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Tetrachloroethene and Cancer. Critical Review and Synthesis of the Epidemiological Literature

Final Report for the Textil- und Bekleidungs-Berufsgenossenschaft (Institution for Statutory Accident Insurance and Prevention in the Textile and Clothing Industry), Augsburg, Germany

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Tetrachloroethene and Cancer
Critical Review and Synthesis of the Epidemiological Literature

Final Report for the Institution for Statutory Accident Insurance and Prevention in the Textile and Clothing Industry

Abstract

Tetrachloroethene (perchloroethylene, PCE) is used for metal cleaning and degreasing, in dry cleanings and as solvent in the chemical industry. In epidemiology studies, which analysed collectives with potential PCE exposure (primarily dry cleaners), increased hazards regarding some specific cancer localisations have been described. However, the findings are not uniform. In the study in hand, the literature on epidemiology regarding cancer research and PCE exposure issues has been extensively consolidated. Each study has been critically reviewed in order to determine the quality of data and methods respectively. Findings of the relevant studies have been summarized individually for specific cancer localisations. The available literature shows strong methodical restrictions (exposition assessment and confounding) and provides heterogeneous results. None of the studies is adequately expressive, and the epidemiologic evidence in its entirety is not suitable to convincingly demonstrate that any connection (whether strong or weak) exists between exposure to PCE and cancer.

Tetrachlorethen und Krebs
Kritische Überprüfung und Synthese der epidemiologischen Literatur

Abschlussbericht für die Textil- und Bekleidungs-Berufsgenossenschaft

Kurzfassung

Tetrachlorethen (Perchlorethylen, Per) wird in der Metallreinigung und -entfettung, in Chemischreinigungen und in der chemischen Industrie als Lösungsmittel eingesetzt. In epidemiologischen Studien, die Kollektive mit potenzieller Per-Exposition untersuchten (primär Chemischreiniger), wurde für einige spezifische Krebslokalisationen ein erhöhtes Risiko beschrieben. Die Ergebnisse waren jedoch nicht einheitlich. In der vorliegenden Arbeit wurde die epidemiologische Literatur zur Fragestellung Kanzerogenität und Per-Exposition umfassend aufgearbeitet. Jede Studie wurde kritisch überprüft, um jeweils die Qualität von Daten und Methoden zu bestimmen. Die Ergebnisse der relevanten Studien wurden für spezifische Krebslokalisationen einzeln zusammengefasst. Die zur Verfügung stehende Literatur hat starke methodische Einschränkungen (Expositionsabschätzung und Confounding) und bietet heterogene Ergebnisse. Keine der Studien ist adäquat aussagekräftig und die Gesamtheit der epidemiologischen Hinweise ist nicht dazu geeignet, überzeugend zu demonstrieren, dass irgendein Zusammenhang – ob stark oder schwach – zwischen Per-Exposition und Krebs vorhanden ist.

Tétrachloroéthylène et Cancer
Examen Critique et Synthèse de la Littérature Épidémiologique

Rapport Final pour l'Organisme d'Assurance et de Prevention des Risques Professionnels dans l'Industrie Textile et l'Habillement

Resume

Le tétrachloroéthylène (perchloroéthylène, per) est utilisé comme solvant dans les produits de nettoyage et de dégraissage des métaux, pour le nettoyage à sec et dans l'industrie chimique. Les études épidémiologiques consacrées à des groupes susceptibles d'être exposés au tétrachloroéthylène (principalement dans le nettoyage chimique) indiquent un risque augmenté pour certaines localisations spécifiques de cancers. Les résultats ne sont cependant pas homogènes. Dans la présente étude, la littérature épidémiologique a été exploitée de façon complète sous l'angle de la relation entre cancérogénicité et exposition au tétrachloroéthylène. La qualité des données et des méthodes de chaque étude a été soigneusement vérifiée. Les résultats des études pertinentes ont été regroupés séparément pour certaines localisations de cancers. La littérature existante présente d'importantes lacunes méthodologiques (estimation de l'exposition et facteurs de confusion) et donne des résultats hétérogènes. Aucune des études ne fournit d'arguments suffisamment pertinents et l'ensemble des indications épidémiologiques ne permet pas de démontrer de façon convaincante l'existence d'une relation quelconque - qu'elle soit forte ou faible - entre exposition au tétrachloroéthylène et cancer.

Tetracloroeteno y Cáncer
Revisión Critica y Síntesis de la Literatura Epidemiológica

Informe Final para el Organismo de Seguros y Prevención de Riesgos Profesionales en los Sectores del Textil y del Vestido

Resumen

El tetracloroeteno (percloroetileno, Per) se emplea como disolvente en la limpieza y el desengrase de metales, en la limpieza química y en la industria química. Los estudios epidemiológicos, que investigan a los colectivos con un potencial de exposición a Per (primordialmente limpiadores químicos), han detectado un riesgo aumentado de cáncer en algunas localizaciones específicas. Los resultados, sin embargo, no ofrecen un aspecto homogéneo. El presente trabajo ofrece un estudio exhaustivo de la literatura epidemiológica que trata el tema de cancerogenidad y exposición a Per. Se ha realizado un examen crítico de todos los estudios para determinar la calidad de los datos y de la metodología. Los resultados de los estudios relevantes se han agrupado según las localizaciones específicas de cáncer. La literatura disponible sufre de considerables limitaciones en referencia a la metodología (evaluación de la exposición y confounding) y, en consecuencia, los resultados se caracterizan por su heterogeneidad. Ninguno de los estudios tiene una relevancia adecuada, y el conjunto de las referencias epidemiológicas no permite demostrar contundentemente la existencia de alguna relación de mayor o menor importancia entre la exposición a Per y el cáncer.

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Executive Summary

Background and objective

The chlorinated hydrocarbon tetrachloroethylene (synonyms: tetrachloroethene, perchloroethylene, PCE) is a non-flammable solvent. The commercial application is in metal cleaning and degreasing, as a solvent in the dry cleaning industry and in the chemical industry. Inhalation of PCE has been described as causing neurological effects as well as damage to the liver and kidney in humans. In some animal experiments an increased cancer risk was observed in the case of oral exposure or by inhalation. However, the relevance of these results for humans is questionable. The EC-commission has classified PCE in the category K 3.

For some cancer sites an increased risk has been described in epidemiological studies for populations assumed to be exposed to PCE. However, the results were inconsistent. The studied populations were predominately from North America and were for the most part groups from the dry cleaning industry.

The primary goal of this project was to critically assess the epidemiological literature on the possible relationship between PCE and specific cancers. For this purpose a summary of the relevant information from the published studies was made. Specific objectives included

1. comprehensive searches of the epidemiological literature addressing the possible carcinogenicity of PCE exposure;

2. critical review of each study to determine the quality of data and methods;

3. meta-analytic synthesis, to record the epidemiological evidence for each cancer site.

Methods of Literature Search and Review

In a comprehensive search of the literature a multistage search and selection procedure was employed. Various information sources were considered: generally accessible scientific literature (e. g. MEDLINE); other specialized databases and references from previously published reviews concerning "PCE", "organic solvents", the "dry cleaning industry" or specific cancer locations. All database searches used the following terms: "Tetrachloroethylene", "laundry/dry cleaning" and "degreasing" including all synonyms. Searches for other relevant occupations, industries or authors were also conducted. Finally, regular updates of the literature searches continued until mid-1999 to ensure a complete body of literature. In all, 81 papers published between 1963 and 1999 were identified. Each paper was reviewed independently by at least two epidemiologists. As part of the project, a database was developed and the results of the critical review for each study were entered using key elements.

The overall strategy was to include as many studies as possible. Epidemiological studies making no valid contribution were not considered in the summary.

45 of the 81 studies were included in further analyses. There were ten cohort studies, 26 case-control studies and nine death certificate studies.

Publications were excluded based on the following criteria:

- Where there were multiple reports on the same study population, only the most recent report was included in the analyses.
- A single study was part of a multi-center study which was included in the analyses.
- No risk estimate was presented as there were no exposed cases.
- The probability of any "substantial" PCE exposure was low, undefined or could not be determined for the study population.

Selection of Cancer Sites for Critical Analysis

Each cancer site was individually assessed. For some sites (bone, eye, thyroid) too few results were available to critically review the association between PCE exposure and the given cancer site. Those cancer sites, where the bulk of the results came from death certificate studies only, were not considered.

17 cancer sites were critically reviewed (see Table I, page 14). Subsequently, nine of these cancer sites were selected after a detailed critical review for synthesis. Sites for the summary were selected according to the number of available studies and if these sites (e. g. renal cell carcinoma) have garnered much response within the epidemiological literature and general discussion.

The eight remaining cancer sites were also critically reviewed. This review was only made in the form of brief analyses because there were either too few studies for a summarization or the available studies showed no allusions to an increased cancer risk (e. g. breast cancer).

Criteria for the Assessment of PCE Exposure

Most of the studies included assessed PCE exposure using surrogate measures (such as job titles or occupational codes). Information was missing regarding the specific agent to which employees were exposed.

PCE exposure was assessed using the following criteria:

1. PCE exposure likely
2. Mixed exposures – PCE exposure likely
3. Mixed exposures – PCE exposure possible
4. PCE exposure unlikely.

Table I:
Reviewed cancer sites according to the International Classification of Diseases (ICD)

ICD-9	Site	Number of Publications	Type of Analysis
140-149	Buccal cavity and pharynx	8	detailed
150	Esophagus	8	detailed
151	Stomach	8	brief
154	Rectum	8	brief
155-156	Liver	16	detailed
157	Pancreas	10	detailed
161	Larynx	6	detailed
162	Lung	14	detailed
172-173	Skin	9	brief
174-175	Breast	8	brief
180 (179-184)	Cervix uteri (Female genital organs)	8	detailed
179, 181, 182	Corpus uteri	6	brief
185	Prostate	10	brief
188, 189.3-189.9	Bladder	16	detailed
189.0-189.2	Kidney	16	detailed
191-192	Brain and other nervous system	5	brief
200-208	Lymphatic/hematopoietic system	6 *	brief

* additional studies reported results for specific types of leukemia

Results

The reviewed body of literature showed serious deficits:

- the absence of adequate exposure information
- too small numbers of observed cases/deaths (especially among possibly exposed persons)
- the lack of consideration of further potential risk factors.

Most study populations consisted of occupational groups with different exposures (dry cleaners and launderers), sometimes including exposure to other solvents. Therefore an assessment of PCE exposure often was not possible. No study was able to provide an assessment of the exposure to PCE usable for the summary.

The majority of studies relied upon surrogate measures of exposure, allowing the inclusion of a substantial number of persons with no or mixed exposures. Surrogates of exposure included "ever" versus "never" having worked in dry cleaning or information on occupation and job of study participants. The quality of exposure assessment also determines the validity of the study results. An inaccurate classification of study subjects into "exposed" and "non-exposed" categories has a profound impact on the estimate and can lead to erroneous conclusions.

Two American cohort studies of dry cleaners (*Blair*, 1990; *Ruder*, 1994) described exposure, but were not able to control for important confounders or biases and often had too few observed numbers of deaths to generate reliable estimates of risk. Case-control studies are usually well-suited for the control of confounding. However, many available case-control studies were population-based which led to a too small number of exposed persons in the diseased and non-diseased groups. Therefore, despite slightly better exposure information, the ascertainment of reliable risk estimates is precluded. The body of published papers available on PCE was qualitatively very weak, making the critical review and synthesis process difficult.

Among studies providing estimates on any specific cancer site or type, it was not clear whether the association was a real one or an artifact or simply a random result. Therefore no quantitative summarizations for the specific cancer sites were calculated. A synthesis of the literature was conducted on a qualitative level for each of the nine cancer sites. Table II shows an overview of cancer sites and conclusions.

These conclusions are based on the actual epidemiological results available.

Table II:
Summary of results for PCE exposure and cancer

Cancer Site	**Conclusion**	
	Strong association	Weak association
Buccal cavity and pharynx	unlikely	unlikely
Esophagus	unlikely	no statement possible
Liver	unlikely	unlikely
Pancreas	unlikely	unlikely
Larynx	no statement possible	no statement possible
Lung	unlikely	no statement possible
Cervix	unlikely	unlikely
Kidney	unlikely	no statement possible
Bladder	no statement possible	no statement possible

An association between PCE and cancers of the buccal cavity and pharynx, liver, pancreas or cervix was considered unlikely. These conclusions would not be liable to change even if the available studies had had better exposure information or had considered additional potential risk factors.

An association between cancer of the buccal cavity and pharynx could not be confirmed and PCE exposure based on the available epidemiological results as control for the main risk factors "smoking" and "alcohol consumption" was missing. Excess liver cancers observed were also more likely explained by factors other than PCE because no excesses were observed in subgroups with the greatest probability of PCE exposure. Therefore an association seems unlikely based on the available epidemiological results. The results of the publications concerning pancreatic cancer were heterogeneous, but there were no increases in risk among those subgroups most likely exposed to PCE. The results concerning cervical cancer were also heterogeneous. Here too was a lack of control for confounding factors and biases.

For esophageal, lung and kidney cancer strong associations are unlikely. No statements concerning weak associations are possible due to methodological problems (exposure assessment, failure to consider other risk factors). The studies of esophageal and lung cancer observed a slight increase in risk. Overall, the results of the studies concerning esophageal cancer were considered inadequate for a firm confirmation of an increased risk in case of PCE exposure. However, because of the magnitude of the observed effects a strong association seems unlikely. Also for lung cancer slight increases in risk were observed. These are more likely due to smoking than due to a possible PCE exposure. The results of the studies concerning renal cell cancer were heterogeneous and therefore no conclusion is possible. However, because of the magnitude of the observed effects a strong association seems unlikely. With regard to weak associations no statements are possible.

Conclusions cannot be made regarding laryngeal and bladder cancer. The results of the laryngeal cancer studies are based on too few cases, limited exposure information and inadequate consideration of other risk factors. The study results concerning bladder cancer showed in most studies increased risks for the whole study population. However, these increases were not significant with one exception. Furthermore, no increase in risk was observed in the subgroup most likely exposed to PCE. Therefore it is doubtful that the observed increases in risk are due to PCE exposure. Furthermore, the problems of imprecise exposure measures and the lack of control for the effect of smoking remain.

The brief analyses (see Table I) yielded no convincing relationships between PCE and the respective cancer sites.

Discussion

A quantitative statistical summarization in the form of a meta-analysis was not considered meaningful, and was not conducted. The available literature has strong methodological restrictions (exposure, confounding) and provides such heterogeneous results that statistical quantitative summarizations would not generate valid estimates.

The extensive review of the publications and the efforts to synthesize the results of the relevant studies on each cancer outcome showed heterogeneous results. This is a basic characteristic that plagues much of the recent cancer epidemiological literature.

From our impression the publications of epidemiological studies were included completely in the literature search. Some of these studies make a limited contribution to the understanding of the role of PCE exposure as a risk factor for cancer. However, none of the studies is adequately strong nor is the body of epidemiological evidence adequate to demonstrate convincingly that any association – strong or weak – is present between PCE and cancer. Therefore the conclusion "occupational exposure to PCE is a risk factor for cancer of a specific site" cannot be supported from the available epidemiological studies. Additional research should be considered which is able to statistically confirm the available results, because in those countries in which most studies have been and continue to be conducted, occupational PCE exposure is low due to legal regulations. It is doubtful, however, whether adequately large populations with greater PCE exposure exist and can be tracked.

1 Introduction

1.1 Background

Tetrachloroethylene (tetrachloroethene, perchloroethylene, PCE)[1], a chlorinated hydrocarbon, is a non-flammable solvent with commercial applications as a chemical intermediary, metal cleaner (vapor degreasing and cold cleaning processes), and as the primary solvent in the dry cleaning industry (International Agency for Research on Cancer (IARC), 1995). PCE is used worldwide with over half of the 1990 PCE demand for use in the dry cleaning industry, by an estimated 75 % of dry cleaners. 23 % of the worldwide use is as a chemical intermediary, and about 13 % for metal cleaning (IARC, 1995). By the late 1980's, 20 to 30 % of PCE consumption in Germany was in the dry cleaning industry, 60 to 70 % was used in metal degreasing and the remainder in other industries (Amtliche Mitteilungen der Bundesanstalt für Arbeitsschutz, 1988).

Carbon tetrachloride was the first chlorinated hydrocarbon used in the dry cleaning industry, primarily in the 1930's and 1940's. It was discontinued and replaced by PCE in the 1950's. Stoddard solvent, a petroleum-based solvent, was used in the USA from the late 1920's until about 1970 (IARC, 1995). Since the 1960's, 75 % of dry cleaning businesses in the USA were using PCE. In Germany PCE has also been used in dry cleaning shops since the 1950's and is the solvent most frequently used today. In addition to PCE, chlorofluorocarbons, other chlorinated hydrocarbons (e. g. TCE) and non-chlorinated hydrocarbon solvents have been used for dry cleaning. Since the beginning of the 1990's hydrocarbon solvents[2] have been increasingly used (Mitteilung Textil- und Bekleidungs BG).

An estimated 500,000 workers are potentially exposed to PCE in the USA, of which 119,000 to 278,000 are employed in the dry cleaning industry (*Weiss*, 1995;

[1] Hereafter the term PCE is used.
[2] Isoparaffin hydrocarbons C_{10}-C_{12}, known as KWL

US Environmental Protection Agency (US EPA), 1998)[3]. The highest exposures occur in the operation of dry cleaning machinery, primarily through inhalation and through skin contact in the transfer process. In 1991, about two-thirds of the estimated 28,100 dry cleaning plants in the USA used a closed process. The remaining plants used an open or transfer process in which solvent-wet clothes are moved from the washer to a dryer by the operator, increasing the potential for exposure (IARC, 1995). In Germany, PCE can only be used in closed facilities according to the second ordinance for the enforcement of air pollution law (the ordinance for emissions limitation of volatile halogenated hydrocarbons — 2nd BImSchV) enacted December 10, 1990.

A 1997 National Occupational Safety and Health (NIOSH) publication reports time weighted average (TWA) exposures of 7.8 to 19.5 ppm for dry-to-dry machine and transfer operators, respectively (US EPA, 1998). Exposure estimates vary according to the job task and process, with the highest exposure found among machine operators who work in shops where the wet transfer process is used. A closed-loop machine with a carbon absorber affords the greatest protection from PCE exposure with a TWA exposure of 1.6 ppm.

PCE was measured in approximately 100 German dry cleaning shops between 1976 and 1978. Exposure for the machine operator of dry-to-dry machines averaged 19.3 ppm (range: 2 to 290 ppm) and in the transfer process 31.1 ppm (range: 3 to 237 ppm). In closed facilities 14 % of the measurements were over 50 ppm compared to 26 % of the measurements in the transfer process (Amtliche Mitteilungen der Bundesanstalt für Arbeitsschutz, 1998). Changes in legislation during the 1990's required a new generation of machines be introduced leading to clear reductions in exposure. In 1997 about 97 % of all measurements were below 5 ppm and during the 1990's between 98 % and 100 % of the studied shops fell under the threshold limit value of 50 ppm (Forschungsinstitut Hohenstein, 1998).

[3] Estimates for exposed workers outside of the USA are unavailable.

PCE emissions from dry cleaning shops are explicitly regulated in Germany. According to the 2nd BImSchV §4 (5) the use of highly volatile halogenated hydrocarbons in operating rooms outside the dry cleaning engines is forbidden. The current permissible exposure limit set by the Occupational Safety and Health Administration (OSHA) in the USA is 25 ppm (TWA), which is also the threshold limit value recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) (US Department of Health and Human Services (DHHS), 1990; ACGIH, 1998). The TWA for occupational exposure to PCE in Germany was set at 50 ppm in 1993. Finland, France, Canada and Japan all have set TWA at 50 ppm, while Denmark has designated the TWA limit at approximately 30 ppm (200 mg/m^3.)

Inhalation of PCE is toxic to various human organ systems. Neurological effects include changes in behavior and coordination, as well as damage to the central nervous system. Damage to the liver and kidneys have also been documented (*Calabrese*, 1991; US DHHS, 1997).

PCE has shown a carcinogenic effect in some animal experiments (*Calabrese*, 1991; IARC, 1995). Mice (B6C3F$_1$) exposed to PCE orally and by inhalation developed liver cancer or liver cancer and adenomas. One strain of rats (F244/N) developed mononuclear cell leukemia and renal tubular cell adenomas and adenocarcinomas (only in male rats) (*Henschler*, 1994). Not all increases were statistically significant and exposure did not produce effects in all strains of rats tested (US DHHS, 1997). The metabolic process that occurs in some species of animals is not found in humans (US DHHS, 1997).

Presently, IARC and the EPA designate PCE as a Group 2A carcinogen, which indicates that sufficient carcinogenic evidence in animals and limited evidence in humans is available. However, occupational exposure through dry cleaning is considered *possibly* carcinogenic to humans and is given a Group 2B designation (IARC, 1995). The EC-commission has classified PCE as carcinogenic in the category K 3 ("Substances which give reason for concern because of a possible carcinogenic effect, however no

sufficient information is available for a satisfactory judgment"; (EC-directive 67/548/EWG, Annex 1).

Epidemiological studies have tried to explore the relationship between PCE exposure and cancer, mostly among populations that include dry cleaning workers, yet few consistent findings have emerged. Dry cleaning workers are considered to have been routinely and highly exposed to PCE in the past. The bladder, esophagus, large intestine, kidney (renal cell) and cervix are among the sites with excess cancer observed within the literature.

Only few studies have evaluated exposure among other occupational cohorts (such as aircraft maintenance workers) where exposure is generally to multiple solvents and therefore an assessment of the specific risks associated solely with exposure to PCE is not possible.

1.2 Project Goals and Objectives

The primary goal of this project was to critically assess the epidemiological literature on the possible relationship between PCE and specific cancers by synthesizing and summarizing relevant information and, if possible, applying quantitative summary and meta-analytical techniques. Specific objectives included:

1. a comprehensive search of the epidemiological literature addressing the possible carcinogenicity of PCE;

2. a critical review of each study to determine the quality of data and methods; and

3. a synthesis of evidence for each cancer site.

An analytical database was constructed in which relevant studies became the individual observations (data points) in order to synthesize the results of the critically reviewed studies. Results are reported by specific cancer site.

This assessment is divided into four parts. This first section, "Introduction", provides an overview of PCE and its use and describes the basic methods of epidemiological and

biostatistical investigations. Included are overviews of study designs, risk estimates and exposure assessment in epidemiology. The second section, "Methods", describes the approach employed in the development of the occupational PCE cancer database, the comprehensive review of the literature and an overview of the techniques for meta-analysis. The third section, "Literature Review and Results", contains results of the critical assessment of the literature. An overview of the key literature is presented, categorized by study design, followed by discussions of major results by specific cancer site. The epidemiological evidence available to address the carcinogenicity of PCE will be evaluated solely on a site-by-site basis. A qualitative summary assessment of risk for each cancer site is presented and discussed. The fourth and final section, "Discussion", summarizes the epidemiological evidence of PCE as a human carcinogen based on the critical review and synthesis. This includes a discussion of critical epidemiological issues relevant to the findings as well as the interpretation of the current analysis.

1.3 Overview of Epidemiological Methods

Epidemiological studies can be broadly classified into experimental and non-experimental (observational) designs. Most studies are observational and include cohort, case-control, and cross-sectional study designs. Additional approaches include studies based on information from death certificates and ecologic studies, where the unit of analysis is a population as opposed to individuals. The epidemiological literature on PCE and cancer consists of published studies using cohort, case-control and death certificate designs, each of which is briefly described below.

1.3.1 Cohort Studies

Cohort studies follow groups of persons over time, stratified by exposure, to observe a variety of outcomes, usually outcomes that are not rare. Subjects in a cohort study are selected with respect to exposure to a specified risk factor. Overall, cohort studies are generally considered the strongest in design for the following reasons: estimated risk can be calculated directly (relative risk); a clear temporal sequence of exposure and disease is established; multiple outcomes can be observed; and a more accurate,

individual-level assessment of exposure may be performed for the exposed groups of interest. Consequently, results of a well-conducted cohort study with adequate numbers of outcomes of interest (e. g. lung cancer) among exposed individuals are usually given more weight than results from other study designs.

On the other hand cohort studies by design allow the assessment of a broad range of mortality or cancer outcomes. Therefore, it is possible to obtain results from cohort studies for specific cancers or causes of death which are based on extremely small observed numbers of cases. These can be highly unstable and therefore possibly misleading.

Furthermore, the manner in which a cohort is assembled or defined impacts the accuracy of exposure measures within the study. Individuals may be placed in the same exposure category based on job title or tasks, though their *actual* exposure may vary due in part to intensity and duration of exposure. Qualitative exposure assessments based on job title are an *estimate* of an individual's real exposure. The true exposure may vary considerably within the defined exposure categories.

1.3.2 Case-control Studies

Case-control studies typically examine one or more hypothesized risk factors for an association with the particular outcome under study. Cases are individuals identified as having a disease or cause of death of interest, and controls are a representative sample of the non-diseased population from which the cases are drawn (e. g. inhabitants of a specific region, hospital patients). The prevalence of risk factors of interest is contrasted between the cases and controls, differences indicating an association.

This design is considered to be cost efficient because the starting point of the study, incident cancer cases, has already occurred and also because information on several risk factors, including potential confounders, can be obtained and examined simultaneously.

By design, case-control studies can be hospital-based or population-based, or they may be "nested" within a defined cohort, such as an occupational cohort. While each of these designs presents advantages, the strength of the nested case-control study lies in the fact that cases and controls are selected from the same defined cohort, reducing the possibility of selection bias. Further, the prevalence of the exposures of interest among the controls is generally high in nested case-control studies. In contrast, population-based studies choose controls from a general population, where the distribution of the exposures of interest may be highly diluted. This exposure infrequency weakens the statistical power of the study to detect results and, in turn, can reduce the study's validity.

1.3.3 Death Certificate Studies

Death certificates are often used in epidemiology to compare the proportion of deaths from an index cause among all deaths within an exposed cohort, to the corresponding proportion of index deaths in an unexposed group or a general population. The result, a "Proportionate Mortality Ratio" (PMR), is a measure of exposure effect for the index cause of death (*Rothman*, 1998). A variation of this measure known as "Standardized Mortality Odds Ratio" (SMOR) is also used to compare mortality in death certificate analyses. The SMOR is the ratio of two odds: it is the odds in favor of the index cause of death among the exposed (i. e. the number of deaths from an index cause in the exposed group/to the number of deaths from other causes) compared to the corresponding odds in the non-exposed group (i. e. number of index deaths/to the number of deaths due to other causes) (*Duh*, 1984).

Because the proportionate mortality approach does not require follow-up information on cohort members, it provides a simple method to investigate crude exposure-disease relationships. However, little or no data on underlying risk factors for the study population are collected, so risk estimates generated from these studies must be interpreted with caution. Further evaluation and confirmation of PMR results by other study designs are necessary. Moreover, while an elevated PMR may represent an increased risk for an index cause of death, the estimate may simply reflect a distributional deficit of

deaths due to other causes. An example of this is termed the "healthy worker effect", where employed individuals are healthier than the general population, and excess mortality (usually cancers) observed for the working population may simply reflect a strong mortality deficit for other causes (usually cardiovascular disease deaths) *(Hennekens*, 1987).

Of the three approaches described above, cohort and case-control studies are considered stronger, and are frequently used to test specific hypotheses. On the other hand, proportionate mortality analyses are usually used for preliminary explorations and to generate hypotheses. Accordingly, death certificate studies using PMR analyses carry less weight in a synthesis of the evidence regarding specific associations. Among case-control studies, community-based studies are considered among the weakest, and those "nested" in a well-defined cohort among the strongest.

1.4 Overview of Risk Estimates in Epidemiology

Specific to the design of an epidemiological study is the risk estimate or measure of association between exposure and disease. The *Relative Risk* (RR) is defined as the ratio of the risk of disease (or death) among the exposed compared to the risk among the unexposed. Other measures of association are derived from various epidemiological study designs. The *Odds Ratio* (OR) is defined as the ratio of the odds of exposure among those with the disease or outcome of interest to the odds of exposure among those without the disease (the comparison population or controls) and is almost always used in the analysis of case-control data. The odds ratio is approximate to relative risk where the disease outcome is rare. The *Proportionate Mortality Ratio* (PMR) has been defined above. The S*tandardized Mortality Ratio* (SMR) is the ratio of the number of deaths observed in the study group to the number of deaths that would be expected if the mortality rate in the study group were the same as the mortality rate in an external (reference) population. The Standardized Incidence Ratio (SIR) is similar, using incident cases and incidence rates rather than mortality information.

All of these measures of association are assumed to be comparable for purposes of critically reviewing and synthesizing study results, although technically they may not be

equivalent. In practice, all are considered estimates of relative risk, and in some contexts (such as journal articles – see for example the medical journal *The Lancet*) are all referred to as relative risk. In all cases, the measures of association are similarly interpreted. A risk estimate of 1.0 indicates that the mortality or morbidity rate in the study group is the same as the mortality or morbidity rate in the comparison population.

An indication of the precision of a risk estimate is the confidence interval (CI). A narrow confidence interval suggests greater precision of the estimate and is based on larger numbers of observed and expected outcomes, such as cases of disease or death. Conversely, wide confidence intervals indicate poor precision (and are typically based on small numbers of observed and expected outcomes). The confidence interval represents a range of possible values.

