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Trichloroethylene Issue Paper 4:

Issues in Trichloroethylene Cancer Epidemiology

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DISCLAIMER

This issue paper does not represent and should not be construed to represent any agency determination or policy. This issue paper has not been externally reviewed. The information is being provided to assist the National Academy of Sciences in their review of the scientific issues surrounding trichloroethylene health risks.

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LIST OF ABBREVIATIONS AND ACRONYMS

IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
JEM	Job-exposure matrix
JTEM	Job-task-exposure matrix
MOR	Mortality odds ratio
NAS	National Academy of Sciences
NHL	Non-Hodgkin's lymphoma
NTP	National Toxicology Program
OR	Odds ratio
PMR	Proportional mortality ratio
RCC	Renal cell carcinoma
REAL	Revised European-American Lymphoma (classification)
SAB	Science Advisory Board
SEER	Surveillance, Epidemiology, and End Results (program)
SES	Socioeconomic status
SIR	Standardized incidence ratio
TCA	Trichloroacetic acid
TCE	Trichloroethylene
U–TCA	Urinary TCA
VHL	Von Hippel-Lindau (gene)

PREFACE

Publication of these issue papers is a part of EPA's effort to develop a trichloroethylene (TCE) human health risk assessment. These issue papers were developed to provide scientific and technical information to the National Academy of Sciences (NAS) for use in developing their advice on how to best address the important scientific issues surrounding TCE health risks. As such, these papers discuss a wide range of perspectives and scientific information (current through Fall 2004) on some of these important issues, highlighting areas of continuing uncertainty and data that may be relevant. They are intended to be useful characterizations of the issues, not a presentation of EPA conclusions on these issues. The papers have undergone internal review within EPA, but they have not been externally reviewed. The concepts presented in these papers will eventually be addressed in EPA's revised risk assessment of TCE, after the advice from the NAS, along with comments from the EPA Science Advisory Board and the public, as well as recently published scientific literature, have been incorporated.

AUTHORS AND CONTRIBUTORS

Many individuals contributed to the completion of this set of tichloroethylene (TCE) issue papers. The TCE Risk Assessment Team identified the topics covered by the papers and prepared them for submission to the National Academy of Sciences. The authors wish to thank Dr. Peter Preuss, Dr. John Vandenberg, Mr. David Bussard, Mr. Paul White, Dr. Bob Sonawane, Dr. Hugh Barton, Dr. Aparna Koppikar, Mr. David Bayliss, Dr. William Wood, and Dr. Ila Cote for their input and comments.

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THE TCE ISSUE PAPERS

BACKGROUND

In August 2001, a draft, *Trichloroethylene (TCE) Health Risk Assessment: Synthesis and Characterization,* was released for external review. This draft assessment drew on 16 "state-of-the-science" papers published as a supplemental issue of *Environmental Health Perspectives* (Volume 108, Supplement 2, May 2000). Subsequent to its release, EPA's 2001 draft assessment underwent a peer review by a panel of independent scientists through EPA's Science Advisory Board (SAB), which provided a peer review report in December 2002. In addition, the public submitted more than 800 pages of comments to EPA during a 120-day public comment period.

There are a number of important issues that EPA will need to examine as it moves forward in revising the draft TCE assessment. These include issues raised not only in the SAB peer review and public comments, but also by new scientific literature published since the release of the state-of-the-science papers and EPA's 2001 draft assessment. Some of this research is specific to the study of TCE or its metabolites while some of it describes advances in scientific fields more generally but which have potential relevance to characterizing the human health risks from TCE.

In February 2004, EPA held a symposium so that authors of some of the TCE-specific research that had been published since the release of the draft assessment could present their findings in more detail. This symposium represented only a limited cross section of recently published research, but was reflective of the breadth of new relevant science that EPA will consider in revising the assessment (the presentation slides and a transcript of the meeting are available separately on EPA's website and have already been sent to the NAS).

In 2004, EPA, in cooperation with a number of other federal agencies, initiated a consultation with the National Academy of Sciences (NAS) to provide advice on scientific issues related to the health risk assessment of TCE. It was recognized that a review by an NAS panel of the important scientific issues would be beneficial and informative to clarify the state-of-the-science as EPA moves forward in completing its health risk assessment. A charge was developed for the NAS through an Interagency Workgroup led by the White House Office of Science and Technology Policy.

PURPOSE OF THE TCE ISSUE PAPERS

Although EPA will need to address all of the issues identified in the charge to the NAS panel in updating its assessment, EPA would like to focus the NAS panel's attention on a subset

of issues that EPA believes to be most critical in developing a revised risk assessment, as summarized in four issue papers developed by EPA staff:

1. Issues in trichloroethylene pharmacokinetics;
2. Interactions of trichloroethylene, its metabolites, and other chemical exposures;
3. Role of peroxisome proliferator-activated receptor agonism and cell signaling in trichloroethylene toxicity; and
4. Issues in trichloroethylene cancer epidemiology.

Each paper provides an overview of the science issues, a discussion of perspectives on those issues (including the SAB and public comments), and an outline of some of the recently published scientific literature. The pharmacokinetics issue paper also summarizes results from a recent collaboration with the U.S. Air Force on TCE pharmacokinetics, as well as EPA's planned approach for further refinement of the pharmacokinetic modeling of TCE and its metabolites. These scientific areas were selected because they are (a) critical to the hazard and/or dose-response characterization of TCE; (b) scientifically complex and/or controversial; and (c) areas in which substantial important scientific literature has been recently published. The input from the NAS on the topics described in the issue papers, as well as other topics put forth in the charge to the NAS, should help to strengthen EPA's revised TCE assessment.

NEXT STEPS

The advice from the NAS, along with comments already received from the EPA SAB and the public, as well as recently published scientific literature, will be incorporated into a revised EPA risk assessment of TCE, strengthening its scientific basis. Because of the substantial amount of new information and analysis that is expected, the revised draft of the assessment will undergo further peer review and public comment prior to completion.

1. INTRODUCTION AND PURPOSE

Epidemiologic evidence holds a unique place in an assessment of potential environmental risk for a number of reasons. Well-conducted epidemiologic studies that show a positive association between an agent and a disease are accepted as the most convincing evidence about human risk (NRC, 1983). First, epidemiologic observations are from humans, the target population for risk assessment practices. Inferences of human risks based on data from epidemiologic studies can have fewer associated uncertainties than inferences of human risks based on data from rodent species. Hertz-Picciotto (1995) notes uncertainties associated with uncontrolled bias or errors in exposure assessment are likely to be less than those stemming from interspecies extrapolation. Additionally, the patterns and exposure concentrations of epidemiologic-studied populations are likely to be closer and more similar to the exposure scenarios of populations for which risks are inferred than exposures of 2-year rodent bioassays. Furthermore, national and international organizations such as the National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC) place greatest weight on epidemiologic evidence in their overall evaluation of human carcinogenicity (NTP, 2002; Siemiatycki et al., 2004). Although epidemiologist have become more introspective with questions on the utility of epidemiologic studies for providing insight on associations of relative risks of 2.0 or lower (Taubes, 1995, Monson, 1980), epidemiologic evidence continues to inform the hazard step in risk assessment and is increasingly examined for dose-response inferences. Epidemiologic data along with toxicological data and data from other biological sciences provide the foundation for toxicity evaluations of health risk assessment.

The purpose of this issue paper is twofold: (1) to provide the National Academy of Sciences (NAS) panel with an overview of the epidemiologic evidence on trichloroethylene (TCE) and the occurrence of cancer, highlighting the new literature published since the U.S. Environmental Protection Agency's (EPA's) external review draft, *Trichloroethylene Health Risk Assessment: Synthesis and Characterization* (U.S. EPA, 2001) and (2) to focus the NAS panel's advice on approaches to synthesizing the body of epidemiologic evidence as EPA moves forward in revising the draft TCE assessment. EPA asks the NAS panel to focus on the issues listed below and discussed in Section 3 as they review the epidemiologic evidence on TCE exposure. NAS input on how EPA can address the following questions would help to strengthen EPA's revised assessment:

- What qualitative and/or quantitative approaches can best inform causal inferences of the TCE body of epidemiologic evidence?

- What are the strengths and limitations of the epidemiologic body of evidence on cancer occurrence and TCE exposure? Specifically, which studies carry a greater weight in the hazard evaluation?

    - For which site-specific cancers can studies of incidence carry greater weight for hazard identification than those of mortality?
    - What advice can NAS provide EPA on weighting the different exposure assessment approaches adopted in the TCE epidemiologic studies?

- What advice can NAS provide EPA on factors that may influence interpretation of epidemiologic observations on non-Hodgkin's lymphoma (NHL)?

- How appropriate and useful is applying meta-analysis methods to synthesize epidemiologic data on TCE, and what strategies could be employed to implement such an analysis?

This issue paper is not intended to provide a complete survey and synthesis of the scientific literature on TCE cancer epidemiology. Section 2 identifies the types of epidemiologic evidence on TCE and carcinogenicity, focusing on more recently published studies. It also provides brief details of the study designs employed by investigators, the site-specific cancers examined in these studies, and the information on potential TCE exposure collected for individual study subjects. The specific methodological issues that arise in analyzing and interpreting the epidemiologic studies are discussed in Section 3. EPA has received public comment on the epidemiologic evaluation in their external review draft TCE Health Risk Assessment (U.S. EPA, 2001) and these comments are also identified and discussed in Section 3.

