      Substantial: OR=1.3 (0.8-2.1)</p> <p>Job Titles:                      Metal Processing OR=1.1 (0.7-1.8)                      Metal Cleaning OR=1.3 (0.7-2.3)</p>
<p>Bruning et al. 2003 (27)</p> <p>Kidney cancer patients from Amsberg, Germany; urology department. (154 cases)</p> <p>Hospital controls from local surgery departments without dementia or cancer, matched by age and sex. (401 controls)</p>	<p>[Self report- cannot provide exposure estimates. Degreasing activities could range from 30-100 ppm based on European IH data (Raaschou-Nielsen, 2002)]</p> <p>Age, sex, smoking.</p> <p>Self reported work history (occupational questionnaire) and TCE use, classified according to British JEM.</p> <p>Self reported TCE:                      Self report: OR=2.5 (1.4-4.5)                      Self report by duration:                      &lt;10 yrs OR=3.8 (1.5-9.3)                      10-20 yrs OR=1.8 (0.7-4.8)                      20+ yrs OR=2.7 (0.8-8.7)</p> <p>Industry, job title or work activity:                      Metal degreasing OR=5.6 (2.3-13.3)                      Degreasing (JEM) OR=1.0 (0.4-2.5)                      Iron/Steel Industry OR=1.2 (0.3-4.5)                      Contact w/ metals OR=1.5 (0.97-2.4)</p>

First Author & Year	Source of Cases (n)	Source of Controls (n) <sup>2</sup>	Confounders Evaluated	Quantitative or Semi-Quantitative Exposure Estimates	Type of Work or Work Activity	TCE Exposure Method/Comments	Reported Relative Risk
Charbotel et al., 2006 (28)	Kidney cancer cases from a region in France with a TCE-using screw cutting industry. (86 cases)	Controls residents in the geographic study area at the time of case diagnosis, matched on age and gender. (316 controls)	Matched on gender and year of birth. Adjusted for tobacco and BMI. [some analyses also adjusted for cutting fluids and other petroleum oils]	Arve Valley (screw cutting): 1960s air: 180-600 ppm 1960s TCA 220-505 mg/L 1975 air: 70-800 ppm washing areas 2- 50 ppm adjacent areas 1984 air: up to 200 ppm within 6m of degreasing machine Of screw cutters: 72% < 35ppm 13% > 50 ppm 5% > 75 ppm	Mostly screw cutting industry, where degreasing and solvent use common. Also general TCE use as solvent in other industries.  Exposure categories in epidemiologic analysis: Very low: 1-35 ppm Low: 35-50 ppm Medium: 50-75 ppm High: 75-100 ppm Very High: > 100ppm	Interviews, questionnaire, Task specific exposure matrix: <u>Open cold degreaser:</u> 1.5-18 ppm; 50 ppm above tank <u>Open hot degreasing:</u> 120 ppm; 300 ppm above tank. <u>Half - Open Hot degreasers:</u> 35ppm; 75 ppm above tank <u>Emptying and refilling degreaser:</u> average levels: 300 ppm Hand dipping: 30 ppm assigned After	Results by TCE Exposure Index: Any TCE exp OR=1.6 (0.95-2.8) Low cuml exp OR=1.6 (0.8-3.5) Med cuml exp OR=1.2 (0.5-2.8) High cuml exp OR=2.2 (1.0-4.6) High confidence in TCE exposure assign: Any TCE OR=1.9 (0.9-4.0) Low cuml exp OR=0.9 (0.1-7.4) Med cuml exp OR=1.0 (0.3-3.7) High cuml exp OR=3.3 (1.3-8.7) Other Exposure measures: Any metal work: OR=1.02 (0.6-1.8) Screw cutting shops OR=1.3 (0.7-2.3) Metal workers OR=1.0 (0.6-1.8)

**Notes:**

- A. Relationship between biological measurements and airborne levels (Fevotte et al): B. 1 ppm ~ 5.27 mg/m<sup>3</sup>
- low UTCA + TCE < 40 mg/g ~ < 30 ppm
- med UTCA + TCE 40-100 mg/g ~ 30-60 ppm
- high UTCA + TCE 100-170 mg/g ~ 60-80 ppm
- very high UTCA + TCE 170-300 mg/g ~ > 80 ppm

1. Comments in italics indicate imputation by authors based on available indicated hygiene literature (Raaschou-Nielsen, 2001, 2002; Fevotte, 2006; Bakke, 2007).
2. RDI = random digit dialing