1.5 Exposure Assessment

Exposure assessment used in occupational epidemiological studies ranges from very simple qualitative to highly quantitative measures.

The quality of exposure assessment directly determines the validity of the study results; however, the full extent of this is rarely recognized, and numerous studies continue to be published with no valid direct exposure measurement. Even in the presence of perfect exposure assessment at a study participant level (which is not yet attainable in most epidemiological or observational study settings), each individual participant may be unique with respect to metabolism, clearance, retention, and sensitivity of biological response. All of these aspects of the dose-response relationship are typically not grasped in epidemiological research. More often, though not necessarily considered is the latency period, the delay between an exposure and the expression or recognition of disease in an exposed individual. Given that most cancers require from a few years to up to several decades between adequate exposure and the detection of disease, exposure assessment must determine the level of exposure at the appropriate time period before the detection of the disease. Exposures sustained after a cancerous process is underway are usually thought to be irrelevant, unless they influence the rate

of development of disease (as in a tumor promoter or suppressor) or the timing of detection (if exposed persons were more likely to be under medical surveillance).

Ideally, an exposure assessment should approximate the dose of the agent delivered to the target tissue or organ as closely as possible given the available data. As the indicator of exposure becomes more indirect and distant from the individual, increased misclassification of individuals with respect to exposure level is likely to occur. Exposure misclassification error can have a profound effect on the ability of a study to derive valid risk estimates.

Therefore, exposure measures based on ongoing biological monitoring of individuals are likely to be strongest, and to produce the most accurate risk estimates. Historically, few substances have been monitored biologically, partly due to the limited availability of appropriate biological media (due to invasiveness of some procedures), lack of analytical ability, poor employee compliance, and high costs of such programs.

More attainable, though still not universal, is the quantitative monitoring of air concentrations of agents in the breathing zones of individuals. These measurements require individuals to wear sampling pumps, which are often cumbersome, uncomfortable, and expensive. Area monitoring devices are much more commonly used, though usually for documenting compliance with established exposure limits. However, the validity of these measures as substitutes for individual-level measurements varies. Agents that disperse rapidly and evenly within a work area may be reasonably measured with area monitors (for example, some forms of radiation) whereas other agents may have considerable person-to-person variability, in which case an area monitor may reflect exposure level at the specific location where the monitor is located.

Variability in the exposure of interest may not be captured by any of these measurement techniques, especially if changes occur within working shifts. Longer-term changes may be characterized if samples are taken frequently within an area or for a specific person.

Far more common but of questionable validity, especially for quantification of risk, are the indirect exposure assessment approaches. At the better end of the range these include the combination of individual work histories (including job and work area) with job- and area-based exposure estimates, using what is called a "job-exposure matrix" or JEM. At the other end, and the least accurate, are indirect exposure assessments, including the use of job titles, whether one has ever worked in an industry, or usual occupation or industry indicated on death certificates, as practiced in the USA. These methods, though inaccurate, are commonly used as preliminary screening devices, as they are easy to use and quite inexpensive. In most contexts, however, more definitive exposure estimating procedures are required before any valid quantification of risk is possible. The simpler approaches may assist in identifying areas worthy of more detailed and often costly research.

Additionally, exposure assessment may be determined and limited by the specific study design selected to study an exposure-disease relationship.

Cohort and case-control study designs, as well as death certificate studies, were employed in the papers reviewed below to provide evidence of carcinogenicity from PCE exposure. However, different study designs have different capabilities of exposure assessment, and so the choice of a specific study design determines to a large extent the quality of the exposure assessment.

Exposure assessment in prospective cohort studies offers the best opportunity to measure an exposure, by documenting changes in exposure levels as they occur, and determining dose-response estimates for each cohort member. Retrospective cohort studies estimate previous exposure, often that occurred at some time in the distant past. This historical exposure assessment is generally the weakest aspect in most occupational epidemiological studies, due to a lack of direct or quantitative exposure measures from the relevant period of exposure as well as a lack of *complete* qualitative measures.

A well-conducted case-control study with adequate power will supply meaningful results, but this design has potential weaknesses due to difficulties estimating past

exposures, possibly leading to substantial information bias. Furthermore, population-based case-control studies are often weaker in terms of exposure estimates due to the low prevalence of exposure in the general population and possibly biased self-assessment concerning exposure, both of which contribute to unstable risk estimates.

Death certificate studies incorporate only a rough exposure measure, and assume that all study subjects within a given job/industry category are exposed equally. These studies rely on the assumption that death categories other than the ones under study are not related to the exposure of interest, and that if an exposure causes or prevents specific disease deaths, there should be a corresponding fractional increase (or decrease) among those who were exposed (*Rothman*, 1998).

While there may be similarities in exposure assessment within and between study designs, not all studies that appear similar with respect to exposure are in truth equal in the assessment of exposure or the actual "real" exposure. For example, if we compare two studies of dry cleaners, we generally assume them to be "equally" exposed. But in reality we do not know that the exposures are the same. This is where issues such as duration, latency, average, peak and cumulative exposure are critical. As stated, exposure assessment ranges from a highly precise quantification of exposure to a simple qualitative measure. In order to fully understand the level of exposure or the likelihood that an exposure actually occurred more information must be considered.

For example, in a cohort of US dry cleaning and laundry workers we can be reasonably certain that the majority of those employed as dry cleaners after 1960 were exposed to PCE at some level (with the exception of regions like Oklahoma, USA). What we do not *necessarily* know in a mixed cohort is how many and which workers were operating dry cleaning machinery, especially relevant for census-based cohort studies where it is not clear if the cases were dry cleaners or launderers. But even if we would be able to determine a sub-cohort of dry cleaners we also should know how often, at what level they were exposed to PCE and for how long and the potential for exposure to other solvents. These other factors, cumulative dose, intensity and duration of exposure, are all crucial in "quantifying" overall exposure. The "true" exposure to PCE

(or other solvents) will be very different for an individual who worked for ten years as a counter cashier compared to an individual who operated a transfer machine for ten years.

The information to fully quantify exposure is not always available. However, even in cohorts or populations where exposure is uncertain an association may still be explored, as information obtained from a study may provide insight into a possible relationship or even rule out a strong exposure-disease relationship.

Finally, how the exposure data are summarized will also influence the accuracy of risk estimation. Indicators of exposure level (whether quantitatively or indirectly measured) are often multiplied by some interval of time (such as duration of employment) to derive a cumulative exposure index, preferably considering an appropriate latency period. However, if the mechanism by which the agent causes cellular or genetic damage leading to a cancer requires that a threshold be exceeded, then cumulative indices of exposure may not be appropriate. Unfortunately, early in the understanding of the mechanisms of a carcinogen, it is not possible to know which approach to exposure estimation is appropriate, and it may be best to use more than just cumulative exposure as the exposure variable, if possible.

1.6 Biases and Confounding

Selection and information biases are potential problems in all epidemiological studies. Selection bias refers to systematic differences influencing who is included in the study population. Information bias relates to the differential measure of exposure or the determination of disease-outcome across comparison groups. A bias specific to case-control studies is recall bias, where a case subject (or, if deceased, a next of kin or other proxy) may have differentially remembered exposures more clearly or even over-estimated exposures compared to control subjects. In addition, confounding may also undermine the validity of an observed effect. A confounder is a risk factor for the disease of interest that is also related to the exposure, but not as an intermediary in the disease process. A number of techniques for eliminating bias due to confounding are

available, including stratified analysis and multivariable analyses (*Rothman*, 1986; *Last*, 1988).

1.7 Principles of Meta-Analysis

In the broadest sense, meta-analysis is "a means of comparing and synthesizing studies dealing with similar health effects and factors" (*Blair*, 1995). The literature review and synthesis described in this report is an example. Our approach followes an explicit protocol that was developed *a priori* and includes, among other tasks, the following:

1. systematic identification of studies,

2. derivation of criteria for inclusion and exclusion of studies, and

3. abstraction of study findings.

A purely quantitative definition of meta-analysis is "a collection of techniques whereby the results of two or more independent studies are statistically combined to yield a single statistic which, it is claimed, has important descriptive or inferential properties" *(Oakes*, 1990). The synthesis of study findings in a meta-analysis entails, at least in part, the application of quantitative techniques.

The statistical techniques of meta-analysis can be grouped into two realms, those which consider the distribution of separate p-values and those which consider the separate estimates of effect. An analysis of p-values is based on an assumed sampling distribution which is limited by biological variation, measurement error, and study design (especially sample size). A statistical combination of separate estimates of effect is potentially informative, but only when the estimates combined evaluate the same cause-effect relationship. The technique of combining separate estimates across studies is an application of stratified analysis methodology. The investigator computes a summary measure of the association of interest and uses this in a formal assessment of the homogeneity of the separate study findings. If judged homogeneous, the separate estimates of effect can be meaningfully combined into a single summary estimate of association which is then evaluated for its departure from the null. One approach to

this is given by *Mantel* and *Haenzel* (1959) as summarized in Table 1. For ease of presentation, the notation is that of *Petitti* (1994):

	Exposed	**Not exposed**	$\sum$
Diseased	a_i	b_i	g_i
Not diseased	c_i	d_i	h_i
$\sum$	e_i	f_i	n_i

Table 1:
"Fixed Effects" model formulae for point (OR_{mh}) and 95 % confidence limit estimate (95 % CI) for a summary Odds Ratio as measure of association between a dichotomous exposure predictor and a dichotomous cancer disease outcome, that can be classified as "existing" or "non-existing", for studies $i = 1 \ldots S$.[1]

	Point estimate	**95 % CI**
"Fixed Effects" Model	$OR_{mh} = \frac{\sum_{i=1}^{S} w_i (OR_i)}{\sum_{i=1}^{S} w_i}$	$95\%\text{CI} = \exp(\ln(OR_{mh} \pm 1.96\sqrt{\text{var}(OR_{mh})}))$
	whereas	whereas
	$w_i = 1/\text{var}_i$	$\text{var}(OR_{mh}) = \left(\frac{\sum F_i}{2\sum R_i^2}\right) + \left[\frac{\sum G_i}{2(\sum R_i)(\sum S_i)}\right] + \left(\frac{\sum H_i}{2\sum S_i^2}\right)$
	$\text{var}_i = \frac{n_i}{b_i c_i}$	$F_i = a_i d_i \left(\frac{(a_i + d_i)}{n_i^2}\right)$ $\quad G_i = \frac{[a_i d_i (b_i + c_i)] + [b_i c_i (a_i + d_i)]}{n_i^2}$
	$OR_i = \frac{a_i d_i}{b_i c_i}$	$H_i = \frac{b_i c_i (b_i + c_i)}{n_i^2}$ $\quad R_i = \frac{a_i d_i}{n_i}$ $\quad S_i = \frac{b_i c_i}{n_i}$

[1] *Mantel* and *Haenszel* (1959)

If the separate estimates of effect do not derive from studies of the same cause-effect relationship, or are determined to be heterogeneous, then the statistical combination of estimates is unwarranted and may lead to erroneous (although possibly statistically stronger) conclusions.

We believe that in most meta-analyses of the observational epidemiological literature the appropriate assumption is that the separate estimates of effect are heterogeneous. It has been our experience that often the separate studies are not separate studies of the same relationship. Rather, they are at best studies of similar relationships because of differences in choice of study population, measurement of exposure, control for confounding, etc. It is also our view that the heterogeneity is a useful tool in gauging the strength of a suspected exposure-disease relationship.

For example, if such a relationship exists, we might expect a non-zero and constant association is found in varying study populations because the biology is the same; for this reason, we find more informative the pattern of study specific results rather than a single summary measure. As the measurement of exposure becomes more precise there is less noise incorporated in the estimates of association.

Therefore, where the evidence indicates that the separate estimate of effects are not similarly adequate to calculate a summary measure, the evidence available for each cancer site is critically reviewed and synthesized, and a conclusion is developed based on the full range of information.

2 Methods

2.1 Identification of Relevant Studies

The first and one of the most critical steps in conducting a critical review and synthesis is the identification of the relevant literature. This is highly dependent on what the author(s) present in the publication itself. For example, in a case-control study the exposure status of cancer cases is compared to the exposure status of a "control" group. Frequently a variety of exposures (in the form of agents or occupation/industries) are taken into account. Generally, only those results which relate to the study hypothesis or any other "positive" findings are reported. Studies finding "no" or "negative" results or associations are often not reported, and literature searches tend to identify studies with more "positive" findings ("publication bias"). Additionally, the assignment of keywords to the publication (based in part on the abstract) effects the identification of relevant literature. As a rule, only the most important results (in the view of the authors or editors) are mentioned in the abstract. So if the question of interest is not part of the main results of a given study, a literature search within a scientific database may not be able to locate the study.

We chose a multistage search procedure in this project, addressing various information sources, to ensure a comprehensive search of the literature. The first phase consisted of a review of general literature (i. e. textbooks, review papers and other secondary sources) leading to searches using MEDLINE. Next, specialized databases (i. e. CANCERLIT, TOXNET, etc.) were searched to identify potential publications. For all searches the following search words were used as the main key words: "Tetrachloroethylene", "Laundry/dry cleaning" and "Degreasing" (respectively including all synonyms). Searches for other relevant occupations, industries or authors were also conducted.

The results of the literature searches were compiled and screened using the following inclusion and exclusion criteria:

- ❒ Studies had to be published in peer-reviewed journals (with the exception of book publications and research reports).
- ❒ Only epidemiological studies were included (i. e. case reports, exposure assessments and reviews of the literature were excluded).
- ❒ Outcomes of interest were limited to cancer mortality or incidence.
- ❒ Source of potential exposure had to be occupational (environmental studies excluded).
- ❒ "PCE" or "laundry/dry cleaning" (or synonyms) had to be mentioned in the abstract or key words.

The results of the literature search were then compared to the bibliographies/reference lists of published reviews concerning "Perchloroethylene" or "organic solvents", the "dry cleaning industry" or specific cancer locations to identify any additional literature (Applied Epidemiology Inc., 1998; *Axelson*, 1986; *Ikeda*, 1992; IARC, 1995; *Lynge*, 1997; *McLaughlin*, 1997; *Shen*, 1998; *Ulm*, 1996; US DHHS, 1997; *Weiss*, 1995/1996).

Some studies identified through this overview could not be identified through the literature searches of scientific databases using key words. In order to ensure completeness of the literature search, including publications in recent years, all epidemiological studies with a reference to occupation and included in MEDLINE from 1995 (year of publication of the IARC report) to 1998 were checked in the event that the original publication contained information relating to PCE or dry cleaning which was not identified by title, keywords or the abstract (i. e. case-control studies of particular cancers). For these studies, the original publications were reviewed for relevancy.

All results were then compared to results of searches conducted by the Berufsgenossenschaftliches Institut für Arbeitsschutz (formely: für Arbeitssicherheit) – BIA between 1997 and 1999. Finally, regular updates of the literature searches were done until the middle of 1999 to identify any new publication.

In total, 81 publications (published between 1963 and 1999) were identified for detailed screening and critical review. Libraries, inter-library loan services, article retrieval services and direct contact with authors/institutions were used to obtain copies of potentially relevant papers.

2.2 Critical Review and Extraction of Information

Each publication was reviewed independently by at least two epidemiologists. The critical assessment considered both objective (e. g. study design, control of confounding, exposure definition and exposure assessment approach) as well as subjective elements (e. g. "quality" of design, reduction of bias, identification of study limitations by the authors).

To standardize the review process a critical review instrument was developed to extract the relevant data from each of the 81 studies (see Appendix C). The reviewers followed the standard critical assessment tool to ensure uniformity of evaluation and database completeness. The overall strategy was to include as many studies as possible, identifying their limitations, rather than excluding studies. Studies making no valid contribution were not considered in the synthesis of evidence.

From the total of 81 publications 45 were included in further analysis and synthesis (see Table 2).

Table 2:
Studies included according to study design, cancer site and country

Study (First author/Year)	Study design	Cancer site(s)	Country
Katz, 1981	PMR/DC study	Multiple	USA
Silverman, 1983	Case-control study	Bladder	USA
Stemhagen, 1983	Case-control study	Liver	USA
Duh, 1984	PMR/DC study	Multiple	USA
Malker, 1984	Cohort study	Multiple	Sweden

Table 2 (continued):

Study (First author/Year)	Study design	Cancer site(s)	Country
Schoenberg, 1984	Case-control study	Bladder	USA
Mabuchi, 1985	Case-control study	Vulva	USA
Nakamura, 1985	PMR/DC study	Multiple	Japan
Smith, 1985	Case-control study	Bladder	USA
McLaughlin, 1987a	Cohort study	Kidney	Sweden
McLaughlin, 1987b	Cohort study	Liver	Sweden
Asal, 1988	Case-control study	Kidney	USA
Doebbert, 1988	PMR/DC study	Multiple	USA
Silverman, 1989	Case-control study	Bladder	USA
Suarez, 1989	PMR/DC study	Liver	USA
Blair, 1990	Cohort study	Multiple	USA
Bond, 1990	Case-control study	Liver	USA
Lynge, 1990	Cohort study	Multiple	Denmark
Silverman, 1990	Case-control study	Bladder	USA
Siemiatycki, 1991	Case-control study	Multiple	Canada
Spirtas, 1991	Cohort study	Multiple	USA
Huebner, 1992	Case-control study	Buccal Cavity and Pharynx	USA
Blair, 1993	Case-control study	Non-Hodgkin's Lymphoma	USA
Brownson, 1993	Case-control study	Lung	USA
Heineman, 1994	Case-control study	Brain	USA
Lynge, 1994	Cohort study	Multiple	Denmark
Ruder, 1994	Cohort study	Multiple	USA
Anttila, 1995	Cohort study	Multiple	Finland

Table 2 (continued):

Study (First author/Year)	Study design	Cancer site(s)	Country
Chow, 1995	Cohort study	Esophagus	Sweden
Clavel, 1995	Case-control study	(Hairy cell) Leukemia	France
Delahunt, 1995	Case-control study	Kidney	New Zealand
Lynge, 1995	Case-control study	Liver, Kidney	Denmark
Mandel, 1995	Case-control study	Kidney	5 Countries
Reviere, 1995	PMR/DC study	Liver	USA
Swanson, 1995	Case-control study	Multiple	USA
Aronson, 1996	Case-control study	Prostate	Canada
Gallagher, 1996	Case-control study	Skin (SCC, BCC)	Canada
Milham, 1997	PMR/DC study	Multiple	USA
Teschke, 1997	Case-control study	Bladder, Nasal cavity	Canada
Vaughan, 1997	Case-control study	Buccal Cavity, Esophagus, Larynx	USA
Walker, 1997	PMR/DC study	Multiple	USA
Clavel, 1998	Case-control study	(Hairy cell) Leukemia	France
Krstev, 1998	PMR/DC study	Prostate	USA
Muscat, 1998	Case-control study	Lung	USA
Dosemeci, 1999	Case-control study	Kidney	USA

Among the studies selected for critical review there were some that drew from the same study or study population, but were determined to be significant or not over-lapping. The three Swedish cohort studies (*McLaughlin*, 1987a, 1987b; *Chow*, 1995) are updates of specific cancer sites for the *Malker* (1984) cohort study. The study by *Lynge* (1994) presents actual results of the cohort study by *Lynge* (1990) for liver cancer and the *Lynge* (1995) study is a nested case-control study of the 1990/1994 cohorts, investigating liver and renal cell carcinoma. The *Aronson* (1996) case-control

study includes a detailed analysis for prostate cancer based on the data of the *Siemyatticki* case-control study (1991). Both French publications *(Clavel*, 1995 and 1998) have the same data basis. However, the analyses differ by gender and exposure (agent, occupation).

The other 36 studies/publications were excluded from full critical review because of at least one of the following reasons:

- There was more than one publication concerning the same study population and study period.
- There was more than one publication concerning the same study population but different study periods (observation periods) and the "older" publication presented no additional results compared with the more recent publication (we used this "older" publication as additional information concerning methodological questions).
- The single study was included in a multi-center study and the results of the larger study were already included in the critical review and synthesis.
- No risk estimate was presented because according to the authors, the numbers of cases and controls was too small for analysis or because either the number of cases and/or controls was "zero".
- The probability of any "substantial" PCE exposure was low or undefined and could not be determined in the study population (e. g. when there was only a risk estimate for "organic solvents" without further differentiation).
- When PCE is mentioned by the authors only as a part of a (long) list of possible exposures without further differentiation.

Additionally, three papers which we could not obtain during the project or were lacking necessary detail were excluded (e. g. a dissertation). Based on the information obtained from these studies (e. g. from the IARC report, 1995) with regard to publication type, study design, exposure estimate, and cancer location(s) it can be assumed

that the exclusion of these papers does not limit the significance of further analysis. Two other studies were excluded because of methodological limitations.

A detailed overview of the 36 excluded publications is presented in Table 3.

Table 3:
Characteristics of publications excluded from further analysis

Study (First author/Year)	**Design/ Country**	**Exposure (Cancer site)**	**Comment**
Aupérin, 1994	Case-control France	Laundry/Dry cleaning (Kidney)	No risk estimate; the authors report that the number of cases and controls were too small for analysis
Austin, 1987	Case-control USA	Laundry/Dry cleaning (Liver)	No risk estimate; 0 cases/4 controls exposed
Blair, 1979	PMR/Death Certificate USA	Laundry/Dry cleaning (Multiple)	Included in *Blair* 1990 cohort; analysis of a preliminary number of death certificates
Blair, 1980	PMR/Death Certificate USA	Electroplaters (Multiple)	Too many different exposures possible; PCE cited as only one of many and further differentiation was not made in the analysis
Blair, 1986	Cohort USA	Dry cleaning (Multiple)	Included in *Blair* 1990 cohort; preliminary results presented at a workshop
Blair, 1992	Case-control USA	Laundry/Dry cleaning (Non-Hodgkin's Lymphoma)	Study identical to *Blair* 1993; preliminary results presented at a workshop
Blair, 1998	Cohort USA	Aircraft maintenance personnel (Multiple)	Update of *Spirtas* 1991 cohort; however, no results reported regarding PCE
Brown, 1987	Cohort USA	Dry cleaning (Multiple)	Included in the *Ruder* 1994 cohort
Carpenter, 1995	PMR/Death Certificate England	Laundry/Dry cleaning (Ovary)	Workshop report; results based on only 22 % of female cancer cases during period of observation (for all others indication of occupation was not available)

Table 3 (continued):

Study (First author/Year)	Design/ Country	Exposure (Cancer site)	Comment
Døssing, 1997	Case-control Denmark	Printing industry (Liver)	Too many different exposures possible, PCE only one of many cited; the authors state that in the past these employees were exposed to large amounts of organic solvents including trichlorethene and PCE, but more specific exposure not determined
Dubrow, 1987	PMR/Death Certificate USA	Jewelry manufacture (Multiple)	Too many different exposures possible; PCE cited as only one of many and further differentiation was not made in the analysis
Fredriksson, 1989	Case-control Sweden	Dry cleaning (Large Intestine)	Under "occupation", "dry cleaner" was indicated, yet in the analysis of substances and in the discussion of results PCE was not mentioned, only trichlorethene
Gallagher, 1989	PMR/Death Certificate Canada	Laundry/Dry cleaning (Multiple)	Report not available; results described in IARC Report 1995 but with no methodological details; based on the study design and the reported cancer sites no fundamental loss of information is expected by its exclusion
Goldberg, 1997	Case-control France	Laundry/Dry cleaning (Larynx)	No risk estimate; 8 cases/0 controls exposed
Greenland 1994	Case-control USA	Installation of transformers (Multiple)	PCE not mentioned; analysis concerned various exposures such as benzene, asbestos, trichlorethene, etc.
Guralnick, 1963	Cohort USA	Laundry/Dry cleaning (Multiple)	The author analyzes death certificates from 1950, so that PCE exposure unlikely
Hardell, 1981	Case-control Sweden	Organic solvents (Morbus Hodgkin's; Non-Hodgkin's Lymphoma)	No risk estimate for PCE; risk estimates only for combined groups (styrene, benzene, trichlorethene and PCE); 1 case/0 controls PCE exposed
Hardell, 1984	Case-control Sweden	Organic solvents (Liver)	No risk estimate for PCE; 1 case/0 controls PCE exposed
Harrington, 1989	Case-control England	Dry cleaning preparations (Kidney)	No risk estimate for PCE; 0 cases/0 controls exposed
Hernberg, 1984	Case-control Finland	Solvents (Liver)	No risk estimate for PCE; 1 case of chloride hydrocarbon in "laundry" or "dry cleaning" exposed (contradictory statements by the author)

Table 3 (continued):

Study (First author/Year)	Design/ Country	Exposure (Cancer site)	Comment
Hernberg, 1988	Case-control Finland	Solvents (Liver)	No risk estimate for PCE; only risk estimates for solvents
Kaplan, 1980	Cohort USA	Dry cleaning (Multiple)	Study included in the *Brown* 1987 cohort and the *Ruder* 1994 update
Lin, 1981	Case-control USA	Dry cleaning or occupations in connection with gasoline (Pancreas)	No differentiation regarding occupation or substances in the risk estimate
Mack, 1985	Case-control USA	Laundry/Dry cleaning; Organic solvents (Pancreas)	No risk estimate for occupation or area of industry documented; no differentiation in risk estimate for "organic solvents"
McCredie, 1993	Case-control Australia	Dry cleaning (Kidney, Renal Pelvis)	Part of the "International Renal-Cell Cancer Study", see *Mandel* 1995; (*Mandel* adopted only a portion of the cases and controls in the multi-center study, but the selection mechanism is not comprehensible)
Mellemgaard, 1994	Case-control Denmark	Dry cleaning (Kidney)	Part of the "International Renal-Cell Cancer Study", see *Mandel* 1995
Morton, 1984	Cohort USA/Canada	Laundry/Dry cleaning (Leukemia)	No applicable risk estimate
Office of Population Censuses and Surveys, 1986	PMR/Death Certificate England	Laundry/Dry cleaning (Multiple)	Report not available; results described in IARC Report 1995 but with no methodological details; based on the study design and the reported cancer sites no fundamental loss of information is expected by its exclusion
Olsen, 1989	Cohort USA	Chemical (Multiple)	Too many different possible exposures, PCE cited as only one of many and no further differentiation in the analysis
Partanen, 1991	Case-control Finland	Dry cleaning (Kidney)	No risk estimate; only 1 case with occupation as "dry cleaner"
Petrone, 1988	PMR/Death Certificate USA	Dry cleaning (Multiple)	Not available; published only as an abstract (dissertation); in the IARC Report 1995 under exposure as "petroleum-based solvent"

Table 3 (continued):

Study (First author/Year)	Design/ Country	Exposure (Cancer site)	Comment
Pukkala, 1995	Cohort Finland	Laundry (Ovary)	Methods not included in copy obtained; relevance regarding occupational group "laundry" unclear; cancer not central question of research
Schlehofer, 1995	Case-control Germany	PCE and tetrachloride carbonate (Kidney)	Part of the "International Renal-Cell Cancer Study", see *Mandel* 1995
Sharpe, 1989	Case-control Canada	Degreasing solution (Kidney)	The authors report that further substance-specific differentiation was not possible
Stewart, 1991	-- USA	Aircraft maintenance personnel --	No risk estimate; Publication of the methods used in exposure estimate for Spirtas 1991 study
Vamvakas, 1998	Case-control Germany	PCE (Kidney)	No risk estimate; 0 cases/2 controls exposed

2.3 Construction of the Analytical Database

A detailed relational database file containing descriptive and critical review elements for each study was created as the product of the critical review process. Source data are those generated by the individual critical reviews.

This computer database contains over 100 fields for elements of interest (i. e. variables), which may be useful in determining heterogeneity among groups of papers addressing single topics (e. g. cancer by site). These fields have been grouped in a number of modules to reflect standard sections within a study (e. g. study design and sample size, methods for exposure assessment, results). Information entered in this database included: study title; author and journal name; length of follow-up period among cohort members; statistical information on risk estimates; measurement of potential confounders; as well as all pertinent results. (See Appendix D for a depiction of the relational database.) Because of the need to evaluate subgroups of studies (e. g. by study design or cancer outcome), the database was constructed to be able to sort several fields simultaneously.

2.4 Selection of Cancer Sites for Critical Review

All included studies were sorted by cancer site. All studies were then assessed by cancer site to evaluate the literature and the potential for critical evaluation. For some sites (e. g. bone, eye, thyroid) too few results were available to critically review and assess the possibility of relationship between PCE and the given cancer site. Additionally, where the bulk of the results came from death certificate studies, the cancer site was not selected for critical review (e. g. for ovarian cancer there was one cohort study and four death certificate based studies).

17 sites in all were critically reviewed (see Table 4). Background literature on each cancer site was reviewed for national and international incidence and mortality rates and for known or possible risk factors. Following this, the studies reporting results for each cancer site were reviewed in the context of the available background literature for each cancer site.