2. EPIDEMIOLOGIC STUDIES ON CANCER EFFECTS AND TCE EXPOSURE

Three types of epidemiologic study designs are most commonly used to assess cancer occurrence and TCE exposure: (1) historical or retrospective cohort studies; (2) case-control studies; and (3) ecologic or community studies. Epidemiologic studies that evaluate TCE exposure and cancer occurrence are listed in Table 1. They include studies cited in the Wartenberg et al. (2000) analysis and literature published since 2000, identified from a search of the National Library of Medicine's PubMed database, (http://www.ncbi.nlm.nih.gov /entrez/query.fcgi) using the keywords "trichloroethylene epidemiology cancer." The *historical*

or retrospective cohort study follows a group or cohort[1] over time to assess vital status: alive at end of followup, lost to followup, or cause-specific morbidity or mortality of sick or deceased individuals. The cohort's health outcomes are compared to those of a reference group, usually cause-specific morbidity or mortality within the U.S. population or another country's population. Many of the TCE cohort studies assess mortality, with a few studies of cancer morbidity in groups of workers who have either documented or presumed exposure to TCE. In some cohort studies, investigators have assigned TCE exposure to individual study subjects. These cohort studies have adopted a number of approaches and include the use of biological (exposure) markers or the job-exposure matrix[2] (JEM). *Case-control* studies are retrospective studies in which exposure to a suspected agent, e.g., TCE, is determined among the individuals with the disease (cases) or without the disease (controls)[3]. Analytical designs such as cohort and case-control studies are generally relied on for identifying a causal association between human exposure and adverse health effects and are necessary to infer causality. *Ecologic studies* are descriptive epidemiologic studies that examine symptom or disease rates among populations in relationship to personal characteristics, such as age, gender, race, and temporal or environmental conditions. Responses, exposure indices, and covariates in an eccological study are at a community level, and information about individual exposure is lacking. Descriptive studies such as ecologic studies, alone cannot provide direct evidence of causation, although their results can provide supporting data concerning a possible causal relationship (NRC, 2005).

2.1. RECENT COHORT STUDIES

More precise exposure assessment methods for qualitative identification of TCE exposure (versus, for instance, nonspecific solvent exposure) and for developing quantitative exposure metrics are increasingly included in cohort studies published since 1990. Exposure assessment in older cohort studies included TCE as a larger category of organic solvents. These studies were unable to attribute TCE exposure to an individual study subject, thus limiting inferences about associations between TCE, specifically, and site- or cause-specific cancer. For epidemiologic data to be useful in determining whether a causal association exists between health effects and exposure to an agent, adequate characterization of exposure information is vital. In general, EPA assigns greater weight to studies with more precise and specific exposure estimates.

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[1] Cohort is defined as any designated group of individuals followed over a period of time.

[2] A cross classification of jobs and occupational exposures (Garcia and Checkoway, 2003).

[3] A case group is identified with the health endpoint of interest along with the control group without the health endpoint of interest.

A large body of the TCE cohort studies has described mortality in occupational cohorts, with cancer incidence assessed as a health endpoint in reports using cancer registries from Nordic countries, registries with documented high accuracies of recorded cancer incidence. Two incidence studies on TCE exposure have been published since EPA's draft assessment in 2000. Hansen and colleagues (2001) reported a study of cancer incidence in 803 Danish workers with TCE exposure as inferred from biomonitoring of urinary trichloroacetic acid (TCA) (U-TCA) or from breathing zone measurements. The accompanying papers of Raaschou-Nielsen et al. (2001, 2002) more fully describe exposure assessment methods for this cohort study. Hansen (2004) reported at an EPA Science Symposium on TCE that the hypothesis of this study was to examine associations between TCE exposure and liver and biliary tract cancers, kidney cancer, cervical cancer, and lung and testicular cancers based on previous epidemiologic or bioassay observations. This cohort of 806 subjects was followed from 1968 to 1996 with 128 cancers (109 male, 19 female) observed and 123.4 cancers (104.8 male, 18.6 female) expected standardized incidence ratio (SIR) = 1.04, 95% confidence interval (CI): 0.9, 1.2). Expected numbers of cancer are derived from cancer rates of the Danish populations for the study period. A second incidence cohort study of 40,049 blue-collar workers further examines the possibility of an association of elevated risks of certain site-specific cancers with exposure to TCE (Raaschou-Nielsen et al., 2003). A total of 3,244 incident cancer cases were observed between 1968 and 1997. No information was available on the TCE exposure of individual subjects; however, Raaschou-Nielsen et al. (2003) attempted to increase the likelihood of a larger proportion of study subjects with TCE exposures by examining blue-collar workers and comparing their cancer incidence experiences with white-collar workers, and by accounting for a number of factors previously identified in industrial hygiene surveys that increased the potential for TCE exposure (Raaschou-Nielsen et al., 2001; 2002).

Both studies report statistically significant elevated relative risks for (NHL)[4]. Hansen et al. (2001) concluded that their study "identified increased SIRs for non-Hodgkin's lymphoma and for cancer of the esophagus and cervix." The conclusions of Raaschou-Nielsen et al. (2003) more strongly associated the increased NHL risk with TCE exposure. Raaschou-Nielsen et al. (2003) noted "the present results and those of previous studies suggest that occupation exposure to TCE to past higher levels may be associated with elevated risk for NHL." NHL rates increase with increasing socioeconomic status (SES) (Raaschou-Nielsen et al., 2003); thus, the finding of an elevated incidence of NHL in this study of lower SES or "blue-collar" workers who comprise these two cohorts is noteworthy, given that SES is less likely to produce a false positive finding.

[4] Hansen et al. (2001): males, SIR = 3.5 (95% CI:1.5, 6.9), 8 cases; females, 0 cases observed, 0.3 cases expected; Raaschou-Nielsen et al. (2003): cohort, both sexes, SIR = 1.2 (95% CI:1.0, 1.5), 96 cases; subcohort with expected higher exposure levels, both sexes, SIR = 1.5 (95% CI:1.2, 2.0), 65 cases.

Both studies also reported statistically significant elevated relative risks for cervical cancer in women. The excess cervical cancer risks reported in both studies may be more related to social class given the higher incidence rates seen among females of lower versus higher social class (Raaschou-Nielsen et al., 2003). Hansen et al. (2001) reported that also noteworthy among males was the observation of five cases of liver and biliary passage cancer, three more cases than expected (SIR = 2.6, 95% CI: 0.8, 6.0). Of the five cases, two were cancers of the primary liver (1.1 expected) and three were cancers of the biliary tract (0.9 expected) (e-mail dated June 13, 2001, J. Hansen to C. Siegel Scott). No cases of liver or biliary tract cancers were observed among females (0.4 case was expected). Raaschou-Nielsen et al. (2003) reported an excess of gallbladder-biliary passage cancer in women (SIR = 2.8, 95% CI: 1.1, 5.8) but not men, and primary liver cancer risk in both men and women was close to that expected. Raaschou-Nielsen et al. (2004) also reported their study indicated an association between TCE exposure and renal cell carcinoma, which was unlikely to be explained by the lower SES status or by smoking patterns of the cohort[5].

An unexpected finding in Hansen et al. (2001) was an excess of esophageal cancer in males that was confirmed in the subsequent study of Raaschou-Nielsen et al. (2003)[6]. Examination of histological subtypes of esophageal tumors diagnosed from 1980 to 1996 from men born during the same period as the TCE study subjects revealed a higher proportion of the adenocarcinoma among TCE cases (83%) compared with 30% of 2,900 esophageal tumors in the Danish Cancer Registry reported as adenocarcinoma (Hansen et al., 2001). No major confounders are known for adenocarcinomas of the esophagus (Hansen, 2004); cigarette smoking and alcohol consumption are more strongly associated with squamous cell carcinoma (Crew and Neugut, 2004).

Obtaining incidence rates in populations other than those in Nordic countries is often difficult, and death certificates are widely used in epidemiologic research owing, in part, to the ease of obtaining this information from national databases where all deaths are recorded. A large number of cohort studies have assessed mortality, generally, using job title to infer exposure. A small number of cohort mortality studies examine aircraft maintenance workers and assign TCE exposure to subjects. These studies present cause-specific mortality risks for the TCE subcohorts. Three mortality studies have been published since EPA's draft assessment,

[5] Raaschou-Nielson et al. (2003): both sexes, cohort, SIR = 1.2 (95% CI: 0.9, 1.5), 76 cases; both sexes, subcohort with expected higher exposure levels, SIR = 1.4 (95% CI: 1.0, 1.8), 53 cases.

[6] Hansen et al. (2001): males, SIR = 4.2 (95% CI: 1.5, 9.2), 6 cases; females, 0 observed cases, 0.1 expected cases; Raaschou-Nielsen et al. (2003): adenocarcinoma, both sexes, cohort, SIR = 1.8 (95% CI: 1.2, 2l7), 23 cases; both sexes, subcohort with expected higher exposure levels, SIR = 1.7 (95% CI: 0.9, 2.9), 13 cases.

those of Chang et al. (2003a, b) and Stern et al. (2001). Chang et al. (2003a) is a proportional mortality ratio (PMR) analysis of deaths among Taiwanese electronic workers, with a fuller cohort analysis published as Chang et al. (2003b). The PMR study of Stern et al. (2001) examines deaths among U.S. construction workers belonging to a union affiliated with the AFL-CIO. All three investigations lack documentation of the TCE exposure of individual study subjects, and the studies provide no information to gauge the percentage of the cohort with potential TCE exposure. Furthermore, the cohort of Chang et al. (2003b) is of a young mean age, and a full latent period for cancer development has not yet elapsed.