Table 4:
Reviewed cancer sites according to the International Classification of Diseases (ICD)

ICD-9	Site	Number of Publications	Type of Analysis
140-149	Buccal cavity and pharynx	8	detailed
150	Esophagus	8	detailed
151	Stomach	8	brief
154	Rectum	8	brief
155-156	Liver	16	detailed
157	Pancreas	10	detailed
161	Larynx	6	detailed
162	Lung	14	detailed
172-173	Skin	9	brief
174-175	Breast	8	brief
180 (179-184)	Cervix uteri (Female genital organs)	8	detailed

Table 4 (continued):

ICD-9	Site	Number of Publications	Type of Analysis
179,181-182	Corpus uteri	6	brief
185	Prostate	10	brief
188, 189.3-189.9	Bladder	16	detailed
189.0-189.2	Kidney	16	detailed
191-192	Brain and other nervous system	5	brief
200-208	Lymphatic/hematopoietic system	6 *	brief

*additional studies reported results for specific types of leukemia

Subsequently, nine of these cancer sites were selected for a *detailed* critical review and synthesis. In addition to the selection criteria of the number of available studies some sites were also selected a priori. These cancer sites (e. g. renal cell carcinoma) have garnered much attention within the epidemiological literature because of conflicting results or because statements that a relationship exists between PCE exposure and the respective cancer site were made. A detailed discussion of these nine cancer sites is presented here in section 3.5 “Cancer Site Summaries”.

The eight remaining cancer sites were critically reviewed; however, because of the limited quality or quantity of evidence available for consideration, only brief summaries are presented. All 17 cancer sites critically reviewed are presented under “Cancer Site Summaries” in section 3.5 to provide a comprehensive picture of the epidemiological literature on PCE and cancer to date.

2.5 Criteria for the Likelihood of PCE Exposure

Most of the studies included in this report tried to assess PCE exposure in an indirect way, using surrogate measures such as occupation or industry, generally without information regarding specific agents.

As part of the critical synthesis we developed a classification scheme to assess the studies according to their probability that study populations and cases were exposed to PCE. This likelihood "rating" is based on the highest category at which some effort was made to isolate at least a subgroup with the given level or probability of exposure to PCE. Information used to "rate" studies included the following: time period of potential exposure, exposure definition and/or measure, exposure history, and knowledge of industry practices with regard to PCE.

1. PCE exposure likely

PCE cohort or sub-cohort is likely exposed to PCE based on exposure measure, time period or history of solvent use in the workplace. It is reasonable to consider that study subjects were exposed to PCE. It does not exclude other exposures, though PCE is considered to be the predominant exposure.

2. Mixed exposures

These study subjects appear to have been exposed to a variety of substances, or the study population included different industry or job categories. Where study populations are mixed, it may be that a larger part of the individuals are not exposed to PCE. However, it was not possible within the study to identify a sub-cohort based on the industry or job category.

a) PCE exposure likely

It is reasonable to consider that PCE was among the solvents or agents that these populations and the cases of disease were exposed to.

b) PCE exposure possible

It is possible that PCE was among the solvents or chemical agents that these populations and the cases were exposed to. However, we have no specific knowledge regarding exposure. Individuals or groups within the populations may or may not have been exposed to PCE.

3. PCE exposure unlikely

Exposure to PCE for these populations is not likely given the information presented in the reports and/or our knowledge of industrial PCE use.

These criteria for likelihood of PCE exposure are based on specific details from a study and an overall sense of the level and quality of exposure assessment. In some instances, studies could have been placed into an adjacent category. The development of the criteria and the application of the criteria to the studies reviewed represent an appraisal of the exposure assessment used by a specific study.

3 Literature Review and Results

45 studies were critically reviewed by cancer site and design. Summaries of the cohort and death certificate studies are provided, as they tend to present results for multiple outcomes and are referred to in several specific cancer sections. A summary overview of the case-control studies is also included, with specific details for those studies that evaluated multiple outcomes. Study details are presented in Tables 5 to 13.

3.1 Cohort Studies

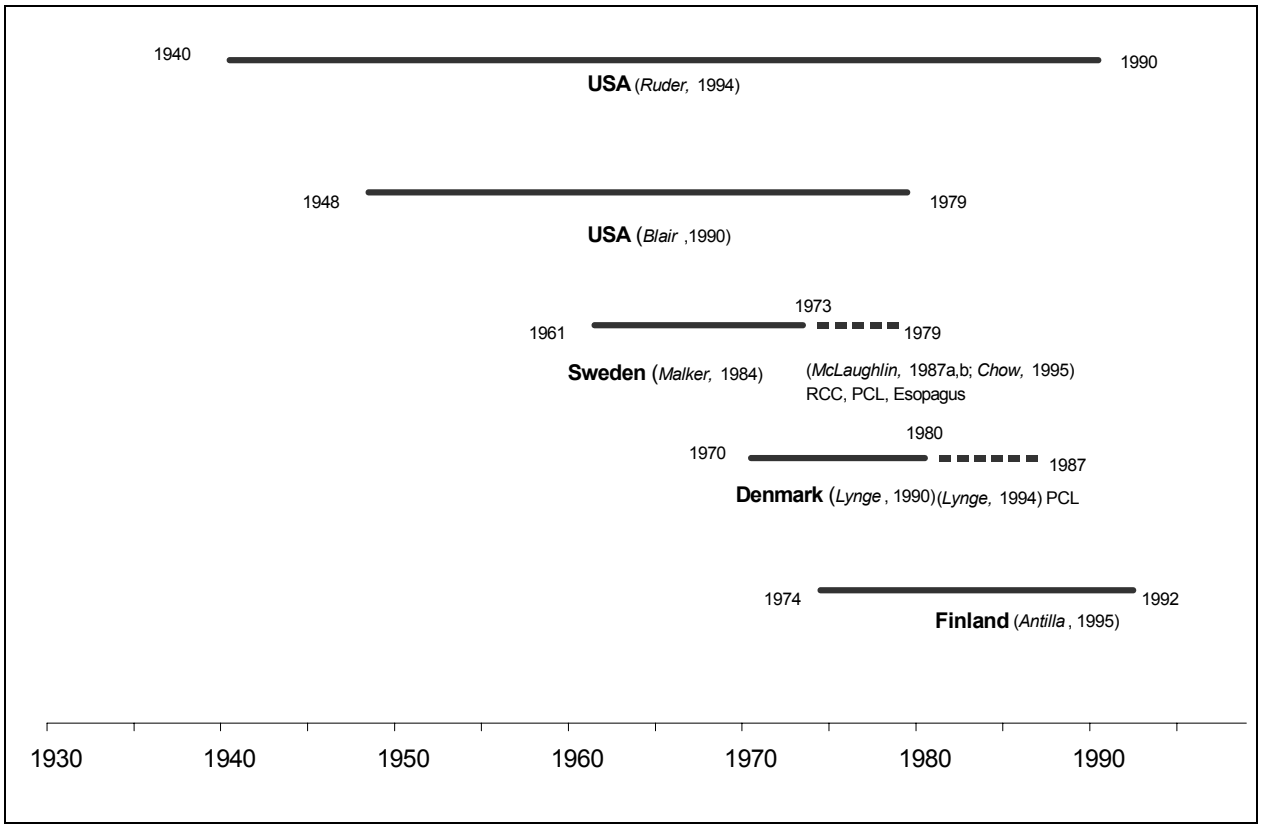
Ten cohort studies were considered in the analysis of PCE exposure and dry cleaning or other exposed jobs; however, only three studies were of well-defined occupational cohorts: two dry cleaner cohorts and one of aircraft workers exposed to multiple solvents. The two dry cleaner cohorts are considered the most likely studies to elucidate the health effects of PCE, despite their limited ability to characterize individual exposure. The remaining seven studies were population-based or registry-based studies, six of which were based on two study populations, and the seventh on a diverse cohort of workers exposed to a variety of solvents across multiple industries. A summary of each study is presented followed by a brief discussion of the collective results (see Figure 1, page 50).

The earliest study, published in 1984 by *Malker* traced the Swedish population from the 1960 census for cancer incidence over a period of 13 years (1961 to 1973). Because these results were published in Swedish, data from this study were obtained from the 1995 IARC review of dry cleaning studies (IARC, 1995). Standardized Incidence Ratios (SIRs) and 95% confidence intervals (CI) were calculated for all cancer sites combined, buccal cavity and nasopharynx, liver and biliary passages, lung, and breast.

An update of the Swedish cohort was later conducted through 1979. Results were published by specific cancer site in several papers. Three of these papers presented results for laundry and dry cleaning workers. The follow-up by *McLaughlin* (1987a)

assessed the occurrence of renal cell cancer among men by occupation and industry classification.

Figure 1:
Follow-up period of cohort studies considered in critical reviews



PCL= primary cancer of the liver;
RCC = renal cell carcinoma (the dotted line refers to extended follow-up periods reported for specific cancer sites only)

The "Cancer Environment Registry" was used which links cancer incidence and census data for all employed Swedes. Over 7,400 cases of renal cell cancer and over 800 cases of renal pelvis cancer among men were identified. SIRs were presented (adjusted for age and region) for major industrial and occupational codes generally for men (though some results for women are included in the discussion). Exposure was qualitative, based on the occupation and industry codes reported in the 1960 census.

In a related study, *McLaughlin* (1987b) evaluated the occurrence of primary liver cancer among men in the same cohort. The "Cancer Environment Registry" was again used to identify cancers cases linked to industry and occupation and follow-up was for the period 1961 to 1979. More than 2,600 primary liver cancer cases were identified.

Finally, *Chow* (1995) followed for 19 years 2,394 men employed in 1960, to assess esophageal cancer incidence by specific industry and occupation. Expected cancer rates were obtained from the general Swedish population for the same time period, while adjusting for gender and geographic region.

All of the four Swedish publications reported results for laundry and dry cleaning workers together. With exception of this job/industry classification at one point in time (1960) no further information concerning exposure is available for this population.

In the United States, researchers at the "National Cancer Institute" (NCI) conducted a cohort study of dry cleaners (*Blair*, 1990). This cohort was comprised of more than 5,000 members of a dry cleaners union in the state of Missouri who had worked a minimum of one year in the industry. The cohort was followed from January 1, 1948 or entry into the union (whichever came later) until January 1, 1979. Union records and social security administration data were used to ascertain vital status at the end of follow-up. Exposure assessment was qualitative, using the available job titles as a surrogate for PCE exposure. Cohort members were assigned an exposure index based on job title and external data in order to approximate exposure. US death rates were used as a comparison for the cohort mortality experience. Confounding due to race, sex, age, and calendar period was controlled in the analysis. The mortality of the cohort was also analyzed according to the date of entry into the union. 1960 was used as a cutoff year as PCE was the predominant solvent used in the majority of shops after that time. The results of this analysis were similar to the main results and so are not reported by the authors. The mortality for this cohort is currently being updated; however, no published report is yet available (personal communication Dr. *Aaron Blair*, October 1999).

In Denmark, *Lynge* (1990) identified a cohort of laundry and dry cleaning workers through the "Danish Occupational Cancer Registry". A ten-year follow-up for cancer incidence was conducted for any person in the 1970 census identified by employment in the industry described as "laundries, cleaning and dyeing". A total of 10,600 persons, aged 20 to 64, were followed for cancer outcome. Exposure assessment was qualitative, presuming exposure to PCE based on its widespread use in Denmark after the 1950's. *Lynge* (1994) later presented results of an extended follow-up of this cohort to 1987 based on data from the Danish Cancer Registry in an article exploring the use of the registry as a resource for occupational research. The registry was linked with census data, pension data, and some company personnel files. Results reported for laundry and dry cleaners in this publication are restricted to primary liver cancer. Both studies present results for the combined group of laundry and dry cleaning workers and no further information regarding the exposure of the population is available.

Further analysis in the form of a nested case-control study was later conducted by *Lynge* (1995) to separate those working in laundries from those working in dry cleaning and assess the risks for primary liver cancer and renal cell cancer.

The National Institute for Occupational Safety and Health (NIOSH) in the USA also conducted a cohort study among dry cleaning union members (*Kaplan*, 1980; *Brown*, 1987). An update of this study by *Ruder* (1994) used union records to identify dry cleaners (1,109 men and 592 women) from four US towns (in New York, California, Illinois and Michigan). The cohort members had to have worked at least one year before 1960 in a shop using primarily PCE. The cohort was followed for 50 years (1940 to 1990). Vital status was ascertained as of December 31, 1990 using the "National Death Index". Exposure was qualitative, indicated by union membership. Within the cohort, a subgroup primarily exposed to PCE was identified for analysis. This subcohort consisted of workers who (at the time of cohort definition) had worked *only* in shops where PCE was the predominant solvent. Observed mortality was compared to national death rates, controlling for gender, race, and calendar period. The mortality for this cohort is currently being updated; however, no published report is yet available (personal communication, Dr. *Avima Ruder*, October 1999).

Anttila (1995) investigated cancer incidence among employed persons in Finland exposed to any of three halogenated hydrocarbons (trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane). A total of 3,974 persons were followed for the time period 1967 to 1992. This cohort consisted of workers who had been biologically monitored for occupational exposures at the "Finnish Institute of Occupational Health". An average of 3.2 measurements per individual were made to determine PCE level of the blood. Among men in this study, the median concentration of PCE was 0.7 µmol/l and 0.4 µmol/l in women. For 45 % of those monitored only one sample had been analyzed. Follow-up was through the Finnish Cancer Registry and comparison was made to the total Finnish population. Results are reported for all halogenated solvents as well as for individual solvents and by specific cancer site. The PCE exposed sub-cohort (292 men and 557 women) was followed from 1974 to 1992. However, the occupation or industry of these workers is not reported. Also, no information regarding duration of exposure is available. The reported SIRs for this sub-cohort are restricted to cancer sites with increased risk estimate, with one exception.

Spirtas (1991) conducted a retrospective cohort study of 14,457 civilian aircraft maintenance workers employed at "Hill Air Force Base" in Utah between 1952 and 1956. The cohort was followed and vital status was ascertained to the end of 1982. SMRs were calculated using the Utah white population to generate expected deaths. Exposure was defined by job title and consisted of mixed solvents, primarily trichloroethylene. A sub-cohort of 851 employees (*Stewart*, 1991) also exposed to PCE was examined, but results were only presented for non-Hodgkin's lymphoma and multiple myeloma. *Blair* (1998) recently published an update of this cohort, but no results specific to PCE were reported.

3.1.1 Cohort Summary

Definition and assessment of exposure was qualitative in all but one of the cohorts reviewed. The only report with a quantitative measure was that of *Anttila* (1995), which linked blood samples for employed persons with cancer registry information. One of the strengths of the *Anttila* study is that there is a quantitative exposure measure for

PCE, though no specific occupational groups are identified. However, a central weakness of the study is that information on duration of exposure is unavailable. Both American cohort studies used membership in a dry cleaning union as a surrogate for PCE exposure. *Blair* (1990) attempted to isolate a sub-cohort mainly exposed to PCE by stratifying the cohort by date of entry. *Ruder* (1994) further stratified her cohort based on potential exposure to other solvents and estimated relative risks for dry cleaners presumably exposed only to PCE. For both of these sub-cohorts it seems reasonable to assume that exposures were predominantly to PCE. The sub-cohort of *Anttila* was certainly exposed to PCE but was more limited due to the potential for mixed exposures and the lack of information on duration of exposure.

The Swedish and Danish studies used occupation or industry classification at one point in time as a surrogate of exposure. These reports presented results for the combined group of laundry and dry cleaning workers but no information regarding duration or intensity of exposure. If and to what extent the populations and the cases were exposed to PCE cannot be determined based on the available information. The sub-cohort of *Spirtas* was almost certainly exposed to PCE; however, it was also likely exposed to other solvents. With the exception of "age", "gender" and in two studies "race", other risk factors were not controlled in any of the available cohort studies.

Total cancer mortality or incidence was reported in five of the cohort studies reviewed and was similar to expectation in all five studies. A small but "statistically significant" excess was found by *Blair* (1990) for dry cleaners (SMR 1.20, 95% CI 1.00-1.30), *Ruder* (1994) among the whole cohort (SMR 1.23, 95% CI 1.07-1.41, $p \leq .01$), as the SMR for PCE only exposed workers was not significant (SMR 1.01, 95% CI 0.76-1.32), and *Lynge* (1990) for males only (SIR 1.3, 95% CI 1.1-1.5). Results for mortality by individual cancer sites varied, and are discussed later on a site-specific basis.

The characteristics of cohort studies examined (see Table 5) and the corresponding exposure data (see Table 6, page 56) are presented. The potential confounders that were considered in these cohort studies are presented in Table 7 (see page 57).

Table 5:
Characteristics of cohort studies examined

Reference	Country	Study population	Comparison population	Cohort size	Follow-up period	
					Begin	End
Anttila 1995	Finland	Employed persons exposed to 3 halogenated hydro-carbons (PCE exposed sub-cohorts)	Population of Finland	3,974 849	1967 1974	1992 1992
Blair 1990	USA	Members of dry cleaners unions (St. Louis, Missouri)	Population of the USA	5,365	1948	1979
Chow 1995	Sweden	Men, employed in Sweden 1960	Population of Sweden	--[1]	1961	1979
Lynge 1990	Denmark	Dry cleaning and laundry workers in Denmark	Population of Denmark, employed 1970	10,600	1970	1980
Lynge 1994	Denmark	Dry cleaning and laundry workers in Denmark	Population of Denmark, employed 1970	10,600	1970	1987
Malker 1984	Sweden	Swedes, employed 1960	Population of Sweden	--[1]	1961	1973
McLaughlin 1987a	Sweden	Men, employed in Sweden 1960	Population of Sweden	--[1]	1961	1979
McLaughlin 1987b	Sweden	Men, employed in Sweden 1960	Population of Sweden	--[1]	1961	1979
Ruder 1994	USA	Members of dry cleaners unions in 4 cities ("only" PCE exposed sub-cohort)	Population of the USA	1,701 620	1940	1990

^

Table 5 (continued):

Reference	Country	Study population	Comparison population	Cohort size	Follow-up period	
					Begin	End
Spirtas 1991	USA	Civilian aircraft maintenance workers in Utah (sub-cohort "ever" exposed to PCE)	Population of Utah	14,457 851[2]	1953	1982

[1] not reported, [2] Stewart, 1991

Table 6:
Characteristics of exposure data in cohort studies

Reference	Occupational/ Industry of relevance to the study	Reported exposures	Exposure measurements	Likelihood of PCE exposure
Anttila 1995	Various (including dry cleaning, degreasing, graphics industry)	PCE, TCE and 1,1,1-trichloroethane	Blood samples	Mixed exposure – PCE likely*
Blair 1990	Dry cleaning	PCE and other solvents	Union membership	Mixed exposure – PCE likely*
Chow 1995	Laundry	Occupation/job	Industry classification (census-based)	Mixed exposure – PCE possible[1]
Lynge 1990	Laundry/Dry cleaning	PCE and trichloroethylene	Industry classification (census-based)	Mixed exposure – PCE possible
Lynge 1994	Laundry/Dry cleaning	PCE and trichloroethylene	Job description (census-based)	Mixed exposure – PCE possible
Malker 1984	Laundry/Dry cleaning	Occupation/job	Job description (census-based)	Mixed exposure – PCE possible
McLaughlin 1987a	Laundry/Dry cleaning	Occupation/job	Industry classification (census-based)	Mixed exposure – PCE possible

Table 6 (continued):

Reference	Occupational/ Industry of relevance to the study	Reported exposures	Exposure measurements	Likelihood of PCE exposure
McLaughlin 1987b	Laundry/Dry cleaning	Occupation/job	Industry classification (census-based)	Mixed exposure – PCE possible
Ruder 1994	Dry cleaning	PCE and other solvents	Union membership, history of solvent use in the work place	Mixed exposure – PCE likely*
Spirtas 1991	Aircraft maintenance	TCE and other solvents	Job description	Mixed exposure – PCE likely

* these studies also have sub-cohorts that were considered predominantly PCE exposed

[1] based on the assumption that Chow's term "laundry worker" also includes dry cleaners, as in the other Swedish studies

Table 7:
Potential confounders considered in the cohort studies[a]

Reference	Gender	Race	Calendar period	Geographic region
Anttila 1995	Yes	–	Yes	–
Blair 1990	Yes	Yes	Yes	No
Chow 1995	–	–	Yes	Yes
Lynge 1990	Yes	–	No	–
Lynge 1994	Yes	–	No	–
Malker 1984	Yes	–	Yes	Yes
McLaughlin 1987a	–	–	Yes	Yes
McLaughlin 1987b	–	–	Yes	Yes
Ruder 1994	Yes	Yes	Yes	No
Spirtas 1991	Yes	–	Yes	Yes

- not relevant/applicable, e. g. when only women or whites, or when "race" is unimportant (Europe)

[a] all cohort studies presented age-adjusted risk estimates

3.2 Case-control Studies

26 case-control studies were critically reviewed as to PCE exposure and cancer morbidity/mortality. Most available case-control studies were population-based (three were hospital-based), meaning that the cases and controls were selected from the general population and not from any specific occupational groups. One study was a population registry-based case-control study, and two of the 26 drew cases and controls from specific occupational groups. Most of the studies evaluated the association between PCE and a specified cancer site. Five of the studies evaluated the association between PCE and multiple cancer sites and are described in more detail in the following section.

Siemiatycki (1991) presents results for eleven of 20 identified cancer sites based on occupation and industry. He excluded all persons from the analysis who had not worked in the respective occupation (or industry) for at least five years prior to the onset of disease. All others were defined as "exposed". Workers who were employed in a specific industry for at least ten years, five years prior to the onset of disease were classified as "substantially exposed". Results are reported for the combined group of launderers and dry cleaners. Risk estimates were calculated utilizing two comparison groups: population-based controls and cases in the study with cancer unrelated to the cancer under examination. For each cancer site, potential confounders were selected based on knowledge of other risk factors for that specific cancer. Age, smoking, alcohol consumption and family income were all considered in the analyses where relevant to a specific cancer site.

While *Swanson* (1995) evaluated occupational risk factors for eleven cancer sites, only results for bladder cancer were relevant to the current report because there was a reference to dry cleaning industry. The population studied was comprised of women in Detroit, Michigan. Information on lifetime work history, demographic characteristics, health status and tobacco use was obtained through telephone interviews. Only six of over 600 bladder cancer cases reported dry cleaning as their usual occupation. Additionally, four eye cancer cases reported having ever worked in the laundry and dry cleaning industry; however, the total number of eye cancer cases was not reported.

There were no other reports for dry cleaners; and only occupations or industries with an elevated risk estimate for a specific cancer site were reported.

Vaughan (1997) investigated cancers of the oral cavity, larynx and esophagus among dry cleaners in Washington State. The exposure definition was qualitative, based on ever having worked in this area for more than six months, as well as duration and calendar period of employment. *Vaughan* defined persons who worked after 1960 in dry cleaning shops as "probably exposed to PCE."

The case-control study by *Lynge* (1995) was undertaken to assess an observed association between primary liver cancer among laundry and dry cleaning workers, as well as to assess the risk of renal cell cancer for this population. A total of 17 cases of liver cancer and 16 cases of renal cell cancer were evaluated. None of the liver cancer cases and only three of the renal cell cancer cases worked in dry cleaning. The remaining cases were launderers.

The study by *Teschke* (1997) investigated occupational risks for nasal and bladder cancers. As with the study by *Swanson* (1995), the reported details of bladder cancer are the most relevant to this report. Of the "exposed" cases, however, only three worked in dry cleaning.

Five other population-based studies specifically evaluated the association between occupation and bladder cancer (*Schoenberg*, 1984; *Silverman*, 1983; *Silverman*, 1989; *Silverman*, 1990; *Smith*, 1985) as part of the "National Bladder Cancer Study", which assessed occupational risk factors for incident bladder cancer in ten areas of the continental USA. Personal interviews were used to collect data on occupational history. Controls were matched to cases on age and geographic area. Results are reported for dry cleaners or for laundry/dry cleaning workers depending on the particular study.

Other cancer-specific sites evaluated include liver (two studies), renal cell cancer (four studies), lung (two studies), hair cell leukemia (two studies), skin, brain, non-Hodgkin's lymphoma, oral cavity, prostate and vulva (one study each). The basic characteristics of these studies are summarized in Tables 9 to 11 (see page 65 to 68 and 72).

3.2.1 Case-control Summary

In general there are a large number of case-control studies, some of which present results on multiple cancers. However, most cancer-specific study analyses include unacceptably small numbers of cases considered "exposed", although none measured PCE exposure directly.

Exposure in the majority of studies was defined as self-reported employment in the laundry and dry cleaning industries or self-reported exposures to dry cleaning solvents, which served as surrogates for PCE exposure. In general, study participants had worked in the industry for at least six months. With a few exceptions specific job titles were not recorded. None of the case-control studies included a quantitative exposure estimate. Additionally, most of the studies selected population-based case and control subjects, among which exposure prevalence was likely to be quite low, limiting study power. With the exception of a small subgroup in the study by *Vaughan* (1997), exposures in the case-control studies were to mixed substances.

The adjustment for potential confounders varied among studies, although most studies controlled for "age" and "smoking". "Race" was also controlled in studies comprising multiple population groups. Alcohol consumption was considered in studies of esophageal and laryngeal cancer, but rarely in other studies. Many of the case-control studies collected information on potential confounders, though the information was not always incorporated into the detailed analysis. In some studies this was appropriate as the covariate did not appear to confound the relationship between PCE/the applied surrogate and the specific cancer site. In a few studies, inclusion of the covariate in subsequent analyses would have elucidated the relationship under consideration.

3.3 Death Certificate Studies

Nine PMR or death certificate studies were selected for critical review; however, as noted above, this study approach has serious limitations, and results can only be considered preliminary.

Wisconsin (USA) death certificate data were analyzed by *Katz* (1981) to investigate the mortality of female laundry and dry cleaning workers for the period 1963 to 1977. Proportionate Mortality Ratios (PMRs) were calculated for 25 causes of death based on 671 records identified. Comparisons were made to all working women and to working women in other low wage occupations.

Table 8:
Characteristics of reviewed case-control studies

Reference	Country	Cases	Controls	Number cases (exposed[1])	Number controls (exposed[1])	Study Period	
						Start	End
Aronson 1996	Canada	Prostate cancer cases, male residents (Montreal)	Other cancer cases (except lung cancer) and population	449 (8)	2,083 (--)	1979	1986
Asal 1988	USA	Renal cell cancer cases, residents (Oklahoma)	Hospital and population	315 (11)	649 (7)	1981	1984
Blair 1993	USA	non-Hodgkin's Lymphoma cases, white males (Iowa, Minnesota)	Population	622 (16)	1,245 (14)	1980	1983
Bond 1990	USA	Liver/biliary tract cancer cases, male chemical workers (Michigan)	Cohort	44 (6[2])	1,888 (231[2])	1940	1982
Brownson 1993	USA	Incident lung cancer cases, white women, non-smokers (Missouri)	Population	429 (30)	1,021 (39)	1986	1991
Clavel 1995	France	Hairy cell leukemia cases, 18 hospitals	Hospital	291 (3)	541 (5)	1980	1990
Clavel 1998	France	Hairy cell leukemia cases, 18 hospitals, males	Hospital	226 (1)	425 (2)	1980	1990

Table 8 (continued):

Reference	Country	Cases	Controls	Number cases (exposed[1])	Number controls (exposed[1])	Study Period	
						Start	End
Delahunt 1995	New Zealand	Renal cell cancer cases, males, residents	Other cancer cases from the Cancer Registry	710 (--)	12,756 (--)	1978	1986
Dosemeci 1999	USA	Renal cell cancer cases, identified through Cancer Registry, whites (Minnesota)	Population	438 (50)	687 (76[2])	1988	1990
Gallagher 1996	Canada	Non-melancytic skin cancer cases, population-based, males (Alberta)	Population	446 (13)	406 (4)	1983	1984
Heineman 1994	USA	Brain cancer deaths, white males (Louisiana, New Jersey, Pennsylvania)	Population, deaths (except cerebral vascular, epilepsy, and suicide deaths)	300 (111)	320 (106)	1978	1981
Huebner 1992	USA	Incident oral cavity or pharynx cancer cases, 4 areas	Population	1,114 (22)	1,268 (29)	1984	1985
Lynge 1995	Denmark	Primary liver and renal cell cancer cases, laundry and dry cleaning workers	Cohort	33 (3)	165 (40)	1970	1987
Mabuchi 1985	USA	Vulvar cancer cases, hospitals in 5 metropolitan locations	Hospital, without cancer	149 (13)	149 (3)	1972	1975
Mandel 1995	5 States	Incident renal cell cancer cases (USA, Germany, Denmark, Sweden, Australia)	Population	1,732 (23/302[3])	2,309 (28/265[3])	1989	1991
Muscat 1998	USA	Incident lung cancer cases, blacks, 24 hospitals[4] (Various cities)	Hospital, except illness connected with tobacco	550 (14[2])	386 (6[2])	1978	1996

Table 8 (continued):

Reference	Country	Cases	Controls	Number cases (exposed[1])	Number controls (exposed[1])	Study Period	
						Start	End
Schoenberg 1984	USA	Incident bladder cancer cases, white males (New Jersey)	Population	658 (7)	1,258 (10)	1978	1979
Siemiatycki 1991	Canada	Male residents (Montreal)	Population, other cancer cases (except lung cancer)	3,730 (54)	533[5] (--)	1979	1985
Silverman 1983	USA	Incident bladder cancer cases, white males (Detroit, Michigan)	Population	303 (12)	296 (5)	1977	1978
Silverman 1989	USA	National Bladder Cancer Study, non-white males, 10 geographic areas	Population	126 (11)	383 (12)	1977	1978
Silverman 1990	USA	National Bladder Cancer Study, white females, 10 geographic areas	Population	652 (23)	1,266 (32)	1977	1978
Smith 1985	USA	Bladder cancer cases, laundry, dry cleaning workers and others	Population	--[6]	--[6]	1978	1978
Stemhagen 1983	USA	Incident primary liver caner (New Jersey)	Hospital, death certificate (except hepatitis, cirrhosis and other liver diseases)	265 (10)	530 (8)	1975	1980
Swanson 1995	USA	Incident cases (11 cancer locations), females (Detroit, Michigan) (Bladder cancer cases)	Population	5,714 (--) (6)	1,972 (--) (16)	1984	1991

Table 8 (continued):

Reference	Country	Cases	Controls	Number cases (exposed[1])	Number controls (exposed[1])	Study Period	
						Start	End
Teschke 1997	Canada	Incident bladder and nasal cancer cases (British Columbia) (Bladder cancer cases[7])	Population	153 (5) 105 (5)	298 (8) 139 (4)	1990	1992
Vaughan 1997	USA	Incident cases of the oral cavity, larynx and esophagus (Washington)	Population	1,120 (16)	724 (8)	1983	1990

-- not reported

[1] employed in laundry/dry cleaning, as dry cleaners or PCE exposed

[2] calculated by the authors

[3] exposed: "ever" worked in dry cleaning/"ever" exposed to dry cleaning solvents

[4] *Morabia*, 1992

[5] population control. The study also related other cancer cases as a control group for each site (n = 1,360 to 2,864)

[6] *Smith* reports number of persons according to status of exposure:
1) ever employed in laundry or dry cleaning (n = 103)
2) employed in other professions/industries, in which similar or the same chemicals were used (n = 5,776)
3) non-exposed group (n = 1,869)

[7] 3 cases and 1 control person were specifically employed in dry cleaning

Table 9:
Characteristics of exposure data in case-control studies

Reference	Relevant occupation/industry	Exposure variables	Exposure measure	Likelihood of PCE exposure
Aronson 1996	Multiple	Occupation, industry and substance classification	Self report (interview); Occupation/industry + Expert assessment	Mixed exposure – PCE likely
Asal 1988	Dry cleaners	Occupation/Industry	Self report (interview)	Mixed exposure – PCE possible
Blair 1993	Laundry/Garment services	Occupation/Industry	Self report (interview)	Mixed exposure – PCE possible
Bond 1990	Chemical workers	PCE and other solvents	Job Title + industrial hygiene data	Mixed exposure – PCE likely
Brownson 1993	Dry cleaners	Occupation/Industry	Self report (interview)	Mixed exposure – PCE likely
Clavel 1995	Dry cleaners	Dry cleaning solvents	Self report (interview)	Mixed exposure – PCE possible
Clavel 1998	Laundry/ Dry cleaning	Occupation/Industry	Self report (interview); Occupation/industry + Expert assessment	Mixed exposure – PCE possible
Delahunt 1995	Dry cleaners	Occupation/Industry	Occupation/Industry classification at time of diagnosis (registry data)	Mixed exposure – PCE likely
Dosemeci 1999	Multiple	PCE and other solvents	Self report (interview); Occupation/Industry + "job-exposure matrix" (JEM)	Mixed exposure – PCE likely
Gallagher 1996	Multiple	Dry cleaning solvents	Self-report (interview)	Mixed exposure – PCE possible
Heineman 1994	Multiple	PCE and other solvents	Self report (interview); Occupation/Industry + JEM	Mixed exposure – PCE likely
Huebner 1992	Laundry/ Dry cleaning	Occupation/Industry	Self report (interview)	Mixed exposure – PCE possible
Lynge 1995	Laundry/ Dry cleaning	Occupation/Industry	Industry description	Mixed exposure – PCE likely[1]
Mabuchi 1985	Laundry/ Dry cleaning	Occupation/Industry	Self report (interview)	Mixed exposure – PCE possible

Table 9 (continued):

Reference	Relevant occupation/industry	Exposure variables	Exposure measure	Likelihood of PCE exposure
Mandel 1995	Dry cleaners; Multiple	Occupation/Industry; Dry cleaning solvents	Self report (interview)	Mixed exposure – PCE likely Mixed exposure – PCE possible
Muscat 1998	Multiple	Dry cleaning solvents	Self report (interview)	Mixed exposure – PCE possible
Schoenberg 1984	Dry cleaners	Occupation/Industry	Self report (interview)	Mixed exposure – PCE likely
Siemiatycki 1991	Laundry/ Dry cleaning	Occupation/Industry	Self report (interview)	Mixed exposure – PCE possible
Silverman 1983	Laundry/ Dry cleaning	Occupation/Industry	Self report (interview)	Mixed exposure – PCE possible
Silverman 1989	Dry cleaners	Occupation/Industry	Self report (interview)	Mixed exposure – PCE likely
Silverman 1990	Dry cleaners	Occupation/Industry	Self report (interview)	Mixed exposure – PCE likely
Smith 1985	Laundry/ Dry cleaning	Occupation/Industry	Self report (interview)	Mixed exposure – PCE possible
Stemhagen 1983	Laundry/ Dry cleaning	Occupation/Industry	Self report (interview)	Mixed exposure – PCE possible
Swanson 1995	Dry cleaners; Laundry/ Dry cleaning	Occupation/Industry	Self report (interview)	Mixed exposure – PCE likely Mixed exposure – PCE possible
Teschke 1997	Laundry/ Dry cleaning	Occupation/Industry	Self report (interview)	Mixed exposure – PCE possible
Vaughan 1997	Dry cleaners	Occupation/Industry	Self report (interview)	Mixed exposure – PCE likely[2]

[1] for renal cell cancer; for primary liver cancer: PCE exposure unlikely

[2] for persons with "likely PCE exposure"

Table 10:
Potential confounders considered in case-control studies

Reference	Age	Gender	Race	BMI[1]	Education	Smoking	Alcohol	Additional confounders
Aronson 1996	Yes	--	--	Yes	No	No	No	Ethnic group, socio-economic status (SES), status of interviewee, exposure to all other materials
Asal 1988	Yes	Yes	No	Yes	No	Yes	No	
Blair 1993	Yes	--	--	No	No	Yes	No	State; family medical history; use of hair dyes, interviewee type
Bond 1990	Yes	--	No	No	No	No	No	
Brownson 1993	Yes	--	--	No	No	Yes	No	Previous lung disease
Clavel 1998	Yes	--	--	No	Yes	Yes	No	Region
Clavel 1995	Yes	Yes	--	No	Yes	Yes	No	Agriculture
Delahunt 1995	Yes	--	No	No	No	No	No	
Dosemeci 1999	Yes	Yes	--	Yes	No	Yes	No	Hypertonia, use of diuretics, antihypertension
Gallagher 1996	Yes	--	--	No	No	No	No	Skin color; hair color; ethnic origin of mother; sun
Heineman 1994	Yes	--	--	No	No	No	No	Location of study, year of death; industry of employment in connection with electronics
Huebner 1992	Yes	Yes	Yes	No	No	Yes	Yes	Location of study
Lynge 1995	Yes	Yes	--	No	No	No	No	Occupation/Industry
Mabuchi 1985	Yes	--	Yes	No	Yes	Yes	No	Coffee, number of marriages, age at first marriage

Table 10 (continued):

Reference	Age	Gender	Race	BMI [1]	Education	Smokung	Alcohol	Additional confounders
Mandel 1995	Yes	Yes	No	Yes	Yes	Yes	No	Center of study
Muscat 1998	Yes	Yes	--	No	Yes	Yes	No	
Schoenberg 1984	Yes	--	--	No	No	Yes	No	
Siemiatycki 1991	Yes	No	No	No[2]	No	Yes	Yes[2]	Family income; place of birth, index for beer and coffee intake, Interviewee type
Silverman 1983	Yes	--	--	No	No	Yes	No	Increased risk industries/occupation
Silverman 1989	Yes	--	--	No	No	Yes	No	Increased risk industries/occupation
Silverman 1990	Yes	--	--	No	No	Yes	No	
Smith 1985	Yes	Yes	Yes	Yes	Yes	Yes	No	Coffee consumption
Stemhagen 1983	No	No	No	No	No	No	No	
Swanson 1995	Yes	--	Yes	No	No	Yes	No	
Teschke 1997	Yes	Yes	--	No	No	Yes	No	Consumption of coffee, tea, and diet soft drinks; previous history of bladder infection, injury to abdomen, chemo-therapy
Vaughan 1997	Yes	Yes	Yes	No	Yes	Yes	Yes	Study period

-- inadequate

[1] Body Mass Index

[2] dependent on cancer site

The report by *Duh* (1984) presents the analysis of death certificates for 440 laundry and dry cleaning workers in Oklahoma (USA) for the period 1975 to 1981. Standardized Mortality Odds Ratios (SMORs) were calculated using the distribution of deaths (by age, race, sex and cause of death) from the standard population. Exposure was defined by "usual" occupation as coded on the death certificate. Dry cleaners could not be separated from laundry workers. Of note is the fact that, unlike in most states, petroleum-based solvents (e. g. Stoddard solvent) comprise greater than 50 % of the total cleaning solvents used in Oklahoma shops.

Nakamura (1985) undertook a death certificate study to evaluate the mortality of Japanese laundry and dry cleaning workers who had died between 1971 and 1980. Both occupational and non-occupational factors were assessed. 1,711 deaths were identified through the "All-Japan Laundry and Dry-Cleaning Association". For persons who died between 1979 and 1981, information about exposure history and possible confounders were collected by questionnaire from family members of the deceased. Comparison was made to the general Japanese population. As in the Oklahoma study, petroleum-based solvents were used more widely than PCE in Japanese dry cleaning shops (approximately 65 % versus 30 %).

Doebbert et al. (1988) reviewed the California mortality data for the period 1979 through 1981 to look for patterns of risk within categories of occupation. Occupation and industry on 173,438 death records were analyzed and SMRs calculated. No direct exposure information was available. Results for laundry and dry cleaning workers are reported for all cause mortality and for other selected causes of death including lung cancer for black women.

Suarez (1989) analyzed 1,742 death certificates of male inhabitants of Texas with a diagnosis of "primary liver cancer" between 1969 and 1980 according to occupation or industry. The study was conducted in form of a case-control study. An equal number of controls with a cause of death different from primary liver cancer (except for cancer, diseases of liver and gallbladder, infectious hepatitis and alcoholism) were selected randomly. Results are reported for dry cleaning and dry cleaners.

Reviere et al. (1995) conducted a study using data from the "National Mortality Follow-back Survey", a representative sample of US adults age 25 or over who died in 1986. Information about occupation and industry was collected by questionnaires completed by informants, usually next of kin. Results reported for laundry and dry cleaning workers are limited to liver cancer.

The *Milham* study (1997) analyzed cause of death by occupation for 588,090 males (from 1950 to 1989) and 88,071 females (from 1974 to 1989) in Washington State (USA). PMRs were calculated using Washington state rates, standardized for age and year of death. The study population was restricted to whites, and all females with "housewife" listed as usual occupation were excluded. Gender-specific results for laundry and dry cleaning workers are presented for the entire time period, as well as for 12-year intervals.

Walker (1997) analyzed death certificate data from 8,163 former laundry and dry cleaning workers in 28 US states for cancer mortality. The study period was 1979 to 1990 and age-adjusted PMRs were calculated using the respective state mortality for comparison. Results are reported for two age cohorts and are race- and gender-specific. Walker also calculated and reported Proportional Cancer Mortality Ratios (PCMR). As with the other PMR studies, exposure is based on usual occupation reported on the death certificate. Given that this study includes data pertaining to deceased individuals from 28 states, there is a partial overlap with some of the death certificate studies described above (*Duh*, 1984; *Milham*, 1997; *Reviere*, 1995) and with the cohort studies by *Blair* (1990) and *Ruder* (1994) for specific years and states.

Krstev (1998) analyzed the risk for prostate cancer by specific occupations or industries based on approximately 60,000 death certificates (from 1984 to 1993) from 24 US states. Mortality odds ratios (MORs) were calculated using approximately 300,000 controls, who had died from causes other than cancer. Results are reported for dry cleaners (job/occupation classification) and for laundry/dry cleaning groups (industry classification). Because data pertaining to deceased individuals from a number of different states are included in this study there is also a partial overlap with some of the

death certificate studies described above (*Duh*, 1984; *Milham*, 1997; *Reviere*, 1995; *Walker*, 1997).

3.3.1 Death Certificate Summary

Most of the studies reviewed share an important limitation related to the exposure: laundry and dry cleaners could not be analyzed separately. This is problematic as the exposure potential of these two distinct occupational groups is very different. Inclusion of non-exposed persons in the exposed categories would attenuate any estimate of relative risk if an association between exposure and disease exists. Exceptions to this are the studies of *Suarez* (1989) and *Krstev* (1998), both of which present results for dry cleaners alone, and to some degree the Japanese study by *Nakamura* (1985), where for a discrete time period estimates for all cancers combined were calculated for dry cleaners only. Even among groups reasonably identified as dry cleaners, individual work histories and therefore actual exposures to PCE are not known. If and to what extent the deceased persons were exposed to PCE cannot be determined on the basis of the available information. Without additional information regarding the time period of exposure and work histories it is impossible to assess individual exposures.

Also of note is that the death certificate studies generally lacked any control for other recognized or potential risk factors.

Analysis of cause of death recorded on the death certificates of laundry and dry cleaning workers from these nine studies showed variable results (see below for cancer-specific results). The PMR for "all cancer" mortality among all causes of death was not elevated in any of these studies with the exception of an observed excess among black men less than 65 years of age in the *Walker* study (PMR 1.3; 95% CI 1.05-1.59). Also of note is a significant deficit of mortality for all cancers among white women in both the under 65 and 65 and older age groups.

Characteristics of death certificate studies examined, corresponding exposure dates and potential confounders that were considered in the death certificate studies are presented in Tables 11 to 13 (see page 72 to 74).

Table 11:
Characteristics of death certificate studies

Reference	Country	Study population	Comparison population	Number of death certificates	Study Period	
					Begin	End
Doebbert 1988	USA	California Occupational Mortality Database	Employed residents, California 1980	173,438	1979	1981
Duh 1984	USA	Dry cleaning and laundry workers (Oklahoma)	US population	440	1975	1981
Katz 1981	USA	White female laundry and dry cleaning workers (Wisconsin)	White females from all professions/from low-wage professions, Wisconsin	671	1963	1977
Krstev 1998	USA	Prostate cancer (24 US States)	Mortality cases except cancer from all other professions/industries as those examined at any one time (24 US States)	26[1] (154[2])	1984	1993
Milham 1997	USA	White employed persons (Washington State)	White residents (Washington State)	2,885[2]	1950	1989
Nakamura 1985	Japan	Members of "All-Japan Laundry and Dry Cleaning Association"	Japan population	1,711	1971	1980
Reviere 1995	USA	"National Mortality Followback Survey" (NMFS)/US sample	US population	272[3]	1986	1986
Suarez 1989	USA	Primary liver cancer cases, males (Texas)	Same number of control persons, all other cases of death except cancer, etc. (Texas)	4[1] (11[4])	1969	1980
Walker 1997	USA	Dry cleaners and launderers from 28 states. NOMS Data (National Occupation Mortality Surveillance)	All employees (28 states)	8,163	1979	1990

[1] dry cleaning workers,

[2] laundry/dry cleaning shops,

[3] dry cleaners and laundry workers/liver cancer,

[4] dry cleaning industry

Table 12:
Characteristics of exposure data in death certificate studies

Reference	Occupation/ Industry relevant to study	Reported exposures	Exposure measurement	Likelihood of PCE exposure
Doebbert 1988	Laundry/Dry cleaning	Occupation/ Job	Usual occupation/ Industry (from death certificate)	Mixed exposure – PCE possible
Duh 1984	Laundry/Dry cleaning	PCE and other solvents	Usual occupation/ Industry (from death certificate)	Mixed exposure – PCE possible
Katz 1981	Laundry/Dry cleaning	PCE and other solvents	Usual occupation/ Industry (from death certificate)	Mixed exposure – PCE possible
Krstev 1998	Dry cleaners; Laundry/Dry cleaning	Occupation/ Job	Usual occupation/ Industry (from death certificate)	Mixed exposure – PCE likely; Mixed exposure – PCE possible
Milham 1997	Laundry/Dry cleaning	Occupation/ Job	Usual occupation/ Industry (from death certificate)	Mixed exposure – PCE possible
Nakamura 1985	Laundry/Dry cleaning	PCE and other solvents	Union data	Mixed exposure – PCE possible
Reviere 1995	Laundry/Dry cleaning	Occupation/ Job	Usual occupation/ Industry (from death certificate)	Mixed exposure – PCE possible
Suarez 1989	Dry cleaners	Occupation/ Job	Usual occupation/ Industry (from death certificate)	Mixed exposure – PCE likely
Walker 1997	Laundry/Dry cleaning	PCE and other solvents	Usual occupation/ Industry (from death certificate)	Mixed exposure – PCE possible

Table 13:
Potential confounders considered in death certificate studies

Reference	Age	Gender	Race	Smoking	Alcohol	Additional Confounders
Doebbert 1988	Yes	Yes	Yes	No	No	
Duh 1984	Yes	Yes	Yes	No	No	
Katz 1981	Yes	–	–	No	No	Low-wage profession; family status
Krstev 1998	Yes	–	Yes	No	No	Geographical region
Milham 1997	Yes	Yes	–	No	No	Calendar interval
Nakamura 1985	Yes	Yes	–	Yes[1]	Yes[1]	Geographical region
Reviere 1995	–	–	No	No	No	
Suarez 1989	Yes	–	No	No	No	
Walker 1997	Yes	Yes	Yes	No	No	

– not applicable or not reported

[1] partly

3.4 Summary of the Critical Reviews

All studies reviewed share a limited exposure assessment for PCE. Exposures were predominately to mixed agents, as far as could be determined from the published reports, or the studies included various occupational groups potentially exposed to numerous substances.

In most cases it was not possible either to confirm or to deny exposure to PCE. None of the studies was able to provide a quantitative assessment of the exposure on an individual level and only a few studies provided a qualitative assessment. All death certificate studies, most of the case-control studies and all census-based cohort studies characterized PCE exposure, if at all, using the weakest and least accurate approaches available.

The two cohort studies of dry cleaners provide the most likely exposure settings, but were not able to control for important confounders and often had too few observed numbers of deaths to generate reliable estimates of risk.

Though case-control studies usually are well-suited for the control of confounding, many available case-control studies were population-based with low prevalence of exposure and so inadequately small numbers of exposed cases and controls. This precludes the estimation of reliable risk estimates, as well as more detailed analyses, even if better exposure information were available.

On the whole, the apparently large body of published papers available on PCE and cancer risk is in fact unusually weak, making the critical review and synthesis process more difficult.

In completing the review and critical synthesis of the literature for PCE and cancer outcomes the quality of each study was individually critiqued and the quality and strength of evidence was determined. Next, the weight of evidence across studies was synthesized and assessed.

Epidemiological studies, unlike experiments, are observational and do not necessarily follow a single set of standards. A critical assessment of the overall quality of studies needs to incorporate many factors, some of which are subjective. The strength of study design (including the study population definition and time period), quality of exposure assessment, the validity of the outcome definition, avoidance of bias and technical aspects of the design and analysis all contribute to the overall quality of a study.

A synthesis of a body of literature considers whether there are an adequate number of studies of reasonable quality for the disease of interest, the consistency of results across studies and the magnitude of an effect, if it is consistent.

The weight of epidemiological evidence can be either positive or negative, arguing for or against an association or may be considered inadequate to draw any conclusion regarding the relationship in question.

Within the body of literature assessing the potential relationship between PCE and specific cancers, the overall quality of evidence is limited. Small number of observed cases for some outcomes, inadequate exposure measures and inconsistent evidence make it difficult to produce an unequivocal assessment of an association for all cancer sites of interest. The greatest limitation in this body of literature is the general quality of the exposure information. However, because several factors taken together contribute to the quality of a study, some evidence is usable and can be synthesized for various cancer sites.

3.5 Cancer Site Summaries

3.5.1 Cancer of the Buccal Cavity and Pharynx (ICD-9 140-149)

Rates of cancers of the oral cavity (ICD-9 143-145) show large demographic and geographical variability worldwide. The highest rates for males are seen in the east central region of France (over 40/100,000) while the highest rates for females are in India (approximately 15/100,000) (*Blot*, 1996). Estimated age standardized incidence ratios (world standard) for Germany are 14/100,000 for males and 3/100,000 for females in 1995. Mortality rates are 6.4/100,000 for males and 1.2/100,000 for females (EUCAN, 1999) The respective mortality rates in the USA are 3.3/100.000 in males and 1.2/100.000 in females (WHO, 1999). Death rates for oral cancer are generally higher in urban areas and higher among lower socioeconomic groups, which reflect risk factor patterns (*Blot*, 1996).

The strongest risk factors for cancers of the buccal cavity and pharynx are use of tobacco products and alcohol. Some evidence for a dietary relationship exists, with low intake of fruits and vegetables associated with increased risk. Occupational factors contributing to cancers of the oral cavity are limited. Few studies, often small, have associated occupation or industry with oral cancer. Because of the strongly demonstrated relationship between oral cancers and tobacco products and alcohol, excess risks that were not calculated with adequate control for these risk factors must be interpreted with caution (*Blot*, 1996).

Eight of the 45 studies included in this review reported results for cancer of the buccal cavity and pharynx. Results from these studies are presented in Table 14 and selected risk estimates and confidence intervals are shown in Figure 2.

Exposure ascertainment was qualitative in all these studies and fairly limited. The "exposed" category in five of the eight studies included laundry as well as dry cleaning workers. For these studies exposure was defined by "usual" occupation from death certificates, by job title at one point in time or by the classification "ever worked in the industry". The remaining three study populations were comprised of dry cleaning workers only as defined by union membership or reported work in the dry cleaning industry.

Figure 2:
Selected risk estimates and confidence limits for cancer of the buccal cavity and pharynx

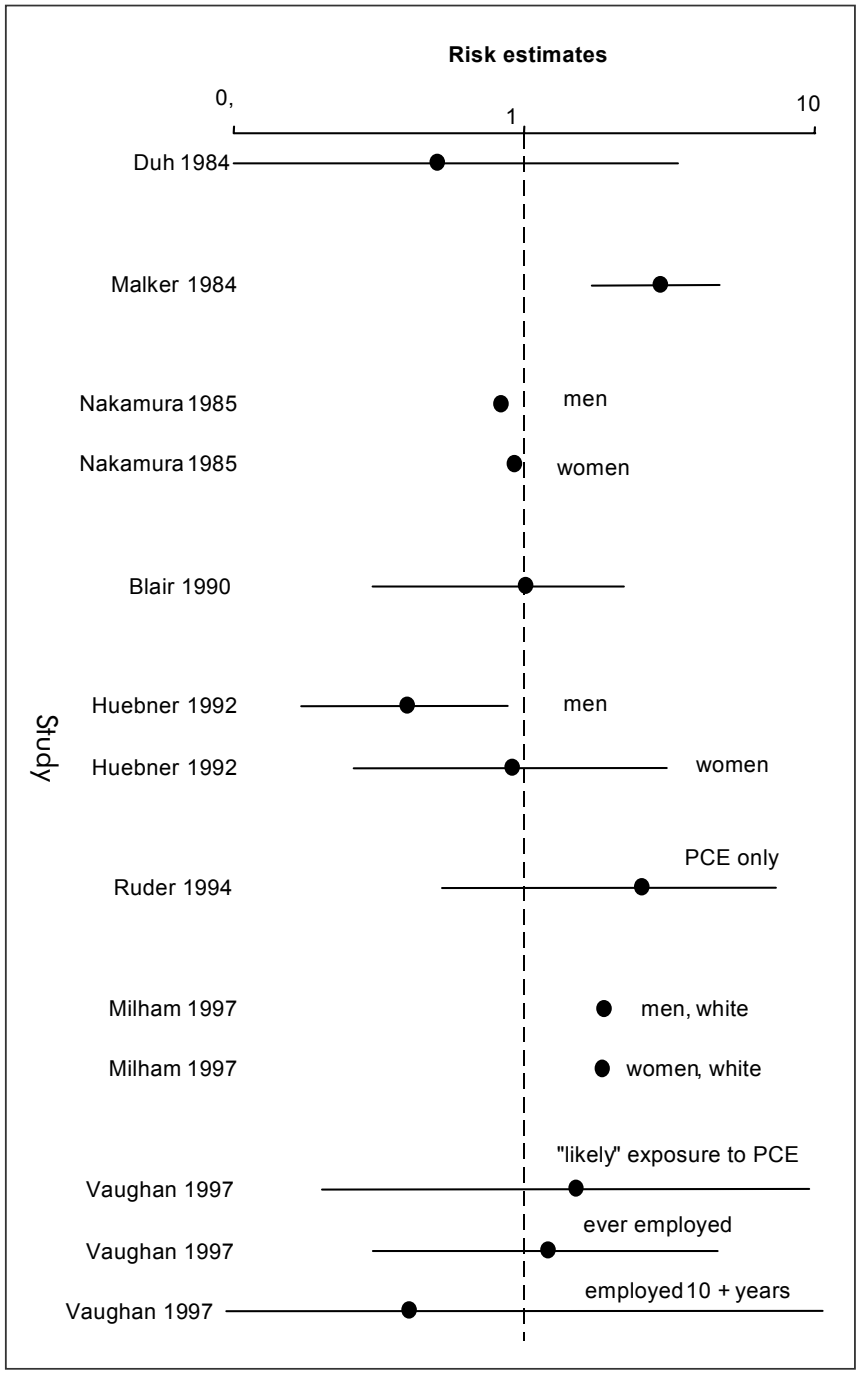


Table 14:
Reported risk estimates for cancer of the buccal cavity and pharynx[1] from eight studies

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[2]
Cohort studies								
Malker 1984	SIR	Laundry/ dry cleaning industry	Both		16	--	2.90	(1.70-4.70)
Blair 1990	SMR	Dry cleaning workers	Adjusted	Adjusted	5	5.20	1.00	(0.30-2.20)
Ruder 1994	SMR	Dry cleaning workers (Full Cohort)	Adjusted	Adjusted	6	--	1.64	(0.60-3.56)
	SMR	Dry cleaning workers (PCE only)	Adjusted	Adjusted	3	--	2.51	(0.52-7.33)
	SMR	Dry cleaning workers (PCE and others)	Adjusted	Adjusted	3	--	1.22	(0.25-3.56)
Case-control studies								
Huebner 1992	OR	Laundry/ dry cleaning workers	Men	Adjusted	14	22	0.39	(0.17-0.88)
	OR	Laundry/ dry cleaning workers	Women	Adjusted	8	7	0.90	(0.26-3.09)
Vaughan 1997	OR	"likely" PCE exposure	Adjusted	All[3]	4	3	1.50	(0.20-9.50)
	OR	Dry cleaning shops (ever)	Adjusted	All	7	8	1.20	(0.30-4.60)
	OR	Dry cleaning workers (1-9 years)	Adjusted	All	6	1	0.40	(0.30-5.70)
	OR	Dry cleaning workers (10+ years)	Adjusted	All	1	1	0.40	(0.00-31.60)
Death certificate studies								
Duh 1984	SMOR	Laundry/ dry cleaning industry	Adjusted	Adjusted	1	2.00	0.50	(0.10-3.40)
Nakamura 1985	PMR	Laundry/ dry cleaning workers	Men		3	3.60	0.83	--

Table 14 (continued):

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[2]
Nakamura 1985	PMR	Laundry/ dry cleaning workers	Women		1	1.10	0.91	--
Milham 1997	PMR	Laundry/ dry cleaning workers						--
	PMR	1950 to 1989	Men	Whites	15	8.00	1.88*	--
	PMR	1950 to 1962	Men	Whites	8	2.00	3.43**	--
	PMR	1963 to 1975	Men	Whites	3	3.00	0.98	--
	PMR	1976 to 1989	Men	Whites	4	3.00	1.55	--
	PMR	1974 to 1989	Women	Whites	8	4.00	1.84	--

SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; OR: Odds Ratio;
PMR: Proportionate Mortality Ratio; SMOR: Standardized Mortality Odds Ratio

--, not reported

[1] *Vaughan* study excludes nasopharynx

[2] 95% Confidence limit

[3] *Vaughan* reports that adjustment for race did not change risk estimate

* $p \leq 0.05$;

** $p < 0.01$

Information on smoking and alcohol consumption was gathered in the *Vaughan* (1997) and *Huebner* (1992) case-control studies through personal interviews with cases or next of kin. Both investigators also adjusted for level of education and *Huebner* additionally controlled for race and study location. The period of observation in the cohort studies allowed for an adequate latency for oral cancer development.

Few cancer cases were ascertained from the eight studies and only two studies reported significantly elevated results. The *Malker* (1984) cohort study reported a SIR of 2.9 (95% CI 1.7-4.7) based on 16 cases; *Milham* (1997) reported a PMR of 1.88 among white males based on 15 cases, though half of all cases occurred in the years 1950 to 1962. Assuming an adequate latency period it is not very likely that these cases were exposed predominantly to PCE. The latter study also reported an increased estimate in females (PMR 1.8) based on eight cases.