2.2. CASE-CONTROL STUDIES

Studies of a case-control design can inform causal associations, and two studies published since 2000 are available on TCE exposure and site-specific cancers. A strength of the case-control design is a better efficiency compared with cohort studies for studying rarer outcomes such as cancer (Breslow and Day, 1980). Both recent studies are of renal cell carcinoma (RCC) and can allow a comparison with previous case-control studies and with findings in cohort studies. Pesche et al. (2004, 2000) examined RCC and occupational TCE exposure using two exposure assessment approaches, the JEM and the job-task-exposure matrix (JTEM). This study of 935 RCC cases and 4,298 population controls identified from 5 regions in eastern and western parts of Germany was adjusted for age, study center, and the number of pack-years smoking. A strength of the study is that exposure information is from participant interviews and not from interviews with a relative[7]. None of the RCC cases in the previous reports of Henschler et al. (1995) or Vamvakas et al. (1998), cases that arose from a cluster, were included in the case series of Pesche et al. (2000). Point estimates in males between RCC and TCE exposure were the same regardless of which exposure assessment was employed (substantial exposure: JEM, odds ratio (OR) = 1.3; JTEM, OR = 1.3). The ORs were not statistically significant, and exposure-response relationships were not observed; Pesche et al. (2000) attributed this finding to nondifferential exposure misclassification that would attenuate the estimate of risk.

The case-control study of Brüning et al. (2003) was designed to examine the hypothesis of an association between RCC and TCE exposure. This is a study of 134 RCC cases and 401 controls from hospitals or nursing homes in Germany who were matched to cases by sex and age. None of the kidney cancer cases in Henschler et al. (1995) or Vamvakas et al. (1998) were

[7] Interviews with relatives are termed “next-of-kin interviews” and are often obtained when cases or controls are deceased. The lack of direct and accurate information confirming whether subjects had exposure to TCE and at what levels, as may occur in interviews with relatives or other next-of-kin, can potentially introduce misclassification bias.

included in this report. Information on occupational TCE exposure was self assessed, obtained from face-to-face interviews with all cases and controls, except for 21 case subjects for whom information was obtained from next-of-kin interviews or inferred from information on job history using either expert-based JEM methods or an occupational exposure database. Brüning et al. (2003) reported "the logistic regression results, adjusted for age, gender, and smoking, confirmed a TCE-related renal cell carcinoma risk in this region." Using the occupational exposure database for a comparison of industries with and without TCE exposure, a significant excess risk was estimated for the longest held job in TCE-exposing industries (OR = 1.8, 95% CI: 1.01, 3.2). Any exposure in "metal degreasing" was an RCC risk factor (OR = 5.6, 95% CI: 2.3, 13.3). Self-reported narcotic symptoms, which Brüning et al. (2003) attribute to peak exposures, were associated with an excess risk (OR = 3.7, 95% CI: 1.8, 7.5). Both studies further suggest associations between RCC and TCE exposure but importantly, as Pesche et al. (2004) discuss, each study by itself does not provide clear evidence of an association.

The identification of altered excretion of kidney enzymes in TCE-exposed individuals with kidney cancer (RCC) and histopathological characteristics and gene mutations in these tumors can provide biological support or plausibility for observations in case-control studies. A high prevalence of multiple mutations of the Von Hippel-Lindau (VHL) gene has been previously reported in a series of renal cell tumors of TCE-exposed subjects (Brüning et al., 1997; Brauch et al., 1999), with Brauch et al. (1999) reporting a C > T transition at nucleotide 454, a mutation not found in peripheral lymphocytes or normal renal tissue from these individuals. A transition of nucleotide 454 has not been observed in other large mutational surveys of RCCs (Brauch et al., 1999), but a few observations of this mutation have been documented in VHL families (Weirich et al., 2002; Hes et al., 2000). The report of Brauch et al. (2004) extends their work with mutational analysis of 21 of the 39 non-TCE-exposed RCCs in Vamvakas et al. (1998), comparing findings in this group to mutational spectra analysis of 17 of the 19 original cases in Vamvakas et al. (1998) identified with TCE exposure reported in their 1999 publication. These reports are suggestive of genetic alterations as associated with RCC risk, and TCE-exposed cases show a higher percentage of alterations, some of which may indicate very specific changes to the VHL gene. The reports of Bolt et al. (2004) and Green et al. (2004) of a mixed pattern of increased concentrations of tubular maker proteins in the urine of TCE-exposed compared to non-exposed subjects suggest altered integrity of renal tubular cells, but such changes may not necessarily predict RCC.

2.3. COMMUNITY STUDIES

Community epidemiologic studies can augment observations in analytical cohort or case-control studies. Community studies on TCE exposure are of residents with exposure determined

by place of residence of water supply; these studies can include individuals of varying ages and susceptibilities, as compared to an occupational population that is of a more restricted age range and health status. Community studies may be helpful for generating hypotheses about life-stage, genetic, and environmental contributions to disease outcomes such as cancer. These aspects may be more difficult to assess in occupational cohort studies affected by the well-recognized healthy work bias (Pearce et al., 1986). Community studies on TCE are of particular interest for two reasons. First, they are of the oral exposure route, in contrast to the inhalation exposure route of occupational cohort studies, which is important because the pharmacokinetics of oral and inhalation TCE exposures differ with respect to delivered dose. Second, community studies have relatively high statistical power even though exposure levels are relatively low. The community studies are of multiple solvent exposures, assessed at the ecological (community) level rather than the individual level. Contemporaneous or retrospective assessment of disease relative to exposure and aggregation bias compromise their interpretability (Wartenberg et al., 2000), as does their limited or, in some cases, lack of adjustment for potential confounders.

Many of the community studies on TCE have assessed relationships between drinking water exposures and leukemia. Age at first exposure may be an important risk factor for subsequent development of leukemia association with drinking water exposure to chlorinated solvents that included TCE. A recent study of Costas et al. (2002) investigated factors potentially responsible for the leukemia cluster in Woburn, MA. This analytical study was a follow up to the studies of the Massachusetts Department of Public Health (1997) and Lakagos et al. (1986). Costas et al. (2002) reported that their study suggested an association with developing childhood leukemia among children whose mothers were likely to have consumed water from wells contaminated with TCE at concentrations an order of magnitude higher than perchloroethylene during pregnancy than for those who did not; OR_{adj}[8] = 8.3 (95% CI: 0.8, 94.7). A statistically significant exposure-response relationship was identified for the period during pregnancy[9]. In contrast, the child's potential for exposure from birth to diagnosis showed no association with leukemia risk. Morgan and Cassady (2002) investigated a 10-year cancer incidence, including leukemia in children younger than 15 years of age, in 13 contiguous census tracts in the city of Redlands, California, with TCE and perchlorate and did not report associations with leukemia or other site-specific cancers. This leukemia finding is similar to the

[8] Odds ratio (OR) from proportional hazards model and adjusted to control for SES, maternal smoking during pregnancy, maternal age at birth of child, and breast feeding using a composite covariate.

[9] Never exposed category, OR = 1.0 (9 cases); least exposure category, OR = 3.5 (95% CI: 0.2, 58.1) (3 cases); most exposed category, OR = 14.3 (95% CI: 0.9, 224.5) (7 cases); chi-square test for trend, $p < 0.05$. OR adjusted to control for SES, maternal smoking during pregnancy, maternal age at birth of child, and breast feeding using a composite covariate.

finding of Costas et al. (2002) for the exposure period from birth to diagnosis. Unlike Costas et al. (2002), however, Morgan and Cassady (2002) did not investigate critical time periods of susceptibility.

The study of Lee et al. (2003) is one of the few studies available evaluating cancer other than leukemia. Lee et al. (2003) assessed liver, stomach, colorectal, and lung cancers in residents in two villages. This study is suggestive of an association between exposure to chlorinated hydrocarbons and liver cancer in males. The exposed village was located downstream from an electronic factory and received water contaminated with chlorinated solvents. TCE concentrations in well water of the downstream community were an order of magnitude higher than perchloroethylene and 1,1-dichloroethylene concentrations. Monitoring of well water from the control village located upstream from the factory did not shown contamination by chlorinated solvents. Lee et al. (2003) reported increased mortality odds ratios (MORs) among males for all cancer, and liver cancer for the periods after 10 years of latency, namely, 1980–89, and 1990–97. The adjusted MOR for liver cancer in males was 2.6 (95% CI: 1.2, 5.5) with a significant linear trend for the period effect. No associations were observed between other cancer sites and residency in the village containing solvent-contaminated well water. The MOR was calculated with cardiovascular-cerebrovascular diseases as the reference diseases, and multiple logistic regression analyses were performed to estimate the effects of exposure and calendar period after adjustment for age. Ecologic studies such as these lack individual information on groundwater exposure and, for this reason, provide only limited inferences about cause-effect associations. This study also did not address potential confounding related to hepatitis viral infection status, a risk factor for liver cancer, or potential misclassification due to the inclusion of secondary liver cancer among the case series.

3. ISSUES RELATED TO TCE EPIDEMIOLOGIC EVIDENCE

Epidemiologic studies clearly provide the most direct information for identification of human hazards (NRC, 1994) and for quantitative dose-response analyses. All studies of acceptable quality, whether yielding positive or null results, or even suggesting protective carcinogenic effects, should be considered in assessing the totality of the human evidence. Analysis and interpretation of the epidemiologic body of evidence, ideally studies of different populations and investigative methods, is carried out with attention to patterns and trends in response and is a critical step in identifying a hazard. An important aspect of the analysis is an evaluation of risk as reflecting a false positive result or due to chance, confounding, or possibly bias in a direction opposite to the null. Equally important in an assessment of risk are false

negative findings attributable to a number of biases, including misclassification and selection biases, the healthy worker effect, or study design limitations. Other anomalous findings can result from insufficient power, small numbers of site-specific cases or deaths, insufficient latent period between exposure and measurement of cancer, insufficient followup in cohort studies of the exposed population, or low exposure prevalence in case-control studies.