Within the large cohort studies in the USA, *Ruder* (1994) reported an increased mortality risk among those primarily exposed to PCE (SMR 2.5, 95% CI 0.52- 7.33) while in the study by *Blair* (1990) there was no increased risk (SMR 1.0, 95% CI 0.3-2.2).

When duration of employment was examined in the *Vaughan* (1997) case-control study, those employed ten or more years in dry cleaning showed a decreased risk (OR 0.4, 95% CI 0.0-31.6) – based on one case – while a small increased risk was found among those who "ever" worked in the industry (OR 1.2, 95% CI 0.3-4.6). Also among those with a "probable exposure to PCE" there was only a small increase in risk (OR 1.5, 95% CI 0.2-9.5).

The case-control study by *Huebner* found decreased risk for males and females who were "ever" employed in the job or industry category for laundry or dry cleaning workers. The adjusted OR for males who ever worked in a laundry/dry cleaning job showed the strongest negative effect (OR 0.39, 95% CI 0.17-0.88).

A synthesis of the literature profits little from the death certificate studies, as their ability to contribute to the overall picture is limited by the level of available data. Therefore three cohort and two case-control studies were considered the most relevant for the critical synthesis of the literature. Separate risk estimates were not combined to generate a quantitative summary for this cancer site. Two of the studies considered in the critical synthesis encompassed laundry workers as well as dry cleaners. Risk estimates from the three studies of dry cleaners were not combined as the separate estimates of effect were considered more informative; the relationship between PCE and cancer of the buccal cavity and pharynx is best understood by a qualitative synthesis of the available studies.

The studies available for review varied in their ability to assess the role of known risk factors for cancers of the oral cavity and pharynx. The cohort studies, by nature of their design, did not control for the use of tobacco and alcohol, which for this cancer site limits the quality of the evidence. Risk estimates in the study by *Vaughan* (1997) were adjusted for smoking and alcohol (alcohol was considered to be a confounder in this study due in part to differences in alcohol consumption among controls). The case-

control study by *Huebner* (1992) also controlled for tobacco and alcohol, as well as length of employment, and observed a reduced risk of cancer, though the study population was "mixed". Due to the strength of an association between these behaviors and cancers of the oral cavity and pharynx, estimates that do not account for these risk factors must be interpreted with caution. Further, given the risk estimates and associated confidence intervals observed in the studies reviewed it is unlikely that control of other risk factors would have generated results that demonstrated a positive association.

The quality of evidence available for understanding the relationship between PCE and cancer of the buccal cavity and pharynx is limited. Different study population definitions, the definition and estimation of exposure and ability to control confounding do not allow neat categorization of the studies or risk estimates. It is believable that some of the study populations were likely exposed to PCE, even though the quality of the exposure information was poor. Further, *Vaughan* (1997) observed only one case in the highest exposed category and only three cases in the *Ruder* (1994) sub-cohort were defined as "exposed only to PCE". The strongest positive effect was observed by *Malker* (1984) and the strongest negative effect by *Huebner* (1992), but both were for study populations comprised of laundry and dry cleaning workers.

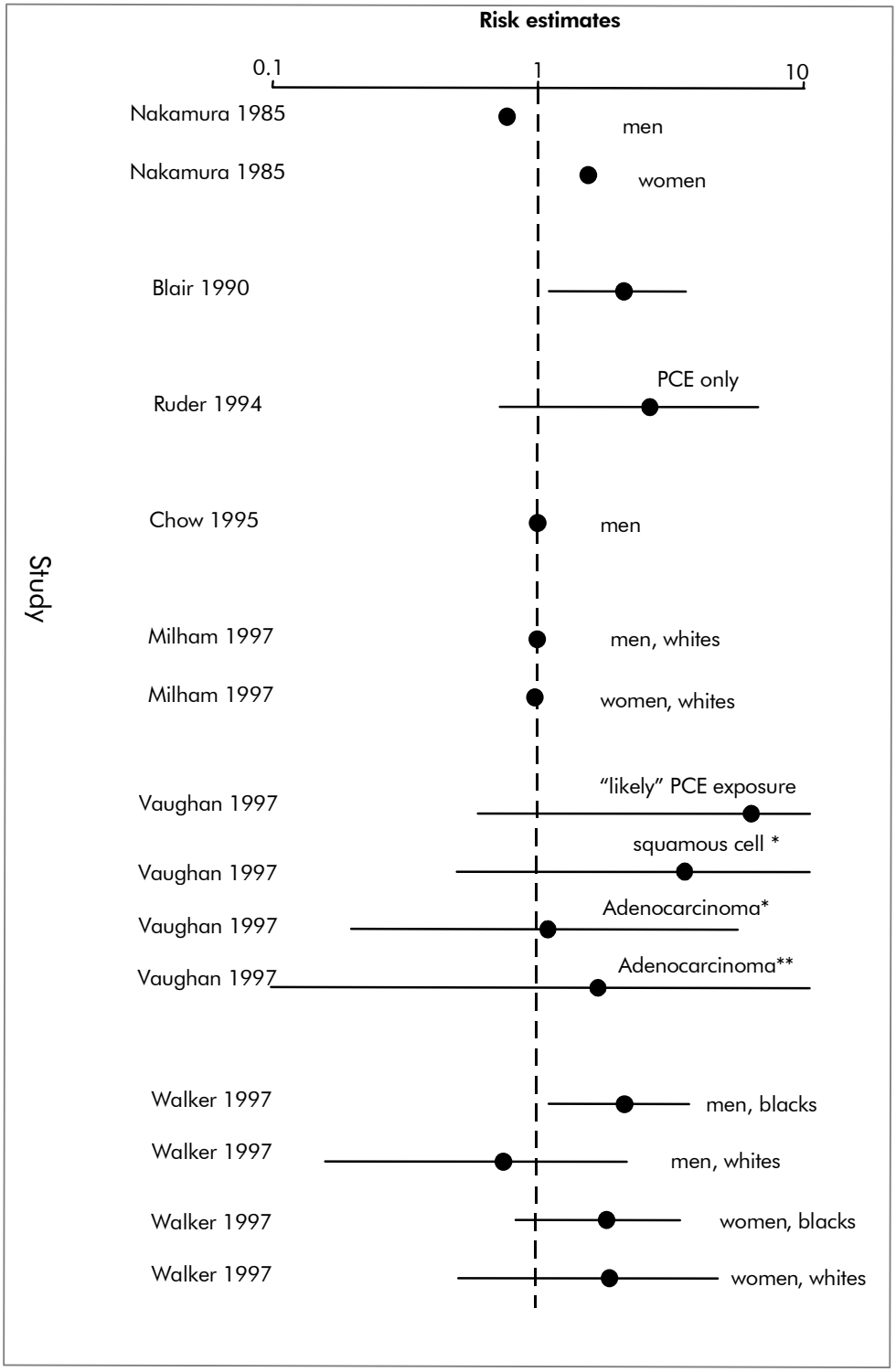
The possibility of an association of PCE exposure and cancer of the buccal cavity and pharynx appears unlikely, given that the two case-control studies that adequately adjusted for important potential confounders found no or only minimal excess risk. Further, the lack of strong effects in the populations restricted to dry cleaning workers undermines support for an association between PCE and oral cancer. Other explanations for these cancers appear more likely, such as exposure to cigarettes and alcohol consumption.

3.5.2 Cancer of the Esophagus (ICD-9 150)

Esophageal cancer ranks ninth among cancers worldwide with an overall incidence in the USA of 3.9 /100,000 (*Muñoz*, 1996; *Ries*, 1996). The highest rates are found in China, Iran, among black men in South Africa and North America, and in some areas

of the Caribbean and Latin America. Survival is poor (the five year survival rate is 9 %), so mortality and incidence rates are comparable (*Ries*, 1996). Estimated age standardized incidence ratios (world standard) for Germany are 5.5/100,000 for males and 1/100,000 for females in 1995 (EUCAN, 1999). Within the USA, rates are highest among urban blacks and in some areas of the Southeastern coasts. US mortality rates from the "Surveillance, Epidemiology, and End Results" (SEER) program for whites are 4.0/100,000 in males and 1.3/100,000 in females as compared with 14.2/100,000 for black men and 3.6/100,000 for black women (*Muñoz*, 1996). While incidence and mortality rates have remained relatively constant for whites, rates among blacks have steadily increased since 1950, and this has not been attributed to access to health care or increases in the prevalence of smoking and alcohol consumption (*Ellis*, 1991; *Ernster*, 1991; *Muñoz*, 1996). Differences in nutritional status could, however, explain this (*Muñoz*, 1996). Documented risk factors for esophageal cancers include alcohol and smoking, with clear dose-response and interactive effects demonstrated (*Ernster*, 1991; *Muñoz*, 1996). Estimates of the mortality from esophageal cancer attributed to smoking alone and in combination with alcohol are high, though socioeconomic status and nutrition (specifically low intake of fruit and vegetables) are also considered important risk factors (*Ellis*, 1991; *Muñoz*, 1996). Esophageal cancer results were reported from eight of the 45 studies included in this review. Table 15 (see page 85) shows risk estimates and other study characteristics from each of these studies. Selected risk estimates and confidence intervals are illustrated in Figure 3 (see page 84).

Figure 3:
Selected risk estimates and confidence limits for cancer of the esophagus



* ever employed in dry cleaning

** 10+ years employed in dry cleaning

Table 15:
Reported risk estimates for esophageal cancer from eight studies

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[1]
Cohort studies								
Blair 1990	SMR	Dry cleaning workers	Adjusted	Adjusted	13	6.10	2.1*	(1.10-3.60)
	SMR	Dry cleaning workers	Men	Black	11	--	3.5	---
Ruder 1994	SMR	Dry cleaning workers (full cohort)	Adjusted	Adjusted	10	--	2.14*	(1.02-3.94)
	SMR	Dry cleaning workers (PCE only)	Adjusted	Adjusted	4	--	2.64	(0.72-6.76)
	SMR	Dry cleaning workers (PCE +)	Adjusted	Adjusted	6	--	1.90	(0.69-4.14)
	SMR	Dry cleaning workers (full cohort)	Men	Adjusted	5	--	1.60	(0.523.73)
	SMR	Dry cleaning workers (full cohort)	Women	Adjusted	5	--	3.24*	(1.05-7.58)
Chow 1995	SIR	Laundry workers[2]	Men		3	--	1.0	--
Case-control studies								
Siemiatycki 1991	OR	Laundry/ dry cleaning workers	Men		0	--		
Vaughan 1997	OR	"likely" exposure to PCE	Adjusted	All[3]	2	3	6.4[2]	(0.60-68.90)
	OR	Dry cleaning industry (ever)	Adjusted	All	2	8	1.1[3]	(0.20-5.70)
	OR	Dry cleaning industry (ever)	Adjusted	All	2	8	3.6[2]	(0.20-27.00)
	OR	Dry cleaning workers (1-9 yrs)	Adjusted	All	2	7	4.6[2]	(0.50-39.40)
	OR	Dry cleaning workers (10+ years)	Adjusted	All	0	1	--	--

Table 15 (continued):

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[1]
Death certificate studies								
Nakamura 1985	PMR	Laundry/ dry cleaning workers	Men		12	15.80	0.76	--
	PMR	Laundry/ dry cleaning workers	Women		4	2.60	1.54	--
Milham 1997	PMR	Laundry/ dry cleaning workers	Men	White	7	7.00	1.0	--
	PMR	Laundry/ dry cleaning workers	Women	White	3	3.00	0.98	--
Walker 1997	PMR	Laundry/ dry cleaning workers	Men	Black	12	--	2.15*	(1.11-3.76)
	PMR	Laundry/ dry cleaning workers	Men	White	3	--	0.75	(0.16-2.19)
	PMR	Laundry/ dry cleaning workers	Women	Black	9	--	1.84	(0.84-3.49)
	PCMR	Laundry/ dry cleaning workers	Women	White	4	--	1.89	(0.51-4.83)

SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; OR: Odds Ratio;
PMR: Proportionate Mortality Ratio; PCMR: Proportionate Cancer Mortality Ratio

--, not reported

[1] 95% Confidence limit

[2] squamous cell

[3] adenocarcinoma

* $p \leq 0.05$

Qualitative exposure estimates were ascertained for all eight studies. Surrogate measures of PCE exposure included usual occupation recorded on death certificates, union memberships and occupation or industry title. Five of these studies included both laundry and dry cleaning workers in the "exposed" population. The study by *Chow* (1995) reported a risk estimate for laundry workers (a group generally considered

"unexposed" to PCE) and it was unclear from the report if this classification included dry cleaning workers as well. However, as discussed earlier, it is likely that the cohort includes dry cleaners, as other reports on the same cohort always classified laundry and dry cleaners together. The remaining three study populations were comprised of dry cleaning workers only. As discussed earlier, the likelihood of PCE exposure is higher for those populations consisting of dry cleaners alone than for populations which include laundry workers as well.

Data on potential confounders, alcohol and cigarettes, were obtained via mail surveys to next of kin in the *Nakamura* (1985) study (57 % return rate) while the *Siemiatycki* (1991) and *Vaughan* (1997) studies ascertained these data through personal interviews with the cases and next of kin. *Vaughan* also adjusted for level of education.

For most of the studies reviewed, few cases of esophageal cancer were observed and reported. The *Blair* (1990) and *Ruder* (1994) cohort studies and the death certificate study by *Walker* (1997) observed statistically significant excesses of esophageal cancer. Both *Walker* and *Blair* found the increase among black males (PMR 2.15, 95% CI 1.11-3.76; SMR 3.5; 11 of 13 death cases) respectively, while the excess reported by *Ruder* was observed in females (SMR 3.24, 95% CI 1.05-7.58), who, as *Ruder* further noted, would have been less likely than males to hold machine operator jobs where PCE exposure would be higher. *Ruder* also reported a significant excess of esophageal cancer deaths among the PCE only sub-cohort with a minimum of five years employment and latency period of at least 20 years (4 deaths, SMR 7.17, 95% CI 1.92-19.82).

In the *Siemiatycki* (1991) study there were no cases of esophageal cancer reported among "substantially" exposed launderers and dry cleaning workers (10+ years accumulated exposure in the occupation occurring at least 5 years before onset of disease). Similarly, there were no cases of esophageal cancer reported by *Vaughan* (1997) among dry cleaning workers with at least 10 years duration of exposure (i. e. employed between 1960 and 1989), and among those with "probable" exposure, an elevated though non-significant finding was reported (OR 6.4, 95% CI 0.60-68.9).

While the *Milham* (1997) PMR results for males and females as well as the SIR result for males in the *Chow* (1995) cohort study were all approximating the null value (risk estimate of 1.0), *Nakamura* (1985) reported an excess among females (PMR 1.54), but not males (PMR 0.76).

The majority of risk estimates reported for esophageal cancer lack precision due to small sample size, resulting in wide confidence intervals. This imprecision is illustrated in Figure 3 for studies reporting interval limits.

Two cohort studies and one case-control study were considered to be the most relevant for a critical synthesis. The death certificate studies were not considered to be informative in the critical synthesis. Because of differences in cancer definitions and because exposed cohorts were defined in different ways, a quantitative summary estimate of effect was not calculated for cancer of the esophagus. *Vaughan* (1997) reported risk estimates for adenocarcinomas and squamous cell carcinomas separately and observed few cases of either type of esophageal cancer (though adenocarcinomas are notably rare). While the studies by *Blair* (1990) and *Ruder* (1994) both reported similarly defined estimates, they were not combined, as the separate estimates, which evaluated latency and duration, were more informative than a summary of the unadjusted estimates. Furthermore, given the observed differences pertaining to race and gender, a combination of effects which ignored the differences in these sub-cohorts would have masked important information regarding esophageal cancer.

Additionally, the degree to which potential confounding was controlled for in the studies varied considerably, thus allowing for alternate explanations of the results.

As not all studies that were of adequate quality to contribute to the critical synthesis were stratified or defined exposure in the analysis in a similar enough way, the overall evidence was considered inadequate to draw firm conclusions for this cancer site.

With risk estimates only slightly to moderately elevated, it would appear reasonable to rule out a strong association between PCE exposure and esophageal cancer. However, the possibility that an association between PCE exposure and esophageal cancer exists

cannot be dismissed, as the risk estimates from the large cohort studies with the highest likelihood of PCE exposure, were elevated.

3.5.3 Liver Cancer (ICD-9 155-156)

Worldwide liver cancer, specifically hepatocellular carcinoma (HCC), is the third most common cause of cancer mortality (*London*, 1996). Primary liver cancer in the United States is rare. Mortality rates (world standard) for primary liver cancer in the USA were 2.1/100,000 for males and 0.7/100,000 for females in 1995 (WHO, 1999). Estimated age standardized incidence ratios (world standard) for Germany are 4.8/100,000 for males and 1.9/100,000 for females in 1995. Respective mortality rates are actually identical (EUCAN, 1999). Five-year survival rates are approximately six percent (*Ries*, 1996). Reported mortality due to primary liver cancer may be overestimated as the liver is a common metastatic site for other cancers.

The known risk factors for liver cancer vary depending on the type of cancer. Eighty percent of HCC is associated with hepatitis B virus (HBV) (*London*, 1996). Cirrhosis of the liver has also been associated with HCC, but the exact relationship between alcohol and HCC has not been established (i. e. whether alcohol is a tumor initiator or promoter is unclear). Other established risk factors for primary liver cancers include aflatoxins, thorotrast, vinyl-chloride and some steroids (*London*, 1996). Liver tumors have been found in mice exposed to PCE; extrapolation of this relationship to humans is questionable (US DHHS, 1997).

16 studies reviewed in the critical analysis included results for liver cancer. These are summarized in Table 16 (see page 92). Selected risk estimates and confidence intervals can be found in Figure 4 (see page 91).

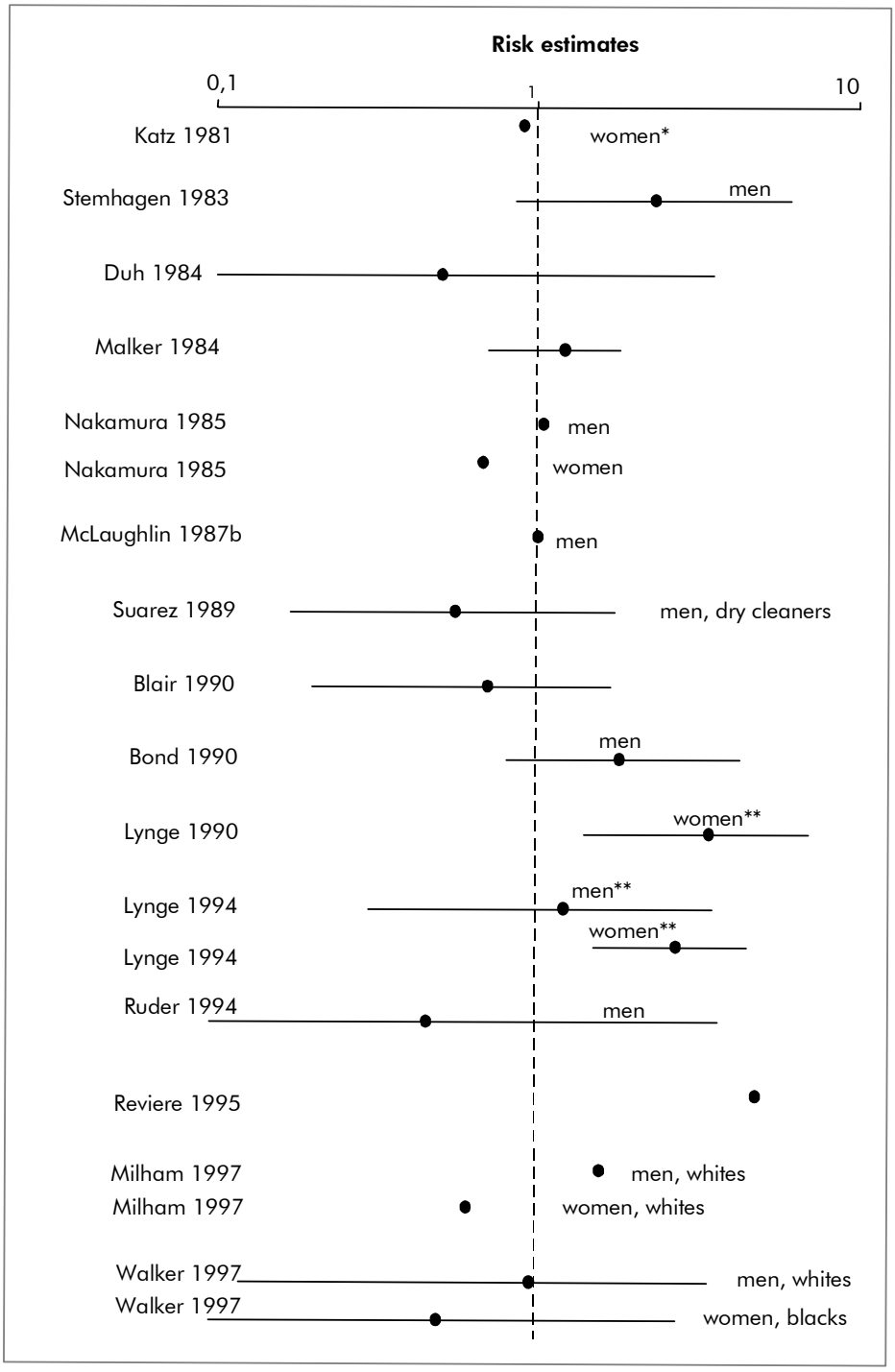
Exposure assessment in the studies reviewed is a problem, as is the lack of control for established risk factors. All studies utilized qualitative exposure measures based on membership in selected unions, occupation or work area. For all studies reporting a risk estimate for liver cancer, exposure was to mixed agents with PCE exposure possible. Only the cohort studies by *Blair* (1990) and *Ruder* (1994) included population

sub-groups that were likely exposed to PCE only. The *Blair* and *Ruder* cohort studies and the *Lynge* (1995) case-control study as well as the death certificate based study by *Suarez* (1989), were the only ones either restricted to dry cleaners or where dry cleaners could be analyzed separately. The case-control study by *Bond* (1990) used work area assignment as a surrogate for exposure to PCE; thus, exposure to PCE could not be separated from other potential chemical exposures. All other study populations consisted of both laundry and dry cleaning workers.

Information on potential confounders was not uniformly collected across studies. The cohort studies were unable to control for important confounders by the nature of their design. *Bond* (1990) reviewed medical department records for alcohol use and hepatitis, but found them of limited use in controlling for confounding. *Stemhagen* (1983) collected information for smoking, alcohol and medical history but did not report adjusted risk estimates. Information on case persons' history of hepatitis and cirrhosis was not available in this study.

Within the literature reviewed here, three studies found a significant excess of liver cancer among workers, which were defined as "exposed". The 1983 case-control study by *Stemhagen* reported an excess risk of primary liver cancers (OR 2.50, 95% CI 1.02-6.14) and a non-significant excess of hepatocellular carcinoma (HCC) (OR 2.29, 95% CI 0.85-6.13) among white males in New Jersey diagnosed between 1975 and 1980. *Lynge* (1990) found an excess of liver cancer among dry cleaners/launderers, that persisted in a follow-up (*Lynge* 1994), but when explored in a nested case-control study (*Lynge* 1995) was found to be restricted to launderers. The absence of any liver cancer among dry cleaning workers in *Lynge's* 1995 study supports the results from *Ruder* (1994) and *Blair* (1990), which do not suggest an association between PCE exposure and liver cancer mortality. *Blair* (1979) had found an excess of liver cancer among dry cleaners in an early report, based on a limited number of death certificates and using the PMR approach, but this did not persist in the final cohort analysis (SMR 0.70, 95% CI 0.20-1.70). *Ruder* observed only one case of liver cancer in the large cohort (SMR 0.45, 95% CI 0.01-3.64) which, when stratified by PCE exposure, appeared in the sub-cohort exposed to a combination of PCE and other solvents.

Figure 4:
Selected risk estimates and confidence limits for liver cancer



* comparison group all professions

** cases were laundry workers

Table 16:
Reported risk estimates for cancer of the liver from 16 studies

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[1]
Cohort studies								
Malker 1984	SIR	Laundry/ dry cleaning industry	Both		17	--	1.2	(0.70-1.80)
McLaughlin 1987b	SIR	Laundry/ dry cleaning industry	Men		7	--	1.0	--
Blair 1990	SMR	Dry cleaning workers	Adjusted	Adjusted	5	7.30	0.7	(0.20-1.70)
Lynge 1990	SIR	Laundry/ dry cleaning workers	Women		7	2.10	3.4*	(1.40-7.00)
	SIR	Laundry/ dry cleaning workers	Both		7	3.20	2.2[2]	--
	SIR	Laundry/ dry cleaning workers	Men		3	2.50	1.2	(0.30-3.50)
	SIR	Laundry/ dry cleaning workers	Women		14	5.20	2.7	(1.50-4.50)
Ruder 1994	SMR	Dry cleaning workers (full cohort)	Men	Adjusted	1	--	0.45	(0.01-3.64)
Case-control studies								
Stemhagen 1983	OR	Laundry, cleaning, other garment service[3]	Men	All	8	7	2.29	(0.85-6.13)
	OR	Laundry, cleaning, other garment service[4]	Men	All	10	8	2.5*	(1.02-6.14)
Bond 1990	RR	Chemical workers, PCE and others	Men	--	6	213	1.8	(0.80-4.30)
Lynge 1995	OR	Laundry workers	Both		17	63	--	--
	OR	Dry cleaning workers	Both		0	20		

Table 16 (continued):

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[1]
Death Certificate Studies								
Katz 1981	PMR	Laundry/ dry cleaning industry	Women	White	4	4.50	0.89	--
Duh 1984	SMOR	Laundry/ dry cleaning workers	Adjusted	Adjusted	1	1.90	0.50	(0.10-3.50)
Nakamura 1985	PMR	Laundry/ dry cleaning workers	Women		6	8.90	0.67	--
	PMR	Laundry/ dry cleaning workers	Men		28	27.00	1.04	--
Suarez 1989	OR	Dry cleaning operatives	Men	Adjusted	4	8.00	0.55	(0.17-1.75)
	OR	Dry cleaning workers	Men	Adjusted	11	12.00	0.98	(0.44-2.20)
Reviere 1995	PMR	Laundry/ dry cleaning industry	Both	--	272	--	4.75	--
Milham 1997	PMR	Laundry/ dry cleaning workers	Women	White	1	2.00	0.60	--
	PMR	Laundry/ dry cleaning workers	Men	White	5	3.00	1.57	--
Walker 1997	PMR	Laundry/ dry cleaning workers	Men	Black	0			
	PMR	Laundry/ dry cleaning workers	Men	White	2	--	0.95	(0.12-3.42)
	PMR	Laundry/dry cleaning workers	Women	Black	1	--	0.49	(0.01-2.71)
	PMR	Laundry/dry cleaning workers	Women	White	0			

SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; OR: Odds Ratio; RR: Relative Risk; PMR: Proportionate Mortality Ratio; SMOR: Standardized Mortality Odds Ratio

--, not reported [1] 95% Confidence limit [2] calculated by the authors

[3] HCC [4] primary liver cancer * $p \leq 0.05$

Bond (1990) reported a slight increase in risk for chemical workers who were exposed to PCE among other substances (e. g. vinyl-chloride). For the most part the death certificate studies did not report an increased risk for liver cancer.

No quantitative summary measure was calculated for cancer of the liver, because most study populations were mixed workers or exposures. Estimates from the *Blair* (1990), *Ruder* (1994) and *Lynge* (1995) nested case-control study were not combined as the cases in *Ruder* and *Lynge* were not among those with the greatest likelihood of PCE exposure. A qualitative summary was based on the available cohort and case-control studies; death certificate studies were not considered as their contribution is limited.

The studies that contribute most to our understanding of PCE and liver cancer are those with risk estimates that pertain to dry cleaners alone. Studies where the population is "mixed" are less useful, especially where other liver cancer risk factors are not considered. No study was able to adequately control for potential confounding, thus raising the possibility that the unexplained inconsistencies in study findings reflect study limitations rather than random results. However, no study that included an analysis of dry cleaners alone found an increased risk for liver cancer. Liver cancer cases observed by *Ruder* (1994) and *Lynge* (1995) were not in the sub-cohorts with the greatest likelihood of PCE exposure and *Blair* (1990) observed fewer cases than expected which undermines evidence for a strong effect.

The quality of evidence was inadequate to fully evaluate an association between PCE and cancer of the liver, though a relationship appears unlikely. Most studies available for review consisted of populations with mixed exposures, other risk factors were not controlled and few cases were observed in the populations restricted to dry cleaners (though primary liver cancer is rare, particularly in the USA). While the case-control study of *Stemhagen* (1983) did find an excess of cancers, *Lynge* (1995) found no cases of liver cancer among dry cleaners. Furthermore, neither *Blair* (1990) nor *Ruder* (1994), found excess cancer among exposed workers, specifically within the sub-cohorts that are presumed exposed primarily to PCE.

The epidemiological evidence in the studies reviewed here, on the whole, does not support a relationship between liver cancer and exposure to PCE. Where excess liver cancers are observed, other explanations may be more likely.

3.5.4 Pancreatic Cancer (ICD-9 157)

Pancreatic cancer is rapidly fatal with an age adjusted mortality (world standard) of 7.3/100,000 in the USA for males (Germany 8.3/100,000) and 5.3/100,000 for females (Germany 5.5/100,000) (WHO, 1999; EUCAN, 1999). There is some variation internationally in incidence and mortality rates that may be an artifact of case ascertainment. In general, incidence is higher for males (though decreasing among US white males). The highest rates in the world have been observed among black males (13.7) and black females (11.9) in California (USA) (*Anderson*, 1996).

Age is an important predictor of pancreatic cancer, with most cases in the USA occurring between 65 and 79 years of age. The epidemiological evidence is strongest for an association between smoking and pancreatic cancer, including evidence of a dose-response relationship. In addition, there is some evidence that diet plays an etiologic role. Fat and animal proteins have been implicated in increasing risk. Conversely, a decrease in risk has been observed with high intake of fruit and vegetables, which may be a reflection of a lifestyle that precludes smoking. There is little conclusive evidence of occupational risk factors for pancreatic cancer, though suggested relationships include products of incomplete combustion of petroleum, pesticides, and specific chemicals and processes (not including dry cleaning or halogenated solvents) (*Anderson*, 1996).

Ten studies reviewed evaluated the association between dry cleaning or exposure to PCE and pancreatic cancer. Results from these studies are presented in Table17 (see page 97) and selected risk estimates and confidence intervals are shown in Figure 5 (see page 96).

Figure 5:
Selected risk estimates and confidence limits for pancreatic cancer

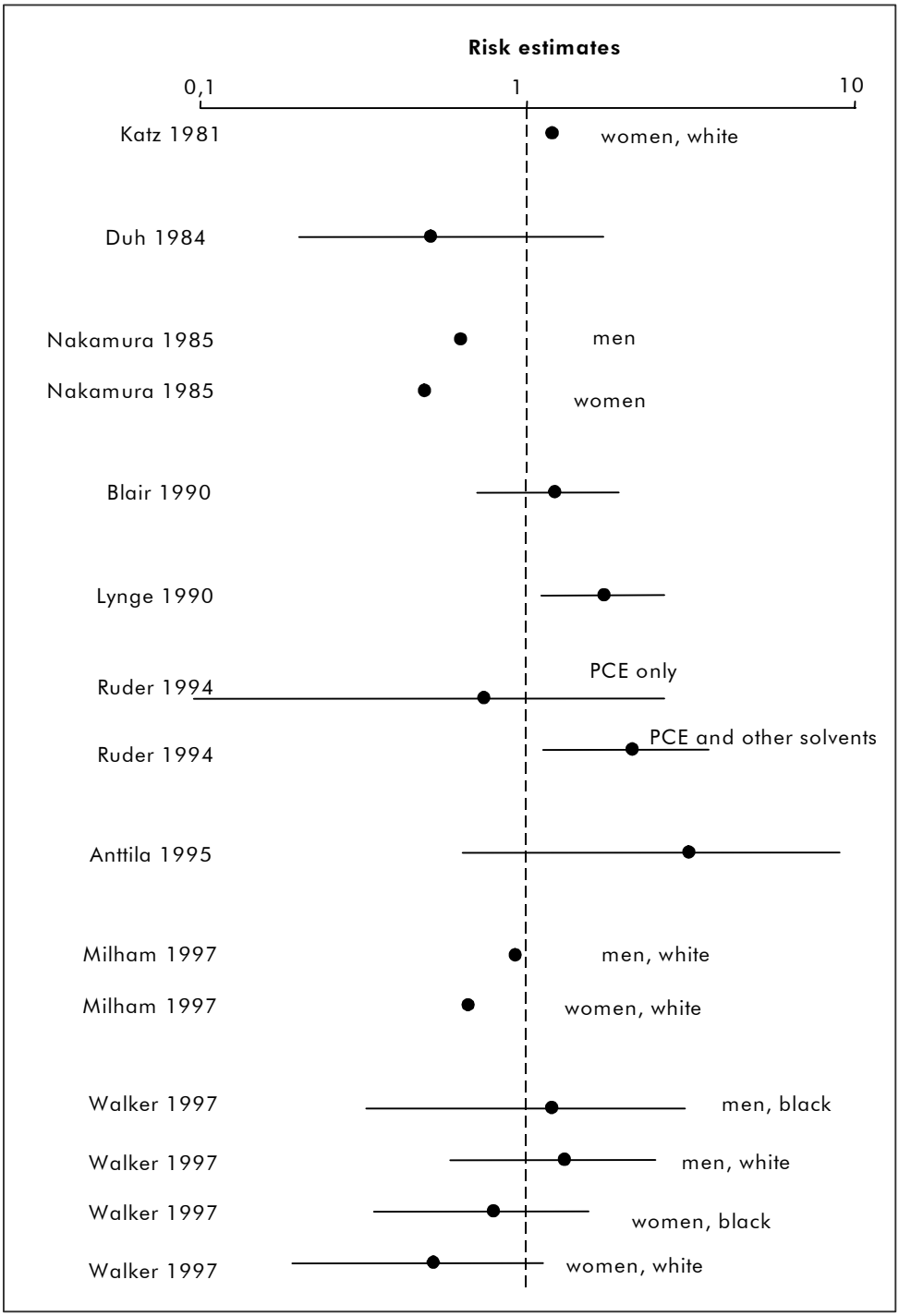


Table 17:
Reported risk estimates for pancreatic cancer from ten studies

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[1]
Cohort studies								
Blair 1990	SMR	Dry cleaning workers	Adjusted	Adjusted	15	12.70	1.2	(0.70-1.90)
Lynge 1990	SIR	Laundry/ dry cleaning workers	Both		22	13.10	1.7*	(1.10-2.60)
Ruder 1994	SMR	Dry cleaning workers (full cohort)	Adjusted	Adjusted	15	--	1.66	(0.93-2.75)
	SMR	Dry cleaning workers (PCE only)	Adjusted	Adjusted	2	--	0.73	(0.09-2.62)
	SMR	Dry cleaning workers (PCE and others)	Adjusted	Adjusted	13	--	2.08*	(1.11-3.55)
Anttila 1995	SIR	PCE	Adjusted		3	--	3.08	(0.63-8.99)
Case-control studies								
Siemiatycki 1991	OR	Laundry/ dry cleaning workers	Men		0			
Death certificate studies								
Katz 1981	PMR	Laundry/ dry cleaning industry	Women	White	9	7.70	1.17	--
Duh 1984	SMOR	Laundry/ dry cleaning workers	Adjusted	Adjusted	3	5.50	0.50	(0.20-1.70)
Nakamura 1985	PMR	Laundry/ dry cleaning workers	Women		3	6.20	0.48	--
	PMR	Laundry/ dry cleaning workers	Men		8	12.90	0.62	--
Milham 1997	PMR	Laundry/ dry cleaning workers	Women	White	11	17.00	0.65	--
	PMR	Laundry/dry cleaning workers	Men	White	17	19.00	0.91	--

Table 17 (continued):

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[1]
Walker 1997	PMR	Laundry/ dry cleaning workers	Men	Black	4	--	1.18	(0.32-3.02)
	PMR	Laundry/ dry cleaning workers	Men	White	9	--	1.28	(0.58-2.43)
	PMR	Laundry/ dry cleaning workers	Women	Black	8	--	0.78	(0.34-1.54)
	PMR	Laundry/ dry cleaning workers	Women	White	6	--	0.51	(0.19-1.11)

SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; PMR: Proportionate Mortality Ratio; SMOR: Standardized Mortality Odds Ratio; OR: Odds Ratio

--, not reported

[1] 95% Confidence limit

$p \leq 0.05$

Exposure assessments were qualitative in all but one study. The risk estimate reported by *Anttila* (1995) was based on levels of PCE in the blood. However, *Anttila* did not report actual occupation and exposure duration. All other studies used occupations or union membership as a surrogate of exposure. The *Blair* (1990) and *Ruder* (1994) cohort studies were the only ones restricted to dry cleaners. Further, they included only those who had worked for at least one year. The population investigated in the *Lynge* (1990) study was comprised of persons not exposed to PCE (laundry workers) and persons who were potentially exposed to PCE as dry cleaning workers. All other studies reported results for laundry and dry cleaning workers together. As discussed for previous cancer sites, this limits the likelihood of PCE exposure.

Only the studies by *Siemiatycki* (1991) and *Nakamura* (1985) gathered information to control for confounding by smoking and no study collected any relevant dietary information. *Siemiatycki* observed no cases of pancreatic cancer and it does not appear that the estimate by *Nakamura* utilized the information on smoking for specific cancer site risk estimates.

Within the literature reviewed here, three cohort studies reported excess mortality due to pancreatic cancer, though this excess was not statistically significant in the study by *Blair* (1990) (SMR 1.2, 95% CI 0.70-1.90) or *Anttila* (1995) (SMR 3.08, 95% CI 0.63-8.99). *Lynge* (1990) observed significant increased risk among those listed as laundry and dry cleaners (SMR 1.7, 95% CI 1.10-2.60). *Ruder* (1994) found no excess among those dry cleaners exposed only to PCE, but did report excess among the cohort exposed to PCE and other solvents (SMR 2.08, 95% CI 1.11-3.55), based on 13 deaths. When the total cohort was stratified by latency and duration, borderline excess was reported for workers with five or more years of employment and at least 20 years latency (SMR 2.22, 95% CI 0.9-4.8). This result was based on seven deaths and was barely statistically significant. The case-control study by *Siemiatycki* (1991) observed no cases of pancreatic cancer among those in laundry and dry cleaning occupations or industries. Finally, the results of the death certificate studies included in this review do not suggest an association.

Only the four cohort studies reporting risk estimates for pancreatic cancer were considered in the critical synthesis; the death certificate studies added little to our understanding of the relationship between PCE and pancreatic cancer due to their inherent limitations and mixed populations. A quantitative summary estimate was deemed inappropriate for this cancer site as the exposure definitions differed among the four cohort studies. Therefore, the available information was assessed at a qualitative level.

The four studies providing the most information regarding pancreatic cancer and PCE are limited in their results. No large effect was demonstrated, though *Lynge* (1990) and *Ruder* (1994) both observed a significant excess of pancreatic cancer. As discussed the *Lynge* study population included laundry workers and the increase observed by *Ruder* was seen only in the sub-cohort believed exposed to PCE and other solvents. No excess was observed by Ruder among the PCE only sub-cohort.

The quality of epidemiological evidence for an association between PCE and pancreatic cancer is limited. Three studies were of populations most likely exposed to PCE. The remaining studies all included both laundry and dry cleaning workers. The study

by *Anttila* did not include occupational information and the two large cohort studies present different results. Also, as noted there were no cases observed in the only case-control study included in the critical review (*Siemiatycki*, 1991).

Given the epidemiological data and the previously mentioned limitations in exposure measures, an association between PCE and pancreatic cancer appears unlikely. The inconsistent effects reported and the mixed occupational groups and exposures suggest that other factors are more likely to explain the excess risk observed in these cohorts for pancreatic cancer.

3.5.5 Laryngeal Cancer (ICD-9 161)

The overall incidence of cancer of the larynx in the USA is 4.5/100,000 (*Ries*, 1996). The incidence among males is approximately four times higher than among females (*Austin*, 1996; *Muir*, 1996). The highest incidence rates among men are seen in Brazil, Cuba, Spain, Italy, and France (ranging between 14.7 and 20.4/100,000). Estimated age standardized incidence ratios (world standard) for Germany are 5.9/100,000 for males and 0.5/100,000 for females in 1995. The respective mortality rates are 2.6/100,000 for males and 0.3/100,000 for females (EUCAN, 1999). Squamous cell carcinomas are the most common histological type of cancer found in the larynx and are believed to be caused by long-term smoking. The occurrence of this type of cancer in non-smokers is rare (*Norris*, 1991). There are distinct sub-sites for laryngeal cancer for which there are unexplained differences across demographic groups. The reasons for these differences are undetermined.

Another important risk factor for laryngeal cancer is alcohol consumption. A dose-response effect and an interactive effect between smoking and consuming alcohol have been clearly demonstrated (*Austin*, 1996). Studies of diet and laryngeal cancer have demonstrated a protective effect for some nutrients (*Austin*, 1996). Studies to assess occupational risk factors generally have not controlled for smoking or alcohol. Nevertheless, exposure to sulfuric acid mist and mustard gas appear to elevate risk. Six studies reported any result for cancer of the larynx. Table 18 (see page 102) shows

specific results from each study included in the critical review. Figure 6 shows selected results for cancer of the larynx.

Figure 6:
Selected risk estimates and confidence limits for cancer of the larynx

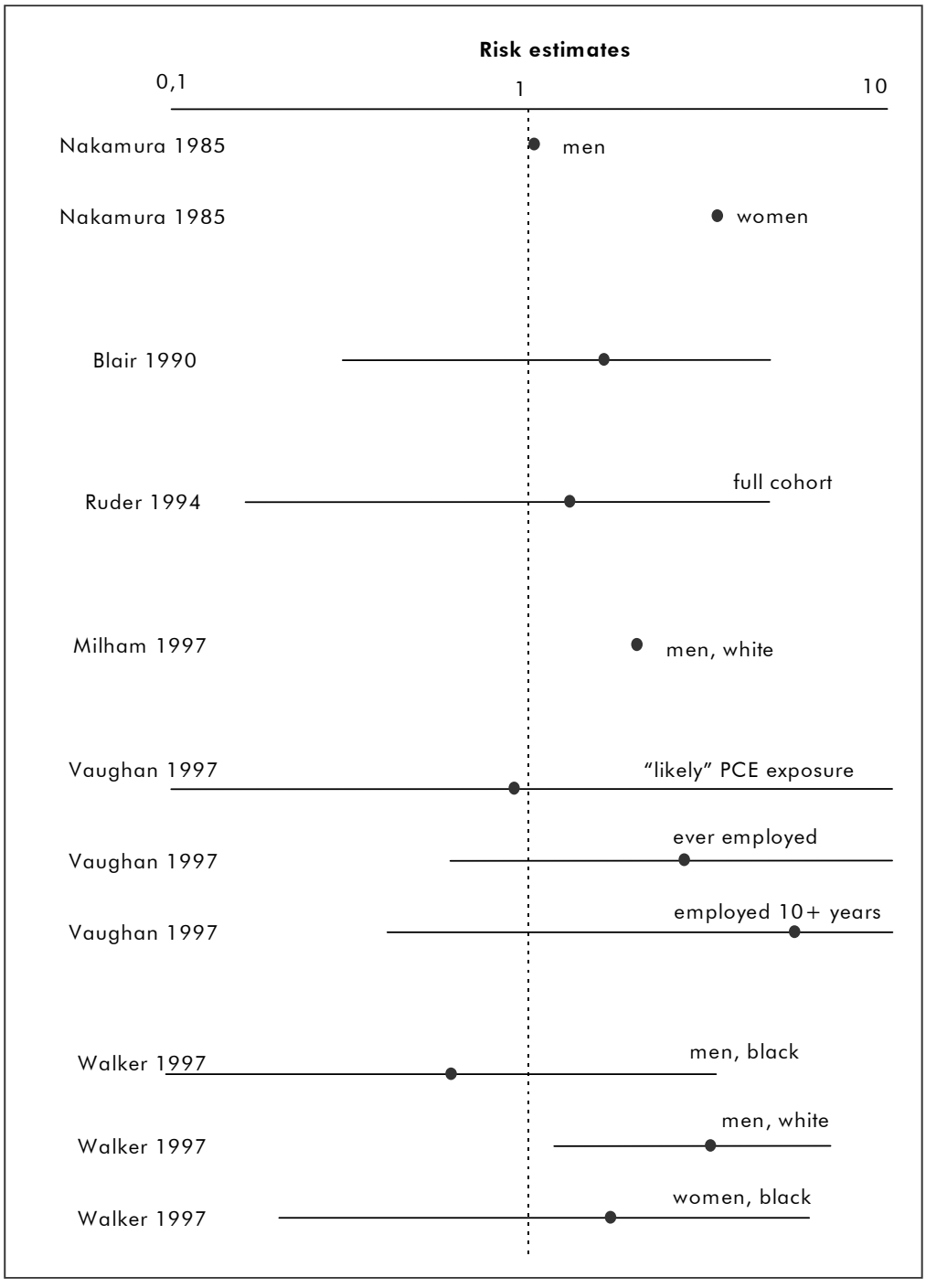


Table 18:
Reported risk estimates for cancer of the larynx from six studies

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[1]
Cohort studies								
Blair 1990	SMR	Dry cleaning workers	Adjusted	Adjusted	3	1.90	1.6	(0.30-4.70)
Ruder 1994	SMR	Dry cleaning workers (full cohort)	Adjusted	Adjusted	2	--	1.29	(0.16-4.67)
Case-control studies								
Vaughan 1997	OR	"likely" exposure to PCE	Adjusted	All[2]	1	3	0.9	(0.10-2.90)
	OR	Dry cleaning industry (ever)	Adjusted	All	5	8	2.7	(0.60-0.90)
	OR	Dry cleaning workers (1-9 yrs)	Adjusted	All	3	7	1.9	(0.30-0.80)
	OR	Dry cleaning workers (10+ yrs)	Adjusted	All	2	1	5.5	(0.40-75.00)
Death certificate studies								
Nakamura 1985	PMR	Laundry/ dry cleaning workers	Women		1	0.30	3.33	--
	PMR	Laundry/ dry cleaning workers	Men		3	2.90	1.03	--
Milham 1997	PMR	Laundry/ dry cleaning workers	Women	White	1	1.00	--	--
	PMR	Laundry/ dry cleaning workers	Men	White	7	4.00	1.99	--
Walker 1997	PMR	Laundry/ dry cleaning workers	Men	Black	1	--	0.60	(0.02-3.32)
	PMR	Laundry/ dry cleaning workers	Men	White	6	--	3.18*	(1.17-6.93)
	PMR	Laundry/ dry cleaning workers	Women	Black	2	--	1.68	(0.20-6.05)

Table 18 (continued):

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[1]
Walker 1997	PMR	Laundry/ dry cleaning workers	Women	White	0			

SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; OR: Odds Ratio;

PMR: Proportionate Mortality Ratio

-- not reported,

* $p \leq 0.05$

[1] 95% Confidence limit,

[2] *Vaughan* reports that adjusting for race effected no change of risk estimate

Exposure in the above studies is presumed, based on ever having worked in dry cleaning, membership in a union or "usual" occupation as reported on a death certificate. No study reviewed could base exposure on a quantitative measure or on individual measurements.

Blair (1990), *Ruder* (1994) and *Vaughan* (1997) all made some attempt to assess the potential for exposure to PCE or the level of exposure using qualitative and semi-quantitative methods. The cohort studies did not control for smoking, though *Vaughan* controlled for smoking and alcohol consumption. Other risk factors were not controlled in the death certificate studies.

The case-control study by *Vaughan* (1997) found a non-significant association for cancer of the larynx among those who ever worked in the dry cleaning industry (OR 2.7, 95% CI 0.6-10.9) based on five cases, as did *Blair* (SMR 1.90, 95% CI 0.3-4.7) based on three cases and *Ruder* (SMR 1.29, 95% CI 0.16-4.67) based on two cases for the total cohort. *Vaughan* also observed an excess among those who reported working in the industry for ten or more years (two cases). However, when stratified by probability of exposure *Vaughan* found no excess among those considered to have a high (> 50 %) probability of exposure to PCE (one case). The number of cases in all three studies is extremely small and therefore these results must be interpreted with caution. Results were not consistent among the death certificate studies reviewed,

though *Walker* (1997) observed an excess among white males (PMR 3.18, 95% CI 1.17-6.93) based on six cases. *Milham* reported a PMR of 1.99 among white males based on seven cases, though four of these cases occurred in the years 1950 to 1962, which was decisive for the magnitude of the risk estimate. Assuming an adequate latency period it is not likely that these cases were exposed predominantly to PCE.

A summary estimate of effect was not calculated for cancer of the larynx. Three studies were considered for inclusion in a quantitative summary estimate of effect for cancer of the Larynx, as they all had reasonable likelihood of PCE exposure. However, the report by *Ruder* (1994) neither provided an estimate for laryngeal cancer for the sub-cohort exposed only to PCE, nor were there sufficient observed cases in the collective cohort. A summary estimate was not calculated based on *Blair* (1990) and *Vaughan* (1997) as only the latter controlled for smoking and alcohol, important risk factors for cancer of the larynx. Further, *Vaughan* observed only one case and no excess in the sub-cohort with the greatest likelihood of exposure.

Given that the number of cases in each study was extremely small, that exposure assessments are limited, and that other risk factors were either not controlled for or self-reported, an association between PCE and laryngeal cancer cannot be confirmed from the current body of epidemiological research. The available evidence (number of observed cases, exposure assessments, potential confounders) is not adequate to draw unequivocal conclusions as to an association. No conclusions regarding an association between PCE exposure and laryngeal cancer can be made.

3.5.6 Lung Cancer (ICD-9 162)

Lung cancer is currently considered the leading cause of cancer mortality in the world (*Muir*, 1996). Estimated age standardized incidence ratios (world standard) for Germany are 54/100,000 for males and 10.6/100,000 for females in 1995. Respective mortality rates are 46.6/100,000 for males and 9.2/100,000 for females (EUCAN, 1999). The age adjusted mortality rate (world standard) for lung cancer in the USA in 1995 was 53/100,000 for males and 26.6/100,000 for females (WHO, 1999). Survival is poor, with approximately 13 % of lung cancer cases surviving more

than five years (*Ries*, 1996). Historically, men have had higher incidence and mortality rates for lung cancer, primarily due to smoking patterns and occupational exposures; however, the smoking pattern is changing as incidence and mortality increase among women and decline among men. Highest rates are observed among black men. International and gender differences are directly related to patterns of smoking.

Smoking is the primary risk factor for lung cancer (*Blot*, 1996). A strong dose-response relationship has been documented. Established occupational risk factors include specific arsenic compounds, asbestos, hexavelant chromium, bis(chloro)methylethers, and polycyclic aromatic hydrocarbons (PAH). Other risk factors include radon, silica, ionizing radiation, and prior non-malignant lung disease (e. g. silicosis).

Consumption of fruits and vegetables has been suggested to have a protective effect (*Blot*, 1996).

14 studies reviewed reported an estimate of risk for lung cancer and dry cleaning or PCE exposure. Results from these studies are presented in Table 19 (see page 107) and Figure 7 (see page 106) shows selected risk estimates and confidence intervals.

As with other cancer sites the results are severely limited by the level of exposure measurement. The study by *Anttila* (1995) provides the only quantitative measure but lacks important further exposure information. In all other studies exposure measures were qualitative, including union membership and occupation indicators, and few of the studies quantified latency or duration of exposure. All death certificate based studies, one of the case-control studies and two cohort studies provided information only for laundry and dry cleaning workers combined. Three of the remaining studies are in the category with the greatest probability of PCE exposure.

Figure 7:
Selected risk estimates and confidence limits for lung cancer

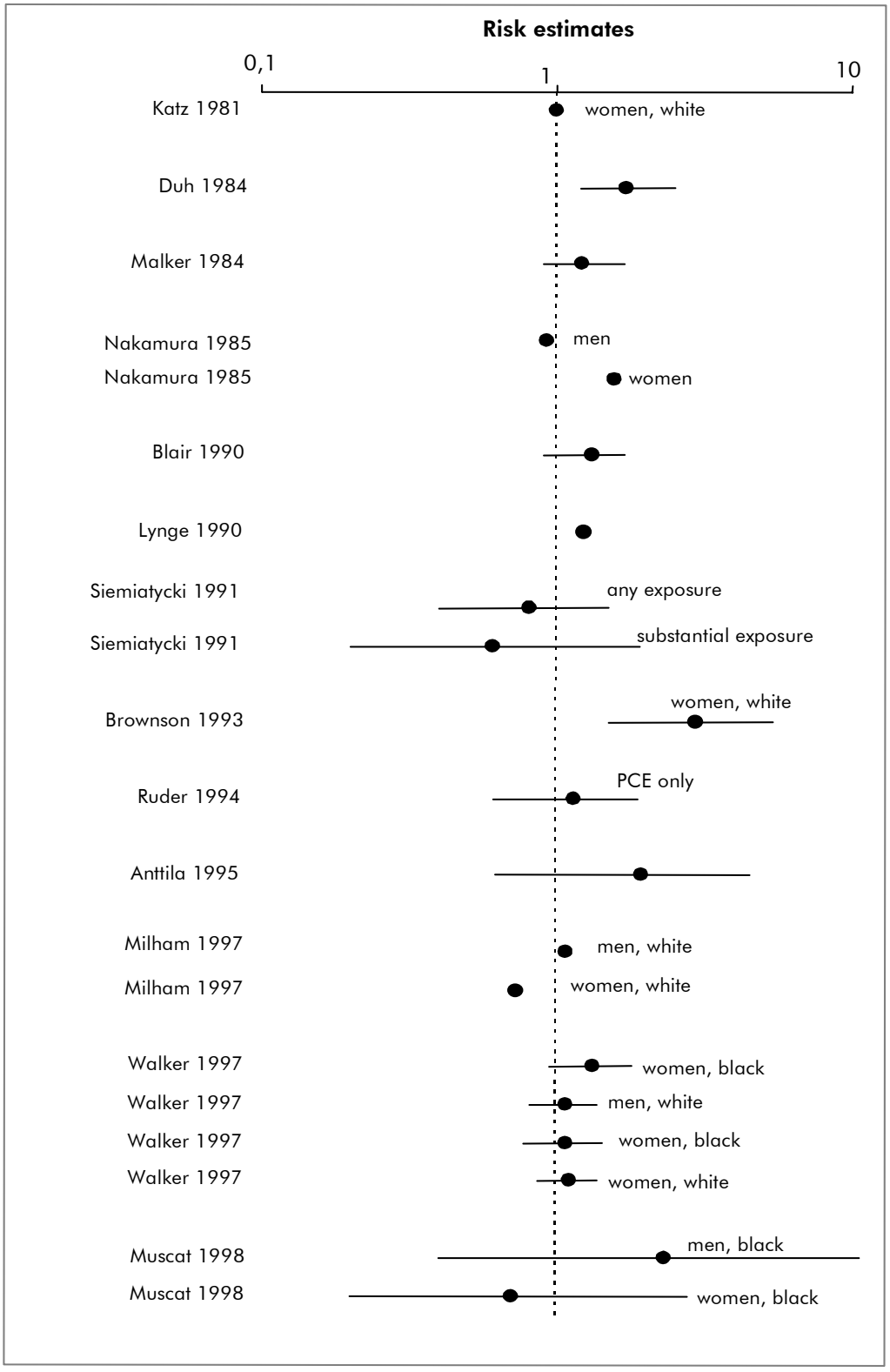


Table 19:
Reported risk estimates for lung cancer from 14 studies

Reference	Estimate type	Exposure group	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[1]
Cohort studies								
Malker 1984	SIR	Laundry/ dry cleaning industry	Both		34	--	1.2	(0.90-1.70)
Blair 1990	SMR	Dry cleaning workers	Adjusted	Adjusted	47	37.10	1.3	(0.90-1.70)
Lynge 1990	SIR	Laundry/ dry cleaning workers	Both		60	49.30	1.22[2]	--
Ruder 1994	SMR	Dry cleaning workers (full cohort)	Adjusted	Adjusted	43	--	1.18	(0.85-1.59)
	SMR	Dry cleaning workers (PCE only)	Adjusted	Adjusted	14	--	1.12[3]	(0.61-1.88)
	SMR	Dry cleaning workers (PCE and others)	Adjusted	Adjusted	32	--	1.23[3]	(0.84-1.73)
Anttila 1995	SIR	PCE	Adjusted		5	--	1.92	(0.62-4.48)
Case-control studies								
Siemiatycki 1991		Laundry/ dry cleaning workers						
	OR	"any" exposure	Men		12	--	0.8	(0.40-1.50)
	OR	"substantial" exposure	Men		5	--	0.6	(0.20-1.90)
Brownson 1993	OR[3]	Dry cleaning industry, high exposure (>1.125 yrs)	Women	White	--	--	2.9[4]*	(1.50-5.40)
	OR[3]	Dry cleaning industry, non-smokers	Women	White	23	31	2.1[4]*	(1.20-3.70)
	OR[3]	Dry cleaning industry, full cohort	Women	White	30	39	1.8[4]*	(1.10-3.00)

Table 19 (continued):

Reference	Estimate type	Exposure group	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[1]
Muscat 1998	OR	Dry cleaning workers	Women	Black	6[2]	3[2]	0.7	(0.20-2.80)
	OR	Dry cleaning industry	Men	Black	8[2]	3[2]	2.3	(0.40-13.00)
Death certificate studies								
Katz 1981	PMR	Laundry/ dry cleaning industry	Women	White	10	10.20	0.98	--
Duh 1984	SMOR	Laundry/ dry cleaning workers	Adjusted	Adjusted	37	22.60	1.7*	(1.20-2.50)
Nakamura 1985	PMR	Laundry/ dry cleaning workers	Women		15	9.7	1.55	--
	PMR	Laundry/ dry cleaning workers	Men		40	43	0.92	--
Doebbert 1988	SMR	Laundry/ dry cleaning workers	Women	Black	--	--	3.83	--
Milham 1997	PMR	Laundry/ dry cleaning workers	Women	White	8	11.00	0.72	--
	PMR	Laundry/ dry cleaning workers	Men	White	57	54.00	1.06	--
Walker 1997	PMR	Laundry/ dry cleaning workers	Men	Black	39	--	1.32	(0.94-1.81)
	PMR	Laundry/ dry cleaning workers	Men	White	61	--	1.06	(0.81-1.37)
	PMR	Laundry/ dry cleaning workers	Women	Black	43	--	1.06	(0.77-1.43)
	PMR	Laundry/ dry cleaning workers	Women	White	75	--	1.09	(0.86-1.37)

SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; OR: Odds Ratio; PMR: Proportionate Mortality Ratio; SMOR: Standardized Mortality Odds Ratio

--, not reported, [1] 95% Confidence limit, [2] calculated by the authors, [3] respiratory system (ICD-9 160-165)
[4] adjusted for age, smoking and history of lung disease, * $p \leq 0.05$

As noted before, the cohort studies were not able to control for important confounders, specifically smoking. The case-control studies reviewed were able to control for confounding by smoking, though not other occupational factors. However, for some studies information on potential confounders was collected from surrogates, generally next of kin, which may be less accurate than information from respondents and susceptible to reporting bias.