The epidemiologic conclusions in EPA's 2001 draft assessment (U.S. EPA, 2001) drew from the state-of-the-science paper of Wartenberg et al. (2000), which presents a comprehensive review of more than 80 published papers and letters to editors on the cancer epidemiology of people exposed to TCE. Wartenberg et al. (2000) found cohort, case-control, and community studies as supporting an overall summary of the epidemiologic evidence as consistent with previous conclusions of some evidence of liver cancer and NHL (IARC, 1995) but more strongly suggested associations with TCE exposure. The authors also found moderate support in terms of aspects of causation as discussed by Sir Bradford Hill (Hill, 1965). The evidence showed a temporal relationship of disease preceding exposure as supported by evidence from cohort studies, which received greater weight in the critical analysis. Relative risks for several cause-specific cancers were between 1.7 and 1.9 and were of moderate strength; elevated cause-specific risks were observed in many studies, suggesting some consistency across studies; the findings of associations with multiple cause-specific cancers implied that TCE was not specific but, rather, was a multisite carcinogen[10]; examinations of biological gradients were limited by data; the coherence or the biology of cancer was not believed to conflict with a TCE etiology; and experimental evidence existed in the animal bioassay literature.

A number of perspectives may be found on the treatment of the epidemiologic studies in the EPA draft assessment, in general, and in Wartenberg's analysis, specifically, and include: (1) EPA's Science Advisory Board (SAB) report (U.S. EPA, 2002a) summarizing their review of the 2001 draft assessment; (2) public comments submitted to EPA on their 2001 draft assessment; and (3) published literature as letters to editors. Moreover, a number of epidemiologic studies have been reported in the open literature subsequent to Wartenberg's comprehensive review and provide additional information, particularly for kidney cancer and NHL.

The SAB comments on the epidemiologic analysis were contained in their responses to Charge Question 2, on whether EPA's conclusion in the cancer weight-of-evidence characterization of TCE as "likely" carcinogenic to humans was adequately supported. Suggested areas of inquiry for the SAB panel discussion included the characterization of the strength of the epidemiologic evidence and the Wartenberg analysis, particularly its inclusion of

[10] Traditionally, specificity has been defined in term of one cause, one disease (Hill, 1965).

the Henschler et al. (1995) study. The panel believed that EPA's overall characterization of TCE was reasonable, based in part, on epidemiologic evidence in humans showing associations between TCE exposure and several cancers, including several at the same sites seen in animal bioassays (U.S. EPA, 2002a). The SAB also noted "among the epidemiological studies, the data appeared strongest overall for liver cancer and, to some degree, for lymphoma." Moreover, the SAB comments endorsed the division of the cohort studies into three tiers and recommended that EPA explicitly weight more strongly the studies with more precise estimates of personal exposure, including case-control studies that specifically focus on TCE, than the other studies that involved exposure to a variety of chemicals.

The SAB report advised EPA to "identify more clearly and then explicitly apply criteria for the selection of the epidemiologic studies, that EPA should select the broadest possible array of studies for each endpoint meeting those criteria, taking into consideration study design, availability of exposure estimates, and the goal of protecting health." The SAB panel's specific suggestions for addressing the conflicting human epidemiologic evidence for kidney tumors focusing primarily on the study by Henschler et al. (U.S. EPA, 2002a) are discussed in more detail below. The SAB report also included opinions of individual panel members, although this advice did not represent a majority or unanimous opinion among panel members on including discussions of prostate cancer and childhood cancer "as there is limited epidemiologic evidence to support both of these endpoints." Several members also gave advice on the Wartenberg analysis by offering either specific comments or opinions on performing a formal meta-analysis of the TCE cancer studies.

Drawing conclusions from epidemiologic data on exposure and disease relationships involves complex judgments about the body of evidence. Several methodological issues need consideration in an integrated analysis of the epidemiologic body of evidence; these issues and perspectives are discussed more fully below. These scientific issues expand upon the general SAB comments discussed above and incorporate discussion of both relevant scientific literature and comments submitted by the public or published in the open literature. NAS input on how EPA can address these issues in integrating the body of epidemiologic evidence would help to strengthen EPA's revised assessment.

3.1. NARRATIVE AND QUANTITATIVE METHODS

The practice of causal inference in environmental epidemiology relies upon three approaches: systematic narrative reviews, criteria-based inference methods, and, increasingly, meta-analysis (Weed, 2002). All three have been employed in various analyses of the epidemiologic literature on cancer and TCE exposure. Interpreting observations in epidemiologic evidence can involve both the quantitative method of meta-analysis and the

qualitative criteria-based method of causal inference (Weed, 2000). The epidemiologic conclusions in EPA's 2001 draft assessment (U.S. EPA, 2001) drew from the state-of-the-science paper of Wartenberg et al. (2000). Wartenberg et al. (2000) present a comprehensive review of the epidemiologic studies evaluating possible associations between TCE and cancer based on studies available at that time, adopting statistical methods for a critical review of these studies. The authors considered cohort studies to be the most reliable design of the studies reviewed and categorized all cohort studies into the following three tiers according to the specificity of the exposure information:

- Tier I–High-quality studies that included direct assessment of exposure using U–TCA, a biological marker of TCE exposure, or exposure reconstruction using JEMs and job histories.

- Tier II–Cohort studies that used indirect methods of exposure assessment such as job titles and other general information to infer potential exposure to TCE; this tier also included a small number of PMR studies.

- Tier III–Studies of dry-cleaner and laundry workers; this tier also included a small number of PMR studies.

Studies were further grouped by incidence or mortality within each tier. Wartenberg et al. (2000) summarized the studies separately for each tier, providing an estimate of the average or weighted relative risk across studies in a tier using a meta-analysis approach. The evaluation of case-control studies and community studies consisted of a descriptive summary, a critical review, and a presentation of risks for each study. Thus one of the major issues for synthesizing epidemiologic evidence is:

What qualitative and/or quantitative approaches can best inform causal inferences of the TCE body of epidemiologic evidence?

The narrative review approach is a common method used in epidemiologic and other disciplines. The purpose of the narrative review is to summarize the available evidence and to make causal association conclusions about exposure-disease relationships (Weed, 2002). Many narrative reviews do not assess quality and weight of associations reported within a published paper or for the literature as a whole. Causal claims can arise from a "tally" or count of positive and nonpositive findings. Frequently, studies are mistakenly cited as "negative" that are

nonpositive or "null" and, in this case, the narrative reflects a strength-of-the-evidence rather than a weight-of-the-evidence determination, which includes an evaluation of study attributes and limitations. Furthermore, a recent analysis of narrative reviews in seven widely read epidemiologic journals revealed that a large proportion of these narrative reviews were of questionable quality, lacking a stated purpose, clear literature search criteria, inclusion and exclusion criteria for the studies summarized in the review, and clear descriptions of the causal criteria used to interpret epidemiologic evidence (Breslow et al., 1998).

Causal claims using criteria-based approaches are made according to a set of criteria or standards applied to the evidence summarized within the systematic narrative review (Weed, 2002). Many, if not most, of the elements first proposed by Sir Bradford Hill (Hill, 1965) form the backbone of the criteria. General guidance on interpreting epidemiologic evidence widely cite these criteria (WHO, 2000; U.S. EPA, 1999; Federal Focus, 1996; Pastides et al., 1991). None of the criteria are conclusive in isolation, and the only criterion that is essential is the temporal relationship. Although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal relationship is increased when several independent studies are concordant in showing the association, when the association is strong, and when other criteria for causality are also met (U.S. EPA, 1999). Some criteria-based approaches may also include quantitative analyses, but this is not a general rule.

Meta-analysis is increasingly adopted as a formal statistical method for reviewing and summing a body of evidence. It is especially useful when results from several studies disagree with regard to direction of effect, or when sample sizes are individually too small to detect an effect (Stangl and Berry, 2000). Common meta-analytic methods can include fitting of meta-regression models, such as a fixed-effects or random effects model; linear regression analysis to assess dose-response; and pooled analyses (Crump et al., 2003; Greenland, 1994; NRC, 1988). Compared with a traditional narrative review, a review incorporating a meta-analysis can be less subjective (Wong and Raabe, 1996). Additionally, benefits of conducting a meta-analysis in a review include enhancing statistical power, an important consideration when original studies are limited by small numbers of site-specific events; more precise risk estimates; fewer statistical comparisons with the benefit of reducing issues associated with multiple comparisons; and the ability to examine heterogeneity across studies (Wong and Raabe, 1996; Morris, 1994). Use of meta-analysis methods is intended to introduce consistency and comprehensiveness into what otherwise might be a more subjective review of the literature. It can contribute to hazard characterization when viewed as a quantitative review of the literature, a "study of studies" (WHO, 2000). The value of such an analysis is dependent upon a systematic review of the literature that uses transparent criteria of inclusion and exclusion. In interpreting such analyses, it is important to consider a number of factors, including the effects of differences in study

quality and publication bias. Blair et al. (1995) discuss the use of meta-analysis in environmental health studies and provide a decision framework for considering whether or not to carry out an analysis.

A number of causal association claims have been provided in reviews of the TCE cancer epidemiologic literature (IARC, 1995; Weiss, 1996; McLaughlin and Blot, 1997; Lynge et al., 1997; McLaughlin and Lipworth, 2000; Brüning and Bolt, 2000; Wartenberg et al., 2000; Lavin et al., 2000; Mandel and Kelsh, 2001; IOM, 2003; NTP, 2002; and Wong, 2004). Table 2 presents conclusions drawn in these reviews. Several reviews focus on one site, such as the kidney (McLaughlin and Blot, 1997; Mandel and Kelsh, 2001; Brüning and Bolt, 2000). Lavin et al. (2000) focus on a few sites, such as liver, lung, kidney, and all-site cancers. The IARC (1995), Lavin et al. (2000), IOM (2003), and NTP (2002) reviews of the TCE literature adopt a criteria-based approach. NTP (2002) also drew upon the criteria-based review of Wartenberg et al. (2000) to support the overall evaluation of TCE exposure and human cancer.

Application of meta-analysis methods to TCE cancer epidemiologic studies appears feasible because a number of studies present summary relative risks using these methods (Table 3). These studies suggest that, with one exception, relative risk measures are homogeneous; that is, heterogeneity or systematic variation in the relative risk measure was not present for an individual cancer site across studies. The exception was for kidney cancer and the inclusion of Henschler et al. (1995), who observed a large relative risk compared with observed relative risks in other cohort studies. Many of the epidemiologic studies in Table 3 examined heterogeneity as part of sensitivity analyses or analyses that examine whether the same or different results are achieved using different statistical methods (Delgado-Rodriquez, 2001), but not all studies present full details of the analytical methods or criteria for study inclusion. Ojajärvi et al. (2001) present a meta-analysis of pancreatic cancer and occupational exposure to chlorinated hydrocarbon solvents and contained an analysis of the TCE cohort and case-control studies. As part of public comment on the U.S. EPA external review draft assessment, Kelsh et al. (2002) employ meta-analysis methods in a sensitivity analysis to examine studies reporting kidney cancer. In a presentation at the Toxicology Forum meetings, Kelsh (2003) expands this analysis to include the liver, liver and biliary passages, and NHL. Both Raaschou-Nielsen et al. (2003) and Morgan et al. (1998) present site-specific summary relative risks using another meta-analysis approach of summing observed and expected numbers of site-specific cancers. Axelson (2004) expands the analysis of Morgen et al. (1998), adding information from the studies of Blair et al. (1998), Boice et al. (1999), and Hansen et al. (2001) that were published following the analysis of Morgen et al. (1998). Furthermore, a comparison of the kidney cancer, liver cancer, and NHL findings in Table 3, the only sites found in common across analyses, suggests several factors as influencing the magnitude and statistical significance of the joint or meta-

relative risk. These factors include choices regarding study selection, cancer site (site-specific cause such as primary liver cancer or a broader category), and endpoint studied (incidence or both incidence and mortality). It is also important to note that some consistency is apparent across studies in the magnitude of the relative risk, suggesting that uncertainties associated with the choice of statistical modeling methods are likely to be small.

3.2. SOUNDNESS OF DATABASE

The body of epidemiologic evidence on TCE exposure is large compared with the body of epidemiologic evidence for other chemicals assessed by EPA. Furthermore, most of the epidemiologic studies on TCE exposure have become available within the past 10 years, and several new studies have been published since EPA's draft assessment. These newer studies examine possible relationships between exposure to TCE and occurrence of liver and kidney cancer, leukemia, and NHL, sites that EPA's draft assessment had associated with TCE exposure. NAS input on the strengths and limitations of the epidemiologic body of data would help to strengthen EPA's revised assessment. Specifically,

Which studies carry a greater weight in the hazard evaluation?

Consideration of a number of issues this issue paper has identified previously is important for answering this question. However, EPA asks the NAS panel to focus its attention on the two issues more fully discussed in Sections 3.2.1 and 3.2.2.

3.2.1. Studies of Morbidity or Mortality

Both incidence and mortality rates are measures of risk, and members of EPA staff have used both measures in identifying hazards and in performing dose-response analyses for estimating risk associated with a unit of exposure. A large body of studies exists that has described mortality in occupational cohorts; fewer studies of cancer incidence in TCE-exposed workers exist. Wartenberg et al. (2000) present joint relative risk estimates for incidence studies and mortality studies separately in an attempt to reduce heterogeneity. For both qualitative and quantitative approaches to synthesizing the epidemiologic evidence for making causal inferences, an important issue is therefore:

For which site-specific cancers can studies of incidence carry greater weight for hazard identification than studies based on death certificates?

Incidence rates give an accurate indication of the risk of a disease in a population. In the absence of incidence data, epidemiologic studies rely on mortality data to assess exposure-disease associations. An understanding of the accuracy of death certificate information as a surrogate for incidence data is important for evaluating observations in the mortality studies. Death certificate inaccuracies would obscure exposure-disease associations toward the null and may explain apparent inconsistencies in observed findings between epidemiologic studies using incidence and those based on death certifications. In diseases for which survival is poor and mortality is 95% or 100% within a short time period (e.g., lung cancer, pancreatic cancer), the mortality rate as inferred from death certificates may be a good surrogate for incidence rate. Conversely, it is also possible that site-specific cancers with a high survival rate may not be accurately recorded on the death certificate as an underlying cause of death. Death certifications, in this case, may be a poorer surrogate for recording incidence for the following reasons. First, incidence can be under reported or miscoded on the death certification, i.e., inconsistencies are seen between incidence and cause of death. Several reasons may explain inconsistencies between incidence data inferred from histological and pathological reports and the causes of death on the death certificate. Factors such as higher 5-year survival rates and changes over time in categories by which site-specific cancers are identified in the International Classification of Diseases (ICD) have been shown as important to the accuracy of death certificate coding (Percy et al., 1990, 1981).

Second, even if a site-specific cancer may be accurately recorded as an underlying cause of death, mortality studies may underestimate the risk of the disease due to better survival. Several site-specific cancers of interest evaluated in the TCE epidemiologic studies have high survival rates; other sites of interest have much lower survival rates. For the U.S. population, the following 5-year survival rates were identified using incidence recorded in the Surveillance, Epidemiology, and End Results (SEER) Program (Ries et al., 2004): invasive cervix uteri cancer, 93%; kidney and renal pelvis cancer, 64%; NHL, 59%; invasive liver and intrahepatic bile duct cancer, 8%; and pancreatic cancer, 4%.

The mortality of liver cancer can be either underestimated or overestimated depending on which disease classification categories are used. The extent of miscoding on death certificates varies by site. For this reason, greater uncertainties resulting from misclassification bias accompany cohort mortality studies that assess associations between exposure and these endpoints. Percy et al. (1990) show that cause-specific deaths with lower survival rates such as liver cancer can also be extensively miscoded on death certificates. Percy et al. (1990), using data from the SEER Program, compared primary liver cancer in 2,388 cases to that recorded on the death certificate. Their study showed that only 53% of the deaths were attributed on death certificates to primary liver cancer. Furthermore, only 24% of the 156 incident cases with

intrahepatic bile duct liver cancer had died with a recorded underlying cause of intrahepatic bile duct cancer. This study also showed inaccuracies in death certificates as a marker of disease diagnosis. Percy et al. (1990), furthermore, showed that of 2,977 death certificates with a underlying cause of death of primary liver cancer, 83% were of patients with a hospital diagnosis of liver cancer; 17% of the deaths had a different primary cancer site at diagnosis. For the 537 deaths from intrahepatic bile duct cancer on the death certification, only 18% of the patients had hospital diagnoses of cancer at this site; 29% were diagnosed as having primary liver cancer, and 28% were found to have extrahepatic bile duct cancers when originally diagnosed (Percy et al., 1990).

The extent of miscoding kidney cancer and NHL on death certificates is less than that for liver cancer and for gallbladder-biliary cancer. Percy et al. (1981) reported detection rates[11] of greater than 80% for both kidney cancer and NHL. Furthermore, Selikoff and Seidman (1992), in their study of lung and kidney cancers, mesothelioma, and asbestosis among asbestos-worker deaths, showed death certificates with kidney cancer as a cause of death as highly accurate of a clinical or histopathologic diagnosis of kidney cancer.

3.2.2. Exposure Assessment Issues in Epidemiologic Studies

Adequate characterization of exposure is a characteristic that is important in epidemiologic studies, with greater weight generally given to studies with more precise and specific exposure estimates. Careful evaluation of a study's exposure assessment method is important in the evaluation of a body of epidemiologic data, particularly if divergent observations may be due to exposure misclassification bias. The methods by which exposure is assessed in epidemiologic studies of TCE are diverse but include a number of studies in which biomonitoring data are utilized. As discussed above, the draft EPA assessment placed greatest weight on cohort studies with the more precise estimate of TCE exposure to individual cohort subjects. One of the important issues for both qualitative and quantitative syntheses of the body of epidemiologic evidence for TCE is thus:

> **What advice can NAS provide EPA on weighting the different exposure assessment approaches adopted in the TCE epidemiologic studies?**

In many cases, actual exposure measurements are lacking and surrogates such as available current or historical monitoring data are often used to reconstruct exposure parameters. Use of surrogates carries a potential for misclassification, i.e., an individual may be placed in an

[11] Detection rate is the proportion of hospital diagnoses with cancer of a certain site in which the cause of death reflects the same as the hospital diagnosis.

incorrect exposure group. All exposure estimation methods, whether used by subjects or experts, can have low validity and reliability and therefore can lead to misclassification bias. If the misclassification is nondifferential, the resulting risk measure could be reduced to the null. Exposure estimation methods need to be carefully designed using evidence about techniques that improve performance and, where possible, tested (Teschke et al., 2002). Sensitivity analysis of exposure uncertainties on effect measures can also provide information (HEI, 1999).

Inaccurate exposure and dose estimates lead to exposure misclassification, a nondifferential bias that can mask possible causal association relationships toward the null and dampen exposure-response gradients (Stayner et al. 1999; Gomez et al., 1994). Biological markers potentially offer excellent measures of exposure (Hulka and Margolin, 1992). Biological markers for dose can take into account individual pharmacokinetic characteristics that can modify the absorption, metabolism, and delivery of the exposure to target tissues. Biological markers can, therefore, improve estimates of dose. The three Nordic cohorts of Axelson et al. (1994), Anttila et al. (1995), and Hansen et al. (2001) identify study subjects using the TCE biological marker of U–TCA. On average, 2.2 (Hansen et al., 2001) and 2.5 (Anttila et al., 1995) samples were available per subject. In most cases, biological monitoring was carried out for one solvent, TCE. In these studies, an estimate of lifetime exposure to individual study subjects is not possible in the absence of duration of exposure information. Although this is not an issue for identifying a hazard, the lack of information on TCE exposure received over the full duration of employment limits inferences about dose-response relationships from these cohorts. For this reason, it is not surprising that Hansen et al. (2001) did not observe strong concentration-response relationships. Additionally, analyses of these studies using EPA's cancer risk estimation procedures will produce overestimates of lifetime excess cancer risks if TCE exposure concentrations had decreased since the period of biological monitoring.