Slightly increased relative risks for lung cancer and PCE exposure were found by some of the studies. The death certificate study by *Duh* (1984) found a slight but significant excess of lung cancer among dry cleaners and launderers (PMR 1.7, 95% CI 1.2-2.5), who presumably were also predominantly exposed to "Stoddard solvent". A significant increase of lung cancer among female never-smokers (OR 2.1, 95% CI 1.2-3.7) was reported from the *Brownson* (1993) case-control study, where exposure was reported (self or surrogate) as employment in the dry cleaning industry. Slight, non-significant excesses were also reported in other death certificate studies, though none of these studies were able to control for competing risk factors or to separate laundry workers from dry cleaners. No statistically significant excess lung cancer was found in the large cohort studies of dry cleaners reviewed here or in the study by *Antilla* (1995). *Ruder* (1994) observed a slight excess among those exposed to PCE only. In addition, for those workers with 20 or more years latency, there was significant excess among those who worked less than five years (SMR 1.67, 95% CI 1.0-2.6), but not among those who worked more than five years (SMR 0.91, 95% CI 0.5-1.6). The evaluation of lung cancer risk among blacks by *Muscat* (1998) found no significant excess for lung cancer when smoking (number of packs per year) was included in the analysis.

No quantitative summary estimates were calculated for the risk of lung cancer and dry cleaners as the exposure measures and populations were not considered to be adequately similar. Three case-control studies reported risk estimates for lung cancer and dry cleaning or PCE exposure. These were adjusted for the effects of smoking. However, two exposure definitions were used in the *Muscat* (1998) study: "ever" exposed in occupational setting and "ever" worked in a specific job category. While *Muscat* reported cases among those ever exposed to "dry cleaning substances", no results for

dry cleaners were reported in the analysis by "usual" occupation. *Brownson* (1993) defined exposure as employment in dry cleaning and conducted an analyses which incorporated duration, but did not conduct analyses which incorporated duration for the lifetime non-smokers.

No cohort studies provided estimates adjusting for the effect of smoking. The cancer definition in the PCE only sub-cohort in the *Ruder* (1994) study included all respiratory diseases. The *Malker* (1984) and *Siemiatycki* (1991) reports did not include all the information required for a quantitative summary. Furthermore, the exposed groups consisted of laundry and dry cleaning workers, as was the case in the *Lynge* (1990) study. *Blair* (1990) observed a significant excess of emphysema, suggesting a strong effect of smoking in the cohort. Because smoking is the strongest risk factor for lung cancer, it seemed inappropriate to combine estimates where smoking status was known with those where it was unknown. Further, differences in lung cancer rates by gender (based presumably on smoking behavior) preclude a summarization of risk estimates across genders.

The small excesses of lung cancer observed in the cohort studies reviewed may indicate differences in smoking behaviors between dry cleaners (or launderers and dry cleaners) and the respective reference population. Lack of control for confounding by smoking might have generated or contributed to these (as well as other) results. The excess observed in the *Brownson* (1993) cohort of reported non-smokers may be related to other lifestyle factors.

The quality of epidemiological evidence for studies evaluating PCE exposure and lung cancer is limited. No strong excess was observed and the only significant excess was reported by *Brownson* (1993). As not all studies reviewed had the ability to adequately control for confounding by smoking or occupational risk factors, the results must be interpreted within the context of the known risk factors for lung cancer. Given this and the imprecision of exposure assessment in these studies a strong association between lung cancer and PCE or employment in dry cleaning shops seems unlikely.

3.5.7 Cervical Cancer/Cancer of the Female Genital Organs (ICD-9 179-184)

The incidence of cervical cancer in the USA is 7.8/100,000 for white women and 14.0/100,000 for black women (*Ries*, 1996). Estimated age standardized incidence rates (world standard) for Germany are 12.1/100,000 in 1995. The respective mortality rate is 3.8/100,000 (EUCAN, 1999). Invasive cervical cancer rises sharply until age 45, peaks around age 55, and then declines. An earlier peak among women with cervical cancer in situ is thought to be caused by the human papillomavirus (types 16 and 18) and herpes simplex virus (type 2). Survival rates have been reported at 90 % among women with localized cancer (i. e. confined to cervix uteri) and as low as 12 % among women whose cancer has spread (*Ries*, 1996).

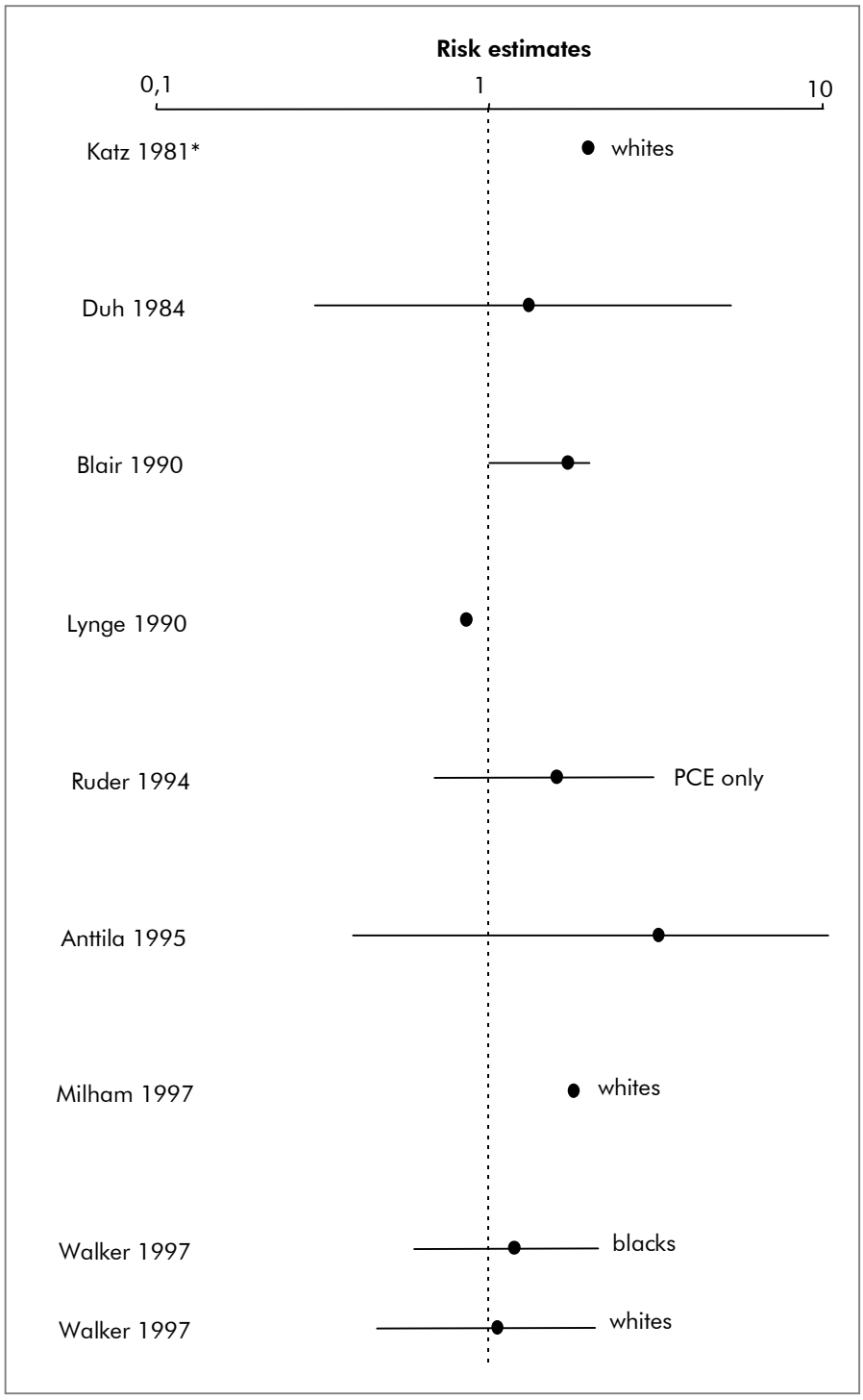
Cervical cancers are generally squamous cell carcinomas, though some are adenocarcinomas (*Gusberg*, 1991). Established risk factors for cervical cancer include multiple sex partners, early sexual activity, sexually transmitted diseases (human papillomaviruses in particular) and low socioeconomic status (SES). Smoking is considered a co-factor for cervical cancer (*Gusberg*, 1991).

Eight studies reported results for cervical cancer. Results are shown in Table 20 (see page 113) and Figure 8 (see page 112) shows selected risk estimates and confidence intervals.

Biological monitoring of PCE (blood tests) was undertaken in the *Anttila* (1995) cohort study from 1974 to 1983 resulting in an average of 3.2 measurements per individual. Among women in this study, the median concentration of PCE was 0.4 µmol/l. Exposure estimates from all other studies were qualitative, using occupation or union membership as a surrogate for exposure. The four death certificate studies and the cohort study by *Lynge* (1990) reported results for the combined group of launderers and dry cleaners.

There was no adjustment for potential confounders (e. g. multiple sex partners), with the exception of the death certificate study by *Katz* (1981), where a lower-wage comparison group was included in the analysis as a surrogate for SES.

Figure 8:
Selected risk estimates and confidence limits for cancer of the cervix uteri/female genital organs



*comparison group – all professions

Table 20:
Reported risk estimates for cancer of the cervix from eight studies

Reference	Estimate type	Population/ Exposure	Race	Cancer	ICD code (revision)	Observed/ Cases	Expected/ Cases	Risk estimate	Confidence limits[1]
Cohort studies									
Blair 1990	SMR	Dry cleaning workers	Adjusted	Cervix uteri	180, 8th	21	12.40	1.7*	(1.00-2.00)
Lynge 1990	SIR	Laundry/ dry cleaning workers		Cervix uteri	171, 7th	34	40.30	0.84	--
Ruder 1994	SMR	Dry cleaning workers (full cohort)	Adjusted	Cervix uteri	180, 9th	10	--	1.8	(0.86-3.31)
	SMR	Dry cleaning workers (PCE only)	Adjusted	Genital	179-184, 9th	8	--	1.57	(0.68-3.10)
	SMR	Dry cleaning workers (PCE +)	Adjusted	Genital	179-184, 9th	12	--	1.17	(0.60-2.04)
Anttila 1995	SIR	PCE		Cervix uteri	171, 7th	2	--	3.2	(0.39-11.60)
Death certificate studies									
Katz 1981	PMR	Laundry/ dry cleaning industry	White	Cervix uteri	171, 7th	10	5.10	1.95*	--
	PMR	Laundry/ dry cleaning industry	White	Cervix uteri	171, 7th	10	7.1[2]	1.41	--
	PMR	Laundry/ dry cleaning industry	White	Genital uns.	176, 7th	4	0.80	4.95**	--
	PMR	Laundry/ dry cleaning industry	White	Genital uns.	176, 7th	4	0.90[2]	4.67**	--
Duh 11984	SMOR	Laundry/ dry cleaning workers	Adjusted	Cervix uteri	180, 8th	2	1.60	1.3	(0.30-5.30)
Milham 1997	PMR	Laundry/ dry cleaning workers	White	Cervix uteri	171, 7th	8	5.00	1.78	--

Table 20 (continued):

Reference	Estimate type	Population/ Exposure	Race	Cancer	ICD code (revision)	Observed/ Cases	Expected/ Cases	Risk estimate	Confidence limits[1]
Walker 1997	PMR	Laundry/ dry cleaning workers	Black	Cervix uteri	180, 9th	11	--	1.18	(0.59-2.12)
	PMR	Laundry/ dry cleaning workers	White	Cervix uteri	180, 9th		--	1.05	(0.46-2.08)

SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; PMR: Proportionate Mortality Ratio; SMOR, Standardized Mortality Odds Ratio

--, not reported, * $p \leq 0.05$, ** $p \leq 0.01$

[1] 95% Confidence limit, unless specified otherwise, [2] *Katz* restricted comparison to lower-wage occupations

All but the *Lynge* (1990) study reported elevated cervical cancer risk estimates though only the studies by *Blair* (1990) and *Katz* (1981) produced significantly elevated results. In the latter study, the increase was observed for cancer of the cervix uteri when controls from all occupations were used for comparison (PMR 1.95) but the risk was attenuated when lower-wage occupational groups were chosen as controls (PMR 1.41). *Katz* additionally reported increased estimates for cancer of the genitals (unspecified) regardless of the control group (PMR 4.95, control group all occupations; PMR 4.67, control group low-wage occupations). The *Anttila* (1995) study produced a moderately elevated risk estimate (SIR 3.2, 95% CI 0.39-11.6) as well, but only two cases were reported.

No quantitative summary estimate of effect for cancer of the cervix was calculated because of the differences in cancer and exposure definitions in the studies. No case-control study included in this review reported a risk estimate for cervical cancer. Of the four cohort studies, the estimate reported by *Ruder* (1994) for the PCE only exposure sub-cohort includes other cancers of the female genitalia. The exposed group in the study by *Lynge* (1990) consisted of dry cleaners and launderers and *Anttila* (1995) reported only two cases.

Although the majority of studies report excess cervical cancer risk, the lack of control for known risk factors such as sexual behavior and SES provide too great an

opportunity for alternative explanations of the results. When SES was controlled in the *Katz* (1981) study by using a lower-wage occupational control group, the elevated risk estimate for cervical cancer was reduced.

The mechanism and biological plausibility for a relationship between PCE exposure and cervical cancer are weak, given the established risk factors for cervical cancer. Overall the quality of epidemiological evidence for an association between cervical cancer and PCE is limited. Even so, an association seems unlikely.

3.5.8 Renal Cell/Kidney Cancer (ICD-9 189.0-189.2)

Worldwide incidence of kidney cancer shows little variation. Incidence is highest in France, followed by some Scandinavian countries, including Denmark, and other parts of northern Europe. The lowest incidence of kidney cancer worldwide is seen in India, China and Japan (*McLaughlin*, 1996). Incidence and mortality rates are similar in the USA for blacks and whites, although men have approximately twice the rate of women (*Ries*, 1996). Age adjusted mortality rates (world standard) for the USA in 1995 were 3.8/100,000 for males and 1.8/100,000 for females (WHO, 1999). Estimated age adjusted incidence rates (world standard) for Germany in 1995 are 11.9/100,000 for males and 5.2/100,000 for females. The respective mortality rates are 6.1/100,000 for males and 2.7/100,000 for females (EUCAN, 1999).

Smoking is recognized as a risk factor for renal cancer (*McLaughlin*, 1996). The population attributable risk for renal cell cancer due to cigarette smoking has been reported to be 30 to 37 % for men and 14 to 24 % for women (*McLaughlin*, 1996). Analgesics (specifically phenacetin) have been associated with renal pelvis tumors and more recently with renal cell cancer. Obesity has been consistently related to increased risk of renal cell cancer; however, the mechanism is unclear and the effect is more pronounced among women. Other exposures that have been associated with renal cell cancer are diet, radiation, coffee, tea, socioeconomic status and genetic susceptibility (*McLaughlin*, 1996). There are conflicting results for many occupational exposures (*Mellemgaard*, 1994; *McLaughlin*, 1996). In animal studies, PCE has been reported to cause renal tumors in male rats; however, there are doubts about the

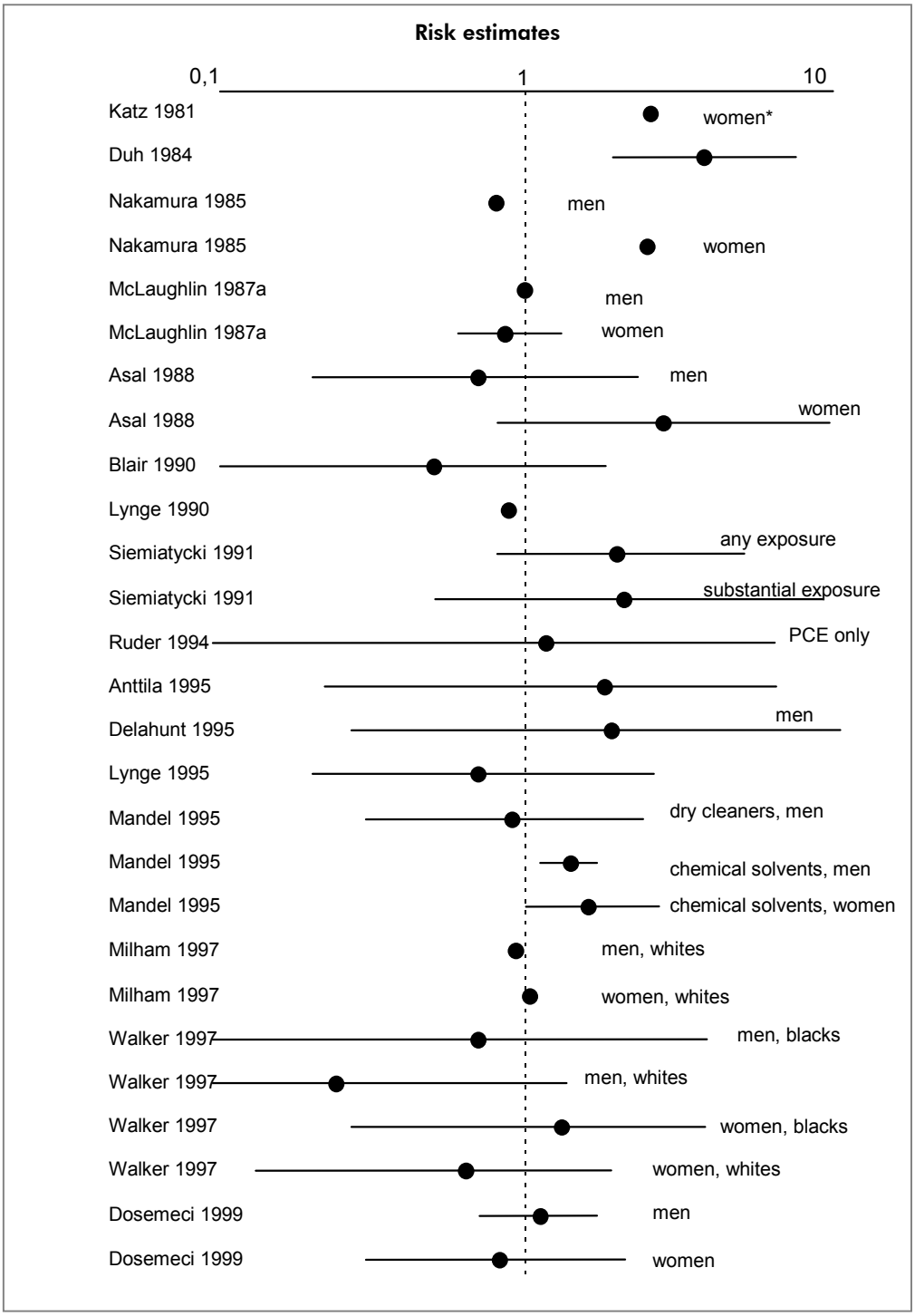
relevance of the rat model to carcinogenicity in humans (*McLaughlin*, 1997; US DHHS, 1997).

Risk estimates for kidney cancer were reported in 16 of the 45 studies critically reviewed. Characteristics of these studies, including assessment of exposure and potential confounders are listed by study design in Tables 5 to 13. Reported results are presented in Table 21 (see page 118) and Figure 9 (see page 117) shows selected risk estimates and confidence intervals.

All of the studies that evaluated the risk of kidney (renal cell) cancer attempted to isolate potential exposure based on occupation. However, the only report with a quantitative measure of exposure to PCE was that of *Anttila* (1995). Exposure measures in all remaining studies were qualitative, with the presumption of exposure based on occupation. Of the 16 studies, the cohort studies conducted by *Blair* (1990) and *Ruder* (1994) were restricted to dry cleaners only. All other cohort and all death certificate studies aggregated laundry and dry cleaning workers into a single exposure class. Within the case-control studies, all but *Siemiatycki* (1991) presented results for those who worked specifically as dry cleaners; *Dosemeci* (1999) presented results for those considered exposed to PCE based on reported occupational histories. Few of the studies could isolate exposure to PCE only. Thus, while the presumption of some level of exposure to PCE may be reasonable, it precludes a quantification and clear understanding of the relationship between "exposure" and disease.

Most of the studies collected information on potential confounders. However, not all results or risk estimates specific to the population/exposure of interest are adjusted for these confounders. For example, the results presented by *Delahunt* (1995) specific to dry cleaners are unadjusted for smoking, though smoking-adjusted results for other occupations are discussed. In other instances, adjusted results were calculated but were not presented in the published report (e. g. *Katz* 1981). There are two factors that have been consistently related to increased risk of renal cell cancer: smoking and, especially in women, obesity.

Figure 9:
Selected risk estimates and confidence limits for kidney (renal cell) cancer



* comparison group – all professions

Table 21:
Reported risk estimates for renal cell carcinoma[1] from 16 studies

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[2]
Cohort studies								
McLaughlin 1987a	SIR	Laundry/ dry cleaning workers	Both		43	47.3[3]	0.91[3]	(0.60-1.22) [3]
	SIR	Laundry/ dry cleaning workers	Men		18	--	0.99	--
	SIR	Laundry/ dry cleaning workers	Women		25	--	0.86	(0.60-1.30) [3]
Blair 1990	SMR	Dry cleaning workers	Adjusted	Adjusted	2	4.00	0.5[4]	(0.10-1.80)
Lynge 1990	SIR	Laundry/ dry cleaning workers	Both		11	12.50	0.88[5]	--
Ruder 1994	SMR	Dry cleaning workers (full cohort)	Adjusted	Adjusted	4	--	1.46[6]	(0.40-3.74)
	SMR	Dry cleaning workers (full cohort)	Men	Adjusted	1	--	0.67[7]	(0.02-3.73)
	SMR	Dry cleaning workers (full cohort)	Women	Adjusted	3	--	2.41[6]	(0.50-7.03)
	SMR	Dry cleaning workers (PCE only)	Adjusted	Adjusted	1	--	1.16[6]	(0.0-6.45)
	SMR	Dry cleaning workers (PCE and others)	Adjusted	Adjusted	3	--	1.60[6]	(0.33-4.68)
Anttila 1995	SIR	PCE	Adjusted		2	--	1.82	(0.22-6.56)
Case-control studies								
Asal 1988	OR	Dry cleaning workers	Men	White	3	6	0.7	(0.20-2.30)
	OR	Dry cleaning workers	Women	White	8	1	2.8	(0.80-9.80)

Table 21 (continued):

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[2]
Siemiatycki 1991	OR	Laundry/ dry cleaning industry[7]	Men		2	--	2.1	(0.60-7.20)
	OR	Laundry/ dry cleaning industry[8]	Men		5	--	2	(0.90-4.40)
	OR	Laundry/ dry cleaning workers[8]	Men		3	--	1.1	(0.40-2.90)
Delahunt 1995	OR	Dry cleaning industry	Men		--	--	1.92	(0.27-13.89)
Lynge 1995	OR	Dry cleaning workers	Both		3	20	0.7	(0.20-2.60)
Mandel 1995	RR	Dry cleaning industry, ever worked	Men		8	12	0.9	(0.30-2.40)
	RR	Dry cleaning solvents	Men		245	223	1.4*	(1.10-1.70)
	RR	Dry cleaning solvents	Women		57	42	1.6*	(1.0-2.7)
Dosemeci 1999	OR	PCE	Both	White	50	--	1.07	(0.70-1.60)
	OR	PCE	Women	White	8	--	0.82	(0.30-2.10)
	OR	PCE	Men	White	42	--	1.12	(0.70-1.70)
Death certificate studies								
Katz 1981	PMR	Laundry/ dry cleaning industry[9]	Women	White	7	2.70	2.57*	--
	PMR	Laundry/ dry cleaning industry[10]	Women	White	7	2.80	2.53*	--
Duh 1984	SMOR	Laundry/ dry cleaning workers	Adjusted	Adjusted	7	1.90	3.8*	(1.90-7.60)
Nakamura 1985	PMR	Laundry/ dry cleaning workers	Women		2	0.80	2.50[11]	--
	PMR	Laundry/ dry cleaning workers	Men		2	2.50	0.80	--

Table 21 (continued):

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[2]
Milham 1997	PMR	Laundry/ dry cleaning workers	Women	White	5	5.00	1.04	--
	PMR	Laundry/ dry cleaning workers	Men	White	7	8.00	0.93	--
Walker 1997	PMR	Laundry/ dry cleaning workers	Men	Black	1	--	0.70[2]	(0.02-3.88)
	PMR	Laundry/ dry cleaning workers	Men	White	1	--	0.24[6]	(0.01-1.35)
	PMR	Laundry/ dry cleaning workers	Women	Black	3	--	1.32[6]	(0.27-3.85)
	PMR	Laundry/ dry cleaning workers	Women	White	3	--	0.64[6]	(0.13-1.88)

SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; PMR: Proportionate Mortality Ratio; OR: Odds Ratio; SMOR: Standardized Mortality Odds Ratio; RR: Relative Risk

--, not reported

[1] risk estimates are for renal cell carcinoma only (ICD-9 189.0), unless specified otherwise

[2] 95% Confidence limit, unless specified otherwise.

[3] from *McLaughlin* 1997

[4] ICD-8 189

[5] calculated by the authors

[6] ICD-9 189.0-189.2

[7] „substantial" exposure

[8] „any" exposure

[9] comparison to all occupations

[10] comparison to other low-wage occupations

[11] ICD-8: 189.0, 189.1

*$p \leq 0.05$

Six of the 16 studies reported that smoking was considered as a potential confounder. Three of these also controlled for weight (Body Mass Index (BMI)). Two early death certificate studies (*Katz*, 1981; *Duh*, 1984) of launderers and dry cleaners and the

multi-center case-control study by *Mandel* (1995) of men and women exposed to dry cleaning solvents, found statistically significant increased risk for renal cell/kidney cancer. The census-based cohort studies by *McLaughlin* (1987a) in Sweden and by *Lynge* (1990) in Denmark found no increase in risk for the combined group of laundry and dry cleaners. The two largest studies of dry cleaners (*Blair*, 1990 and *Ruder*, 1994), found no excess risk of kidney cancer among those with a presumed exposure to PCE. Slightly elevated but not statistically significant risks were found by *Ruder* for the PCE plus sub-cohort (SMR 1.60, 95% CI 0.33-4.68) and by *Anttila* (1995) for PCE exposed employees from different occupations (SIR 1.82, 95% CI 0.22-6.56). *Ruder's* stratified analysis showed no evidence of increased risk with increasing latency or duration of exposure for the total cohort.

With the exception of the study of *Mandel* (1995) all other studies which reported risk estimates by gender (see Table 21) showed either a decreased or only a slightly increased risk for men. *Mandel* reported a statistical significant increased risk for men, exposed to dry cleaning solvents (OR 1.4, 95% CI 1.10-1.70) but not for men, ever employed as dry cleaners (OR 0.9, 95% CI 0.30-2.40). However, exposure in these studies was not limited either to dry cleaners or PCE exposure, and only three of these studies controlled for smoking and weight.

Elevated risks for women were statistically significant in two studies that presented results by gender. A statistically significant elevated risk for laundry and dry cleaners was reported in the death certificate based study by *Katz* (1981) (PMR 2.57) and *Mandel* (1995) reported an increased risk for women exposed to dry cleaning solvents (OR 1.4, 95% CI 1.0-2.7). Results for women employed as dry cleaners were not reported. (The crude OR, calculated by the authors, was about 1.2.) Non-significant elevated risks for female dry cleaners were reported in the case-control study by *Asal* (1988) (OR 2.8, 95% CI 0.80-9.80), in the total cohort by *Ruder* (1994) (SMR 2.41, 95% CI 0.50-7.03) and for female launderers and dry cleaners in the death certificate study by *Nakamura* (1985) (PMR 2.50). There is some suggestion in the literature (*Dosemeci*, 1999) that the effects of PCE or other solvents may be different for women than for men, based on body fat content and renal function among other anatomical

and physiological factors. Specifically, *Dosemeci* suggests that these differences may be the result of a longer "internal" exposure to solvents for women compared to men. *Dosemeci's* study, however, suggested no increased risk among females exposed to PCE (OR 0.82, 95% CI 0.30-2.10) though he did observe excess risk for other solvent exposures. Additionally, the Danish nested case-control study by *Lynge* revealed that there were no cases of renal cell cancer among women in that cohort. There was also no observed excess in the Swedish cohort study by *McLaughlin* for females (SIR 0.86, 95% CI 0.6-1.3).