Other cohort studies adopt a number of approaches for exposure assessment. Several studies assign TCE exposure to study subjects using surrogate information on patterns of TCE use by job title obtained from historical job descriptions, from historical industrial hygiene surveys, or from personal interviews to develop job exposure matrices. Raaschou-Nielsen et al. (2003) lack TCE exposure attribution to individual study subjects but use such surrogate information to increase the likelihood of correctly identifying subjects as having TCE exposure. For several cohorts, industrial hygiene measurements were either absent before the 1970s (Boice et al., 1999; Morgan et al., 1998) or were quite limited (Blair et al., 1998; Stewart et al., 1991). Furthermore, both Ritz (1999) and Greenland (1994) classify study subjects as TCE exposed using information obtained from personal interviews in the absence of historical monitoring.

Many more cohort studies identify TCE as one of a number of potential exposures but do not identify individual subjects with TCE exposure. The main shortcoming of analyses by

occupation and industry is that they do not identify specific agents as risk factors (Teschke et al., 2002). For example, Garabrant et al. (1988) identify TCE exposure in 37% of the jobs held by 70 of 14,067 study subjects employed at an aircraft manufacturing plant. While offering limited information about this cohort's exposure to TCE, this analysis does not provide information on exposures of the roughly 14,000 remaining study subjects to TCE. Another shortcoming of this type of study is that the lack of an association with a particular job or industry may mask the effect of exposure to a specific chemical to which only some individuals in the job are exposed (Teschke et al., 2002). In this case, relative risks are close to the null value. EPA allots greater weight to studies with more precise and specific exposure estimates for these reasons.

As reviewed in Teschke et al. (2002), case-control studies adopt a number of approaches to occupational exposure assessment. Some case-control studies adopting JEMs or JTEMs to identify jobs to assign potential TCE exposure lack industrial hygiene monitoring data for the industries from which cases and control arose. Attribution of TCE exposure in these studies is based on self-reported information or job lifetime history codes according to standard occupational classification for either recent, usual occupation or industry. Several studies assign TCE exposure to cases and controls using a JEM that incorporates concepts such as probability and intensity of exposure, and assignment of exposure by time to account for changing patterns of chemical use. These features are intended to increase the accuracy of exposure assessment and were first included in the JEM of Gomez et al. (1994) and then adopted in the studies of Dosemeci et al. (1999) and Heineman et al. (1994). Generic JEMs have also been adopted in the RCC case-control studies of Brüning et al. (2003) and Pesche et al. (2000). An issue associated with the use of generic JEMs is the sensitivity, or ability to identify study subjects as exposed, and specificity, or ability to identify study subjects as not exposed. The JEMs used by Brüning et al. (2003), Dosemeci et al. (1999), and Pesche et al. (2000) may be sensitive for solvent exposure. Dewer et al. (1991), in their study of Canadian jobs and specific chemical exposures comparing information from expert interviews and generic JEMs, show that a generic JEM has a high sensitivity (84%) and specificity (97%) for solvent exposure; TCE exposure was not uniquely examined. Both generic and study-specific JEMs are able to show associations where expected, although only the study-specific expert assessment produced clear exposure-response trends (Teschke et al., 2002). This may be one reason for the observed absence of an exposure-response relationship reported by Pesche et al. (2000).

A number of solvents have been documented in TCE cohort studies (Marano et al., 2000; Morgan et al., 2000, 1998; Boice et al., 1999; Blair et al., 1998; Stewart et al., 1991) and TCE-exposed subjects likely have potential exposures to other chlorinated solvents, including perchloroethylene and 1,1,1-trichloroethane. Potential exposure to multiple chlorinated solvents other than TCE is an important consideration in the TCE epidemiologic studies for two reasons.

First, these chemicals can share a metabolic profile similar to that of TCE, and, second, some epidemiologic studies also report associations between exposure to these other solvents and cancer. Two other EPA staff papers discuss interactions of TCE, its metabolites, and other chemical exposures: *Issues in Trichloroethylene Pharmacokinetics* and *Interactions of TCE, Its Metabolites, and Other Chemical Exposures*. Little information is presented for individual subjects on the concentration of exposure, the duration of exposure, and the time period of exposure to these other solvents. Exposure to solvents other than TCE should not be thought of as confounding the association between TCE and cancer, as might be considered in traditional epidemiology. The metabolic profile in humans for several of the solvent exposures is similar, at least qualitatively but not quantitatively, to that of TCE. In this case, the metabolite represents an integrated measure, i.e., cumulative exposure, and an evaluation of observed associations in the epidemiologic studies also should take into consideration mode-of-action hypotheses.

3.3. NON-HODGKIN'S LYMPHOMA

NHL is an endpoint of interest in the TCE epidemiologic studies. Conclusions drawn by IARC from the epidemiologic evidence in 1995 noted associations with NHL in the TCE cohort studies, as did EPA's draft assessment (U.S. EPA, 2001). More recently, NTP (2002) and Wartenberg and Scott (2002) discussed the evidence supporting associations between TCE exposure and NHL. Furthermore, both Hansen et al. (2001) and Raaschou-Nielsen et al. (2003), two studies published since EPA's draft assessment, observed statistically significant associations between NHL and TCE exposure.

Malignant lymphomas include a diverse group of diseases, such as NHL, Hodgkin's disease, multiple myeloma, and leukemia. Lymphomas are characterized not only on histological features but also on cell surface markers, and cytogenetic and clinical features (Seto, 2004). Moreover, NHL, like the larger lymphoma category, is a disease composed of numerous, etiologically distinct neoplasms (Herrinton, 1998). NHL incidence has been increasing and now represents the sixth leading cause of cancer deaths in males in the United States (Fisher, 2003). In contrast, deaths due to liver and intrahepatic bile duct cancer and to kidney cancer in U.S. males are ranked lower than NHL as the eighth and tenth leading causes of death, respectively (ACS, 2004).

Several issues arise that may affect interpretation of NHL associations in the TCE epidemiologic studies and that also may be important to examinations of consistency, or lack thereof, across studies. NAS input on how EPA can weigh NHL observations in the epidemiologic studies would help to strengthen EPA's revised assessment.

What advice can NAS provide EPA on factors that may influence interpretation of the epidemiologic observations on NHL?

First, most studies did not use the most current classification scheme to code incident cases or deaths. Epidemiologists code cause-specific incident cases or mortality diagnoses according to the ICD. The ICD has been revised several times during the followup period in cohort studies. Furthermore, the classification system used by pathologists for lymphomas has undergone a number of significant revisions within the past 10 years, and revisions to the ICD reflect the changes in the pathology classification system. Many concepts of contemporary knowledge of lymphomas have been incorporated into the International Lymphoma Group's Revised European-American Lymphoma (REAL) classification that was proposed in 1994 and adapted into the International Classification of Diseases (ICD-0) (Herrinton, 1998). More recently, the World Health Organization (WHO) has proposed a classification scheme that may be considered an updated version of the REAL classification (Cogliatti and Schmid, 2002). Before the REAL and WHO classifications, the National Cancer Institute Working Formulation was designed to provide a common basis for interpreting older classifications, such as the Rappaport, Luke-Collins, Kiel, and WHO lymphoma systems (Fisher, 2003).

The TCE epidemiologic studies evaluating NHL have used a number of different ICD classifications. All four Nordic studies classified NHL according to the 7th revision of the ICD (ICD-7) and all reported consistent findings. Other revisions of the ICD were used in the more recent studies of Blair et al. (1998) [ICDA-8], Boice et al. (1999) [ICD-9], Garabrant et al. (1988) [ICD in effect at date of death; ICD-7, ICDA-8, or ICD-9], Morgan et al. (2000, 1998) [ICD in effect at date of death; ICD-7, ICDA-8, or ICD-9], and Ritz (1999) [ICD-9]. Few case-control studies on lymphoma are available. NHL cases in Hardell et al. (1994) were histologically verified and were classified using the Rappaport system. Persson et al. (1989) does not identify the system used to classify NHL cases in their study.

Epidemiologic studies are only now beginning to examine associations between exposure and cell-specific malignancies such as B-lymphocyte lymphoma. An example is the recent study of Bukowski et al. (2003). None of the TCE studies have examined associations by cell type. Lymphomas are many distinct, definable diseases that are grouped together (Fisher, 2003) defined broadly as B-cell and T-cell lymphomas with further divisions into precursor neoplasms and mature neoplasms (Cogliatti and Schmid, 2002). This implies that although lymphomas have been classified in the past into distinct categories, they can share common biological properties and differentiation pathways. For example, a B-cell lymphoma in origin may be classified under older schemes into several distinct categories, e.g., NHL, multiple myeloma, or leukemia. Epidemiologic studies would appear to lack consistency and specificity, that is, exposure is not associated with a unique endpoint, if associations were shown with several

cause-specific cancers. Thus, individual TCE study observations of excess risks of NHL and multiple myeloma may not be inconsistent with a mode-of-action argument, although the EPA's draft TCE assessment (U.S. EPA, 2001) noted that mode-of-action information for toxicity in the lymphopoietic system was more limited than that for the liver, kidney, and lung.

3.4. CONSIDERATIONS FOR META-ANALYSIS

In addition to the issues discussed above that are applicable to both qualitative and quantitative syntheses of epidemiologic data, decisions on whether and how to undertake a meta-analysis entails the consideration of a number of additional issues. Blair et al. (1995) discuss a number of desirable and undesirable attributes of meta-analysis. Specifically, EPA would benefit from input from the NAS as to:

> **How appropriate and useful is applying meta-analysis methods to synthesize epidemiologic data on TCE, and what strategies could be employed to implement such an analysis?**

Public comments submitted to U.S. EPA after the release of its draft TCE assessment emphasize that application of meta-analyses is informative when studies are homogeneous (HSIA, 2002; DOD, 2002). An assumption is made in meta-analysis that summary estimates of effects are homogeneous or equal across individual study findings (Petitti, 1994), and an analysis of heterogeneity or variation in study results can be an important function of meta-analysis (Greenland, 1998). Blair et al. (1995) further note that possible sources of inconsistencies or heterogeneity in the relative risk or other effect measure in individual studies should be examined in the meta-analysis. Variability in exposure characterization, study design, and control for confounding may explain observed inconsistencies in the relative risks from multiple studies and because of this may limit or even preclude the statistical combination of multiple studies.

A pooled analysis, an approach that combines studies of a similar design and of similar exposure patterns and concentrations, is compatible with this perspective. The summed SIRs reported by Raaschou-Nielson et al. (2003) come closest to a pooled analysis of the Nordic cohorts. It is also important to consider which studies to include in the meta-analysis and how to group these studies. The epidemiologic studies included in the meta-analysis mentioned above are not consistently treated across reports. Each of the analyses in Table 3 has based its findings on a combination of different studies; no one analysis appears to share a common set of studies, although some individual studies are commonly found. Most reports in Table 3 include the incidence studies of Axelson et al. (1994) and Anttila et al. (1995) with the more current ones, including Hansen et al. (2001), Blair et al. (1998) (or the earlier report of this cohort by Spirtas et

al. [1991]), Morgan et al. (2000, 1998), and Boice et al. (1999). All studies except those of Axelson et al. (1994), Anttila et al. (1995), and Hansen et al. (2001) assessed mortality. The meta-analyses in Table 3 report summary risk estimates and do not consider differences in the qualities of the exposure assessment or measured outcome. For example, the incidence study of Anttila et al. (1995) with information on TCE exposure for individual study subjects as well as the mortality study of Garabrant et al. (1988), which lacks individual-specific TCE exposure information, have been placed into the same grouping in one analysis. This treatment is in contrast to the statistical approach taken by Wartenberg et al. (2000), who considered exposure assessment characteristics and measured outcome as leading to possible heterogeneity. A stratified analysis is the most common tool in meta-analysis for minimizing potential heterogeneity in relative risks or effect measures resulting from study design factors (Morris, 1994).

As discussed above, Wartenberg and Scott (2002) show a lack of heterogeneity in cause- or site-specific relative risks except that for kidney cancer in the studies considered to have more robust inferences of TCE exposure (Tier I incidence studies), with analyses examining fewer sites drawing similar conclusions (Kelsh, 2003; Borak et al., 2000). Heterogeneity in kidney cancer risk is introduced from the inclusion of Henschler et al. (1995), who reported a strong association for kidney cancer incidence. Public comments (DOD, 2002; HSIA, 2002; Rhomberg et al., 2002a) to EPA on the external draft TCE synthesis and characterization (U.S. EPA, 2001) note criticisms in the scientific literature of the study of Henschler et al. (1995) and suggest this study should not be included in a quantitative analysis. Much of the criticism focused on the study's development originating from a cluster of kidney cancer cases (U.S. EPA, 2002b) and lacking an *a priori* hypothesis (Rhomberg, 2002b). Concerns mentioned by the SAB peer review panel included the variability of underlying population rates for kidney cancer in German and Danish cancer registries; the magnitude of the indicated risk, which was far out of proportion to risks observed in most other studies; and the significance of the study in light of the whole epidemiologic database (U.S. EPA, 2002a). In their letter to the editor to the journal where Wartenberg et al. (2000) was published, Borak et al. (2000) wrote that the contribution to the overall joint relative risk of Henschler et al. (1995) was not proportional to the size of the study (the increase in the combined study population by 169 exposed and 359 total subjects, 1.3% and 2.0%, respectively, was shown to increase the relative risk by nearly 74%).

This leads to the question as to why the relative risks in Henschler et al. (1995) are heterogeneous and larger than relative risks reported in other Tier I incidence studies. Exposure conditions may be different for these subjects compared with other cohorts. Cherrie et al. (2001) developed exposure concentrations for this study using information provided in Henschler et al. (1995) to examine this hypothesis. Cherrie et al. (2001) estimated long-term average exposure

during cleaning activities as between 10 ppm and 225 ppm, the lower end of this range similar to average time-weighted-average concentrations reported for the Nordic cohorts (Hansen et al., 2001; Anttila et al., 1995; Axelson et al., 1994); however, peak exposure concentrations were of approximately 1,800 ppm to 4,000 ppm, which is consistent with the reports of narcotic effects in cardboard workers studied by Henschler et al. (1995). Other possible explanations are identified by the SAB panel (U.S. EPA, 2002a) and include variation in cause-specific cancer rates in the reference or comparison population and the use of sonographic screening of exposed workers, which would increase the ability to detect renal cell carcinomas in the exposed group compared with the comparison population.

Overall, SAB panel members agreed that the inclusion of Henschler et al. (1995) in an overall meta-analysis would introduce significant heterogeneity. The SAB panel also suggested that this study may provide some information and recommended that EPA consider this study in their revision of the TCE assessment. The SAB panel recommended that EPA include this study in the overall analysis of the epidemiologic body of evidence, taking into account information on exposure levels and potential biases in this study (U.S. EPA, 2002a). It is important to point out that this study was published roughly 10 years ago and that more information has become available. Additionally, the recent case-control studies of Pesche et al. (2000) and Brüning et al. (2003) may have a greater statistical power than cohort studies to evaluate renal cell carcinoma and TCE exposure. EPA seeks guidance from the NAS panel as to how Henschler et al. (1995) can inform EPA's overall weight-of-evidence judgments.

Approaches for conducting a meta-analysis that use fixed or random effects models weigh the contribution of an individual study to the overall summary relative risk using the inverse of the study's variance. However, the TCE database limitations was for this approach. Several studies lack symmetry on a log scale between the point estimate and the upper or lower confidence bound, due to either rounding error or alternative calculation algorithms. A variance derived from the difference between the natural log of the upper 95% confidence interval and the natural log of the point estimate cannot be calculated in two cases: (1) where no cause- or site-specific cancer cases were observed in an individual study, and (2) where a lower 95% confidence interval is reported as zero; the lognormal value of zero is undefined. However, public and other comments (DOD, 2002; Boice and McLaughlin, 2001) discuss the use of the lower 95% confidence interval as an alternative for estimating variance. Several approaches may be employed to examine asymmetry of the confidence interval and the overall impact on a meta-analysis of choices concerning confidence intervals. First, EPA can ask the principal investigator to provide more information such as the number of site-specific cancers observed and expected in the study if asymmetry is a result of rounding error resulting from insufficient information presented in the published study. In most cases, this information will reduce

rounding error with greater adherence to statistical demands for symmetry. In cases of zero reported site-specific cases, Bayesian methods can be examined to obtain an estimate of the observed number with a confidence interval developed using the posterior information. Sensitivity analysis can examine the overall influence of variances calculated from both the upper and lower 95% confidence intervals on the overall site-specific finding. Finally, methods using a summed value of observed and expected site-specific cases can be examined, although this approach excludes information contributed by studies with internal referents, such as Blair et al. (1998).

4. SUMMARY

The issues raised in the above sections suggest a number of potential approaches for evaluating the TCE cancer epidemiologic evidence. EPA proposes to carry out a systematic review of the epidemiologic body of literature, carefully considering the utility of criteria-based approaches and meta-analysis approaches to an appropriate subset of studies. This review will be characterized according to well-characterized principles for evaluating studies,such as clearly stated purpose, careful literature searches, explicit inclusion and exclusion criteria, assessment of study validity and bias, and well-articulated definitions and rules of inference for selected causal criteria. EPA will use these criteria in weighing the overall epidemiologic evidence and provide tables summarizing critical information for each key study,including type of study, number of subjects, sources of exposure information, years and estimated levels of exposure, and basis for the estimated exposure levels.

Table 1. Epidemiologic studies assessing cancer and trichloroethylene exposure

Study	Outcome
I. Cohort Studies	
Anttila et al. (1995) (Tola et al., 1980; Axelson et al., 1978)	Incidence
Axelson et al. (1994)	Incidence
Blair (1980)	Mortality
Blair et al. (1989)	Mortality
Blair et al. (1998) (Spirtas et al., 1991)	Mortality/Incidence
Boice et al. (1999)	Mortality
Chang et al. (2003a,b)	Mortality
Dubrow and Gute (1987)	Mortality (PMR)
Henschler et al. (1995) (Swaen, 1995; Bloemen and Tomenson, 1995)	Site-cancer for mortality, kidney cancer incidence
Garabrant et al. (1988)	Mortality
Hansen et al. (2001)	Incidence
Morgan et al. (2000, 1998)	Mortality
Raaschou-Nielsen et al. (2003)	Incidence
Ritz (1999)	Mortality
Sinks et al. (1992)	Mortality/Incidence
Shannon et al. (1988)	Mortality
Shindell and Ulrich (1985)	Mortality
Stern et al. (2001)	Mortality (PMR)
II. Case-Control Studies	
Brüning et al. (2003)	Renal cell carcinoma
Dosemeci et al. (1999)	Renal cell carcinoma
Fredriksson et al. (1989)	Colon cancer
Fritschi and Siemiatycki (1996)	Melanoma
Greenland (1994)	Several cancer sites
Hardell et al. (1981)	Lymphoma
Hardell et al. (1994)	Lymphoma
Heineman et al. (1994)	Astrocytic brain cancer
Persson et al. (1989)	Lymphoma
Pesche et al. (2000)	Renal cell carcinoma
Vamvakas et al. (1998) (Green and Lash, 1999; Vamvakas et al., 2000; Mandel, 2001; Vamvakas et al., 2001)	Renal cell carcinoma

Table 1. Epidemiologic studies assessing cancer and trichloroethylene exposure (continued)

III. Community Studies

Cohn et al. (1994)	Leukemia, NHL
Costas et al. (2002) (MaDPH, 1997; Lagakos et al., 1986)	Leukemia (case-control)
Fagliano et al. (1990)	Leukemia
Flood and Chapin (1988)	Leukemia
Flood et al. (1990)	Leukemia
Isacson et al. (1985)	A number of site-specific cancers
Lee et al. (2003)	Liver, stomach, colorectal, and lung cancers
Mallin (1990)	Bladder cancer
Morgan and Cassady (2002)	Total cancer and 12 site-specific cancers
Turnbull et al. (1990)	Leukemia
Waller et al. (1992)	Leukemia
Waller and Turnbull (1993)	Leukemia
Vartianinen et al. (1993)	Liver, Hodgkin's disease, NHL, leukemia

Note: Epidemiologic studies were identified through a search of the National Library of Medicine's PubMed database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) using the keywords "trichloroethylene cancer epidemiology" or were cited in Wartenberg et al. (2000).

PMR = proportional mortality ratio; NHL = non-Hodgkin's lymphoma.

Table 2. Causal inferences as reported in reviews of TCE body of evidence

IARC (1995)	"Overall, the important observations are the elevated risk for cancer of the liver and biliary tract and the modestly elevated risk for NHL in all three of the most informative cohort studies. The suggested marginally increased risk for NHL in areas with TCE-contaminated groundwater is noted."
Weiss (1996)	"It is clear from a review of the data that, both in terms of the small relative increases seen and the small number of observations upon which those increases are based, the evidence currently available in support of a causal hypothesis is quite limited."
McLaughlin and Blot (1997)	"There is little evidence of an increased risk of renal-cell cancer and exposure to TCE or perchloroethylene." "Although it is virtually impossible using epidemiology data to rule out conclusively a small increase in risk of renal-cell cancer, the totality of data reviewed herein are not remotely close to suggesting a cause-effect relationship between renal cancer and TCE and perchloroethylene."
Lynge et al. (1997)	"The three most informative cohorts consistently indicated an excess relative risk for cancer of the liver and biliary tract with 23 observed cases and 12.9 expected. The risk for these cancers also was elevated in one of the two less informative studies." "The results for NHL were consistent across the three most informative studies indicating a modest excess relative risk, with 27 observed versus 18.9 expected cases." "There is evidence for increased risks of cancer following exposure to: trichloroethylene (for the liver and biliary tract and for NHL). . . ."
McLaughlin and Lipworth (2000)	"There have been 6 published cohort studies of TCE-exposed workers, with none reporting a significantly increased risk of renal cell cancer. There have been 6 case-control studies that tried to evaluate TCE specifically and none has reported a significant association. Thus, the weight of the epidemiologic evidence provides no credible support for the hypothesis that TCE causes renal cell cancer in humans."
Brüning and Bolt (2000)	"In general, the human nephrocarcinogencitiy of trichloroethylene appears practically to be a high-dose phenomenon."
Wartenberg et al. (2000)	"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 cancer and some support for Hodgkin's disease and NHL. There is also a possible association of cervical cancer with TCE and PER exposure. Some data suggest associations between TCE exposure and multiple myeloma and prostate, laryngeal, and colon cancers." "In terms of Hill's aspects of causation, we find moderate support."

Table 2. Causal inferences as reported in reviews of TCE body of evidence (continued)

Lavin et al. (2000)	"In summary, the epidemiological evidence as a whole does not support a causal association between human occupational TCE exposure and an increased incidence of lung, liver, or kidney cancers."
Institute of Medicine (2003)	Consensus Not Reached on Category of Association • Trichloroethylene and colon cancer • Trichloroethylene and cervical cancer Summary of the Committee's Consensus Conclusions Inadequate/Insufficient Evidence to Determine Whether An Association Exists: Cancers • Specific solvents other than tetrachloroethylene and dry-cleaning solvents and bladder cancer • Specific solvents other than tetrachloroethylene and dry-cleaning solvents and kidney cancer • Specific solvents other than benzene and brain and other central nervous system cancers • Specific solvents other than benzene and NHL Specific solvents other than benzene and acute and adult leukemia
NTP (2002)	"Trichloroethylene (TCE) is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, and which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in multiple species of experimental animals, and information suggesting TCE acts through mechanisms that indicate it would likely cause cancer in humans." "Evidence for the carcinogenicity of TCE in humans comes from seven cohort studies with specific TCE exposure well characterized for individual study subjects. A meta-analysis of these cohort studies found that occupational exposures to TCE was associated with excess in liver cancer, non-Hodgkin's lymphoma, prostate cancer, and multiple myeloma, with the strongest evidence for the first three cancers (Wartenberg et al., 2000)." "Findings from other cohort studies, with less accurate assessment of TCE exposures, have more variable results. Exposure to TCE was assessed less accurately in case-control studies; in many studies, TCE exposure was estimated from exposure to solvents in general. These studies typically reported higher cancer rates for tumor site similar to those observed in the cohort studies."

Table 2. Causal inferences as reported in reviews of TCE body of evidence (continued)

Wong (2004)	"A review of epidemiologic studies of workers exposed to TCE does not support a causal association between exposure to the solvent TCE and an increased risk of any site-specific cancer (including cancer of the liver and biliary passages and NHL)." "Ingestion of water with typical TCE contamination levels does not result in any significant increase in cancer risk."

NHL = non-Hodgkin's lymphoma; IARC = International Agency for Research on Cancer; PER = perchloroethylene

Table 3: Summary of relative risks in analyses using meta-analysis methods

Study	Statistical approach	Studies in analysis	Meta-relative risk (95% CI) [Site]
Morgan et al. (1998)	Sum observed/expected	Anttila et al. (1995) (TCE subcohort)	1.2 (0.8, 1.6) [Bladder]
		Axelson et al. (1994),	1.1 (0.7, 1.6) [Kidney]
		Morgan et al. (1998, 2000) - TCE subcohort[1],	1.3 (0.8, 2.1) [Liver]
		Spirtas et al. (1991) - TCE subcohort	1.3 (0.9, 1.7) [NHL]
			1.1 (0.9, 1.4) [Prostate]
Ojajärvi et al. (2001)	Random-effects model[2]	Anttila et al. (1995) - all subjects	1.2 (95% CI: 0.8, 2.0) [Pancreas]
	(w/o covariates)	Axelson et al. (1994), Greenland (1994),	
		Spirtas et al. (1991), Siemiatycki (1991)	
Kelsh et al. (2002)	Fixed effects model	Tier I[3]	
		- incidence	1.7 (1.1, 2.7)[4] [Kidney]
		- incidence, w/o Henschler et al. (1995)	1.0 (0.6, 1.7)[5] [Kidney]
		- incidence and mortality	1.4 (1.1, 1.8)[4] [Kidney]
		- incidence and mortality, w/o Henschler et al. (1995)	1.0 (0.8, 1.4)[5] [Kidney]
		Tier I and II[3]	
		- incidence and mortality	1.3 (1.1, 1.6)[4] [Kidney]
		- incidence and mortality, w/o Henschler et al. (1995)	1.2 (0.9, 1.4)[5] [Kidney]
Kelsh (2003)	Random effects model	Anttila et al. (1995), Axelson et al. (1994),	1.6 (1.0, 2.4)[4] [Kidney incidence]
		Blair et al. (1998), Boice et al. (1999)[1]	1.5 (1.1, 1.9)[4] [Kidney incidence and mortality]
		Garabrandt et al. (1988), Hansen et al. (2001),	1.1 (0.8, 1.4)[5] [Exclude Henschler et al. (1995)]
		Morgan et al. (2000, 1998)[1], Ritz (1999),	1.6 (0.96, 2.4)[5] [Primary liver incidence and mortality]
		Sinks et al. (1992)	1.1 (0.8, 1.4)[5] [Liver and biliary passage mortality]
			1.9 (1.3, 2.7)[5] [NHL incidence, 4 studies]
			1.5 (1.2, 1.8)[5] [NHL incidence and mortality, 7 studies]
			1.2 (1.0, 1.5)[5] [NHL incidence and mortality, 10 studies]
			1.1 (0.9, 1.4)[5] [NHL, exclude Hansen et al. (2001), 9 studies]

Table 3: Summary of relative risks in analyses using meta-analysis methods (continued)

Study	Statistical approach	Studies in analysis	Meta-relative risk (95% CI) [Site]
Raaschou-Nielsen et al. (2003)	Sum observed/expected	Anttila et al. (1995), Axelson et al. (1994), Hansen et al. (2001)	1.0 (0.6, 1.6) [Kidney] 1.8 (1.2, 2.9) [Liver or biliary passage] 2.1 (1.3, 3.1) [NHL]
Axelson (2004)	Sum observed/expected	Anttila et al. (1995) - TCE subcohort Axelson et al. (1994), Morgen et al. (2000, 1998) - TCE subcohort[1], Blair et al. (1998), Boice et al. (1999) – TCE subcohort[1], Hansen et al. (2001)	1.0 (0.9, 1.3) [Bladder] 1.2 (0.9, 1.6) [Kidney] 1.4 (1.01, 1.9) [Liver] 1.1 (0.9, 1.2) [Prostate] 1.6 (1.2, 1.9) [NHL]

[1] Primary liver cancer for all cohorts except that of Morgan et al. (2000, 1998) and Boice et al. (1999), which is of liver and biliary passage mortality.

[2] Fixed-effect models were also fitted to the data with similar findings.

[3] Tier I studies of Wartenberg et al. (2000).

[4] Heterogeneity p-value, $p \leq 0.05$; heterogeneity is present.

[5] Heterogeneity p-value, $p > 0.05$; heterogeneity is absent.

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