Of the eleven cohort or case-control studies reporting a risk estimate for renal cell or kidney cancer three did not report all the information required to calculate a summary estimate (*McLaughlin*, 1987a; *Siemiatycki*, 1991; *Delahunt*, 1995). Based on the remaining studies available it was decided not to calculate summary estimates for renal cell carcinoma. Few cases were observed and not all studies presented results stratified by gender. Furthermore, the case definition included other cancers of the kidney.

The differences in the likelihood of PCE exposure precluded calculating a summary estimate. The differences in exposures between these studies were partly due to exposed populations that included both laundry and dry cleaning workers. Additionally, in *Asal's* study (1988) the possibility of PCE exposure is very small because petroleum-based solvents, such as "Stoddard solvent", are predominately used in the US state of Oklahoma (the same situation as for the death certificate studies by *Duh* and *Nakamura*). *Mandel* (1995) presented information that was not consistent between the number of people who ever worked in dry cleaning and the number reporting ever exposed to dry cleaning solvents. This discrepancy raised concerns about the reported exposures. Therefore the information is best evaluated at a qualitative level to understand the possible relationship between PCE and renal cell carcinoma.

Most of the results considered in this critical analysis were not statistically significant. Those of borderline significance need to be considered with caution; the p-value, in addition to reflecting biological variability, is also dependent on sample size and the accuracy of exposure assessment. Furthermore, some studies evaluated the risk of

renal cell cancer specifically (ICD-9 189.0), while others evaluated the risk of all kidney cancers combined.

Given the differences in case definition, the quality of exposure assessments, small number of observed cases and inconsistencies in the available literature it is not possible to draw a definitive conclusion regarding the relationship between PCE and renal cell (or the broader category of kidney) cancer. It seems unlikely that a strong association exists as a large effect would likely have been apparent despite the limitations of the studies reviewed.

3.5.9 Bladder Cancer (ICD-9 188, 189.3-189.9)

The highest incidence rates for bladder cancer worldwide have been observed in North America and Western Europe. Bladder cancer accounts for approximately 6 % of all new cancer cases among men and 2 % among women in the USA each year (*Silverman*, 1996). White males have the highest incidence rates of bladder cancer in the USA with a rate of 32.3/100,000 as compared to 7.8/100,000 for white females (*Ries*, 1996). Estimated age standardized incidence ratios (world standard) for Germany are 18/100,000 for males and 4.1/100,000 for females in 1995. The respective mortality rates are 6.3/100,000 for males and 1.7/100,000 for females (EUCAN, 1999). The median age at diagnosis is 70 with a five-year survival of approximately 80 % for localized cancer (*Ries*, 1996).

Smoking is a well-established risk factor for bladder cancer with estimated relative risks ranging from two to three (*Ernster*, 1991; *Silverman*, 1996). Although approximately 40 occupations have been identified as high risk, most relative risk estimates from these studies were less than two, and many studies had small numbers of exposed subjects (*Silverman*, 1996). The main occupations/industries and exposures which have been identified as high risk include rubber and dye manufacturing, the leather industry, painting, truck driving, aluminum, and aromatic amines (*Silverman*, 1996). Changes in mucus membranes, cancer or other effects to the urinary tract by the cancer causing aromatic amines are a recognized occupational illness in Germany.

16 studies included in this review reported results for an association between bladder cancer and employment in dry cleaning or exposure to PCE. These are presented in Table 22 (see page 126). Risk estimates and confidence intervals for selected results are presented in Figure 10 (see page 125).

Exposure ascertainments were qualitative in all studies reviewed and were based on union membership or occupation. Five studies reviewed were part of the National Bladder Cancer Study (NBCS), a national study conducted in the USA in the late 1970's. In this study occupational histories were collected for every job held longer than six months. Five of the 16 studies reviewed defined the exposed population as dry cleaners. The remainder defined the exposed category as "laundry and dry cleaning workers". All of the NBCS collected occupational information in the same way. Not all NBCS publications defined the exposed population as "dry cleaners only". It is unclear if this reflects differences in categorization or if the populations are actually the same. With the exception of the cohort studies by *Blair* (1990) and *Ruder* (1994) exposures were mixed and at best PCE exposure was "likely", but in many studies PCE exposure was only considered "possible".

All of the case-control studies reviewed collected information on cigarette smoking as a potential confounder. In addition, studies that were part of the NBCS collected information on employment in other high-risk industries and occupations. A few of the case-control studies also collected information on coffee consumption and *Teschke* (1997) collected information on history of bladder infection.

Figure 10:
Selected risk estimates and confidence limits for bladder cancer

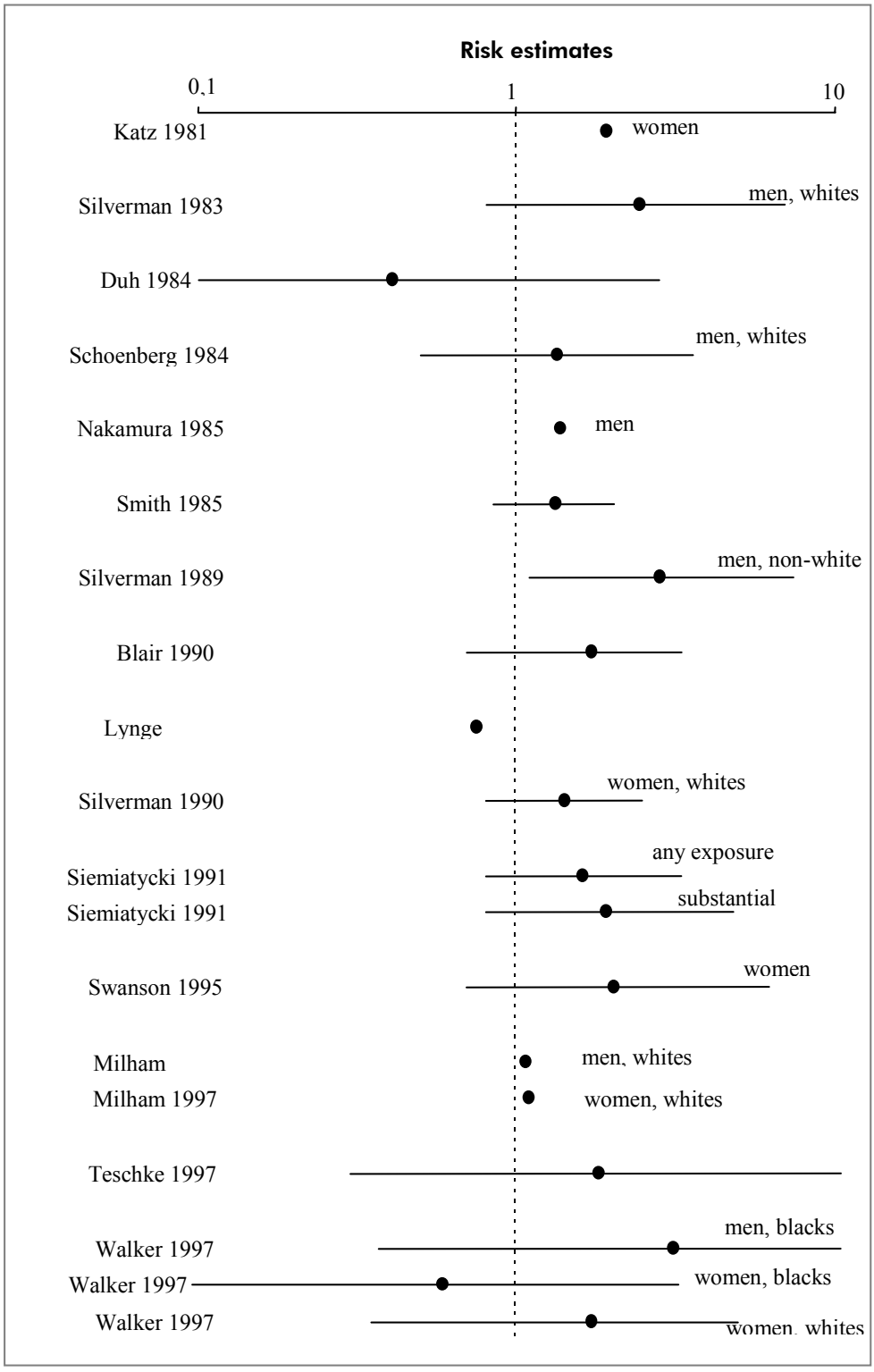


Table 22:
Reported risk estimates for bladder cancer[1] from 16 studies

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[2]
Cohort studies								
Blair 1990	SMR	Dry cleaning workers	Adjusted	Adjusted	8	4.80	1.7	(0.70-3.30)
Lynge 1990	SIR	Laundry/ dry cleaning workers	Both		14	18.90	0.74[3]	--
Ruder 1994	SMR	Dry cleaning workers (full cohort)	Adjusted	Adjusted	9	--	2.54*	(1.16-4.82)
	SMR	Dry cleaning workers (PCE only)	Adjusted	Adjusted	0	--		
	SMR	Dry cleaning workers (PCE and others)	Adjusted	Adjusted	9	--	3.52**	(1.61-6.68)
Case-control studies								
Silverman 1983	OR	Laundry/ dry cleaning industry (ever exposed)	Men	White	12	5	2.4	(0.80-6.90)
	OR	Laundry/ dry cleaning industry (adjusted for smoking)	Men	White	12	5	2	--
Schoenberg 1984	OR	Dry cleaning workers (ever employed)	Men	White	7	10	1.33	(0.50-3.58)
Smith 1985	RR	Laundry/ dry cleaning workers (employed 10 years)	Men		--	--	1.05	(0.63-1.76)
	RR	Laundry/ dry cleaning workers (non-smokers)	Adjusted		--	--	1.31	(0.85-2.03)
Silverman 1989	RR	Dry cleaning workers	Men	Non-white	11	12	2.8*	(1.10-7.40)

Table 22 (continued):

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[2]
Silverman 1989	OR	Dry cleaners workers (ever employed)	Women	White	23	32	1.4	(0.80-2.50)
Siemiatycki 1991	OR	Laundry/ dry cleaning industry [4]	Men		4	--	1.2	(0.50-3.30)
	OR	Laundry/ dry cleaning workers [4]	Men		7	--	1.9	(0.90-4.20)
	OR	Laundry/ dry cleaning industry [5]	Men		8	--	1.2	(0.60-2.30)
	OR	Laundry/ dry cleaning workers [5]	Men		10	--	1.6	(0.90-3.10)
Swanson 1995	OR	Dry cleaning industry	Women	Adjusted	6	16	2	(0.70-6.20)
Teschke 1997	OR	Laundry workers (last 20 yr employment excluded)	Adjusted		4	4	1.8	(0.30-11.30)
	OR	Laundry workers (ever employed)	Adjusted		5	4	2.3	(0.40-13.90)
Death certificate studies								
Katz 1981	PMR	Laundry/ dry cleaning industry [6]	Women	White	5	2.60	1.89	--
	PMR	Laundry/ dry cleaning industry [7]	Women	White	5	2.60	1.90	--
Duh 1984	SMOR	Laundry/ dry cleaning workers	Adjusted	Adjusted	1	2.40	0.4	(0.10-2.80)
Nakamura 1985	PMR	Laundry/ dry cleaning workers	Women		0	1.40	1.36	
	PMR	Laundry/ dry cleaning workers	Men		6	4.40		--
Milham 1997	PMR	Laundry/ dry cleaning workers	Women	White	5	5.00	1.09	--

Table 22 (continued):

Reference	Estimate type	Population/ Exposure	Gender	Race	Observed/ Cases	Expected/ Controls	Risk estimate	Confidence limit[2]
Milham 1997	PMR	Laundry/ dry cleaning workers	Men	White	13	12.00	1.06	--
Walker 1997	PMR	Laundry/ dry cleaning workers	Men	Black	2	--	3.09	(0.37-11.16)
	PMR	Laundry/ dry cleaning workers	Men	White	0	--		
	PMR	Laundry/ dry cleaning workers	Women	Black	1	--	0.58	(0.02-3.23)
	PMR	Laundry/ dry cleaning workers	Women	White	3	--	1.70	(0.35-4.97)

SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; OR: Odds Ratio; RR: Relative Risk; PMR: Proportionate Mortality Ratio; SMOR: Standardized Mortality Odds Ratio

--, not reported; *p ≤ 0.05

[1] *Ruder* reported risk estimate for bladder cancer and other cancers of urinary organs (ICD-9 188, 189.3-189.9)

[2] 95% Confidence limit unless otherwise specified [3] reported by the authors

[4] substantial exposure, controlling for coffee consumption and respondent type

[5] any exposure, controlling for coffee consumption and respondent type

[6] compared to all occupations [7] compared to other low-wage occupations

The cohort studies and death certificate studies were not able to control for confounding by other risk factors.

Excess bladder cancer mortality was observed in both of the cohort studies of dry cleaners reviewed. The excess reported in the *Ruder* (1994) study, though significant, was restricted to the subgroup of dry cleaners exposed to PCE plus other solvents (SMR 2.54, 95% CI 1.16-4.82). There were no cases of bladder cancer among those union members exposed only to PCE. The increased bladder cancer mortality observed in the *Blair* (1990) study was not statistically significant (SMR 1.7, 95% CI 0.70-3.30) nor was the excess related to PCE exposure dose-indicators (low, medium, high). All of the case-control studies reviewed found an excess of bladder cancer; however, only one

excess achieved statistical significance and this was based on only eleven exposed cases (non-white males) (*Silverman*, 1989). When duration of employment was considered in the analysis, those with fewer than five years of employment showed a higher risk (RR 5.3) than those with more than five years (RR 1.8) employment. The *Lynge* (1990) cohort study reported fewer than expected cases of bladder cancer in a population that included laundry workers.

The critical review of the available literature on bladder cancer and PCE did not include a quantified summary estimate. *Smith* (1985) and *Siemiatycki* (1991) did not report all the information required for additional calculations. Within the cohort studied by *Ruder* (1994), no cases were observed among the cohort presumed to be exposed to PCE only. Furthermore, the case definition within the *Ruder* study included other urinary organs in addition to the bladder. The study by *Lynge* (1990) added little to the synthesis as the exposed population included laundry and dry cleaning workers in the same cohort. Finally, only the case-control studies adjusted for the effect of smoking.

The four remaining studies were comprised of populations considered to have mixed exposure, though likely including exposure to PCE. The case-control study by *Swanson* (1995) observed an excess of bladder cancer among women who had ever worked in dry cleaning (OR 2.0, 95% CI 0.7-6.2) and *Swanson* notes that the excess is consistent with that observed by *Katz* (1981). The other study which looked specifically at women was the 1990 report from *Silverman*. A small increase in risk was observed for women who had ever worked in dry cleaning (RR 1.4, 95% CI 0.8-2.5). The two remaining case-control studies were also part of the National Bladder Cancer Study. One focused on white males in New Jersey (*Schoenberg*, 1984) and the other focused on non-white males in Detroit (*Silverman*, 1989). As noted earlier, a significant increased risk was observed by *Silverman* (1989) among non-white males in Detroit (RR 2.8, 95% CI 1.1-7.4). The New Jersey population study observed slight, non-significant increase (OR 1.3, 95% CI 0.5-3.58). No compelling explanation exists for gender or racial differences in bladder cancer, especially given that the studies which were part of the National Bladder Cancer Study all controlled for smoking.

Almost all of the studies reviewed reported an excess of bladder cancer cases, though few of these risk estimates were statistically significant. Furthermore, many of the studies reporting an excess of bladder cancer consisted of both laundry and dry cleaning workers. The absence of any bladder cancer cases in the *Ruder* (1994) sub-cohort exposed primarily to PCE is inconsistent with the other findings, suggestive of some factor other than PCE contributing to the excess bladder cancer observed in the full *Ruder* cohort. Further, the inconsistency in effect by duration observed in the *Silverman* (1989) study may be due to differential exposures for short-term workers or that other exposures or risk factors for bladder cancer that were not controlled for in the literature reviewed contributed to the slight excesses observed.

The imprecision of exposure measures and the lack of control for potential confounders, specifically smoking but also other occupational risk factors, precludes a clear understanding of the relationship between bladder cancer and PCE exposure. The available evidence is inadequate to base a conclusion as to the relationship between bladder cancer and PCE.

3.5.10 Other Cancer Sites

Many studies reported risk estimates for several major cancer sites in addition to those cancer sites where excess risk among dry cleaners or those exposed to PCE had been previously observed. A brief overview of results drawn from the literature reviewed is presented for the following eight additional cancer sites: stomach, rectum, breast, corpus uteri, prostate, skin, brain, and lymphatic and hematopoietic tissues.

3.5.10.1 Stomach (ICD-9 151)

Stomach cancer is one of the leading cancers worldwide. Overall incidence is approximately 10 % with a fatality rate around 80 % (*Nomura*, 1996; *Muir*, 1996). The highest incidence is among Japanese males, with an average age adjusted annual incidence rate of 85.4/100,000. US rates vary widely by ethnicity and race. Estimated age standardized incidence ratios (world standard) for Germany are 16.2/100,000 for males and 8.6/100,000 for females in 1995. The respective mortality rates are

12.3/100,000 for males and 6.6/100,000 for females (EUCAN, 1999). Differences in stomach cancer have been observed by type, gender, age and country. There is a strong relationship between stomach cancer and diet and observed differences between ethnic and race groups may be due to dietary or environmental factors.

Occupational factors are not thought to be a major contributor to the risk of stomach cancer. Associations between specific occupations (coal mining, chemical industry, rubber industry, oil refinery, and metal products) and specific substances (asbestos, polycylic aromatic hydrocarbons, and N-nitroso compounds) have been observed. The strongest observed associations for stomach cancer are to diet (specifically salted foods, or nitrates and related compounds), ionizing radiation, intestinal metaplasia, and possibly smoking. The most consistent of these is the inverse association between dietary intake of fruits and vegetables and stomach cancer (*Nomura*, 1996).

The association between stomach cancer and PCE was evaluated in seven studies included in this report. Risk estimates were approximate to the null for all studies, indicating no association between exposure and stomach cancer. The two cohort studies (*Blair*, 1990; *Lynge*, 1990) used national populations for comparison, as did the PMR studies. *Siemiatycki* (1991) conducted additional analyses using other cancer patients. All but one of the studies defined the exposed group as launderers/dry cleaners. *Blair* (1990) included only dry cleaners. The other large cohort study by *Ruder* (1994) observed no cases of stomach cancer among PCE only exposed dry cleaners.

Given what is understood about the etiology of stomach cancer and the studies reviewed in this critical analysis an association between stomach cancer and PCE exposure is very unlikely.

3.5.10.2 Rectum (ICD-9 154)

The incidence of rectal cancer shares a geographic distribution with colon cancer. Rates tend to be higher among males (*Muir*, 1996; *Schottenfeld*, 1996), and are similar in North America and Europe (in the range of 15 to 20/100,000). Rectal cancer is generally not viewed as an occupational disease, and apparent associations between

specific occupations and rectal cancer may be a result of confounding by other factors, particularly social class and lifestyle factors. Known risk factors include diet, other diseases of the large intestine and heredity.

Eight studies reported any result for an association between rectal cancer and laundry workers/dry cleaners. The large cohort studies by *Blair* (1990) and *Ruder* (1994) found no excess risk, and all five cases observed in the *Ruder* cohort were among the sub-cohort exposed to PCE and other solvents and not within the PCE only sub-cohort. PMR estimates calculated by *Katz* (1981), *Milham* (1997) (only concerning women) and *Nakamura* (1985) found non significant excesses, though given the nature of the PMR risk estimate, this may reflect deficits of other causes of death. Exposure measures for all studies were qualitative and no study collected information on other identified risk factors.

There is no suggestion of an association between PCE exposure and rectal cancer based on the studies reviewed.

3.5.10.3 Skin (ICD-9 172-173)

Both melanomas and non-melanomic skin cancers are more common among light-skinned individuals. Melanoma is a rare disease, while basal and squamous cell carcinomas are fairly common (*Muir*, 1996; *Armstrong*, 1996; *Scotto*, 1996). Estimated age standardized incidence ratios (world standard) for melanomas in Germany are 6/100,000 for males and 6.4/100,000 for females in 1995. The respective mortality rates are 1.7/100,000 for males and 1.1/100,000 for females (EUCAN, 1999).

Nine of the studies reviewed reported a risk estimate for skin cancer. Four studies reported a risk estimate for melanoma and non-melanomic cancers combined. The largest study by *Blair* (1990) observed a slight deficit (SMR 0.8, 95% CI 0.1-2.8). The other three studies all observed a non-significant excess based on small numbers of observed cases: *Duh* (1984) (OR 1.5, 95% CI 0.4-6.1), *Katz* (1981) (PMR 2.07, 95% CI not reported) and *Nakamura* (1985) (PMR 1.43 95% CI not reported). Four of the remaining studies reported results for melanoma alone. Of those, *Lynge* (1990)

found incidence of melanoma below the average, based on ten observed cases and 13.8 expected. Death certificate studies by *Milham* (1997) and *Walker* (1997) both observed deficits. *Siemiatycki* (1991) reported an OR of 4.2 (90% CI 1.1-15.0) for launderers and dry cleaners classified as substantially exposed based on only two cases. For non-melanomic cancer, *Gallagher* observed a significant excess of basal cell carcinoma (OR 3.7, 95% CI 1.1-19.7) among those reporting having ever been exposed to dry cleaning agents.

While the probability for skin exposure to solvents was high (especially during the time that wet transfer machines were in general use) no consistent pattern of excess is apparent and the number of cases studied is small. Furthermore, studies reporting excess were not able to control for all potential confounders (most importantly sun exposure). Given the potentially high exposures, and common occurrence of skin cancer, an association between PCE and skin cancers, if present, would likely have been seen.

3.5.10.4 Breast (ICD-9 174-175)

Breast cancer is the most frequent cancer among women in developed nations. The highest rates worldwide (over 100/100,000) are found among white women in the San Francisco Bay Area of California (*Muir*, 1996; *Henderson*, 1996). The estimated age standardized incidence ratio (world standard) for Germany is 63.4/100,000 in 1995. The respective mortality rate is 22.2/100,000 (EUCAN, 1999).

Hormones are presumably the major etiologic factor, especially cumulative estrogen exposure. Breast cancer rates are strongly related to social class, reflecting differences in reproductive risk factors.

Eight studies reported results for breast cancer among laundry and dry cleaning workers. Notable for this cancer site is a significant deficit of cases observed by *Duh* (1984) (SMOR 0.1, 95% CI 0.0-0.4) and *Nakamura* (PMR 0.28), although in both studies the estimate was based on very small numbers (one and two cases observed, respectively). Other results were close to or equal to one, indicating no observed excess in risk.

3.5.10.5 Corpus Uteri (ICD-9 179, 181-182)

Cancer of the uterus, like breast cancer is more common in developed than developing nations. Mortality is low and in general is on the decline (*Muir*, 1996; *Grady*, 1996). US incidence in 1994 was 5.4/100,000; in Germany in 1995 8.5/100,000 (world standard) with a mortality rate of 1.8/100,000 (EUCAN, 1999).

Risk factors include exogenous hormones, obesity, smoking, and reproductive characteristics.

No increased risk was observed among the six studies reporting results for dry cleaning and laundry workers.

3.5.10.6 Prostate (ICD-9 185)

Prostate cancer is frequent among older males, generally occurring over the age of 65 (*Muir*, 1996; *Ross*, 1996). Estimated age standardized incidence ratio (world standard) for Germany is 41.4/100,000 in 1995, the respective mortality rate is 17.2/100,000 (EUCAN, 1999). Incidence among males under 40 is rare.

The etiology is not well understood, but is thought to be related to diet, hormonal patterns and family history.

Ten studies reported results for prostate cancer risk. Three studies observed non-significant excesses; *Walker* (1997) for black males (PMR 1.62, 95% CI 0.65-3.35), *Siemiatycki* (1991) for launderers and dry cleaners (OR 2.1, 95% CI 0.7-6.0, from IARC, 1995) and *Aronson* (1996) for cases reporting exposure to PCE (OR 1.54, 95% CI 0.96-2.48). In contrast, *Krstev* (1998) observed a significant deficit of prostate cancer among dry cleaning operators (MOR 0.6, 95% CI 0.4-0.9). All other studies reporting a risk estimate for prostate cancer showed decreased risk. *Aronson* alone attempted to control for other occupational exposures, though those reporting exposure to PCE were from many occupations including dry cleaners, aircraft maintenance workers and industrial equipment mechanics. Exposure measures for all studies

considered were qualitative, which makes it difficult to reasonably relate the cancers to exposure.

Given what is understood about the etiology of prostate cancer it is unlikely that an association exists between PCE and prostate cancer.

3.5.10.7 Brain and Nervous System (ICD-9 191-192)

Primary brain tumors are not uncommon, although incidence rates reflect inclusion criteria for reporting cancers as well as the diagnostic sophistication. Approximately 17,000 new nervous system tumors are reported in the USA each year (*Muir*, 1996; *Preston-Martin*, 1996). Estimated age standardized incidence ratios (world standard) for Germany are 7.1/100,000 for males and 5.1/100,000 for females in 1995. The respective mortality rates are 4.8/100,000 for males and 3.4/100,000 for females (EUCAN, 1999).

Although the etiology is not understood, the clearest identified risk factor for brain cancer is ionizing radiation. Occupational epidemiological studies have associated industries or exposures to increased risk of brain cancers, including vinyl-chloride, electromagnetic fields, agriculture, the nuclear industry, and tire manufacturing; however, the associations are generally suggestive of an association and no firm conclusions can be made.

Five studies reported specific results for brain cancer. *Blair* (1990) and *Milham* (1997) both found no excess and *Lynge* (1990) and *Anttila* (1997) reported results close to one. *Heineman* (1994) reported a non-significant excess for workers classified in the highest exposure category (OR 1.8, 95% CI 0.6-5.9) based on ten exposed cases. Exposure assessment in the *Heineman* case-control study incorporated a semi-quantitative estimate of both the probability of exposure to the specific chlorinated hydrocarbon and an estimate of the intensity of exposure based on information collected in interviews with next of kin. However, efforts to validate the job exposure estimate for another solvent were unsuccessful (*Gomez*, 1994). While the results suggest a possible association, they are not supported by the other studies, especially the large cohort

study by *Blair* (1990). Further evidence is needed to support an association between PCE and brain cancer.

3.5.10.8 Lymphocytic and Hematopoietic System (ICD-9 200-208)

The total incidence for all leukemia in the USA is 10/100,000 (*Ries*, 1996). Incidence rates, in contrast to mortality rates, are generally considered the best estimates of risk, due to the wide variation in survival depending on the specific type of leukemia. Age standardized incidence ratios (standard: Federal Republic of Germany 1987) for the Saarland were 34.5/100,000 for males and 21.2/100,000 for females between 1988 and 1990 (*Pesch*, 1994).

The etiology of leukemia is generally unknown, as there are a large number of recognized leukemia subtypes (*Linet*, 1996). The occupational risk factors most commonly associated with leukemia are benzene and ionizing radiation. Some other solvents including carbon tetrachloride are discussed. Other risk factors include certain medical treatments, some viruses and retroviruses and smoking, due in part to components of cigarette smoke including benzene and hydrocarbons (*Linet*, 1996).

Reported results from the reviewed studies include overall estimates for all lymphatic cancer sites and some site specific results. The overall results do not suggest a relationship between PCE and lymphatic cancers. Similarly, results for leukemia (ICD-9 204-208) and lymphosarcoma/reticulosarcoma (ICD-9 200) are unconvincing. Reported results for non-Hodgkin's lymphoma (NHL) are not so clear, as three of five studies reported an excess of NHL. *Spirtas* (1991) reported a significant excess among females only (SMR 9.68, 95% CI 1.17-34.96) based on two cases, and *Blair* (1990) and *Anttila* (1995) both observed non-significant excesses.

Any conclusions regarding leukemia and PCE exposure needs to take into account the specific leukemia. The current evidence and study limitations preclude a conclusion regarding a PCE-leukemia association. Additional studies with respect to NHL specifically would be helpful.

4 Discussion and Conclusions

4.1 Limitations of the Available Literature

A comprehensive search for and systematic review of all available epidemiological literature pertaining to the carcinogenic effects of PCE was conducted. Although the total number of published papers meeting the preliminary screening criteria was relatively large (81 papers were identified), only about half of these met the more restrictive criteria, which are necessary for a critical assessment of the epidemiological evidence from a body of literature. These criteria included a reported risk estimate for an association between PCE and specific cancers, non duplication of study population or report and a reasonable likelihood of PCE exposure or differentiation of exposures. However, even among those papers meeting these criteria, no study could be considered very strong and only a few studies could make a limited contribution to our understanding of the role of PCE exposure as a risk factor for cancer. Some of the key limitations within the body of literature are summarized below.

4.1.1 Exposure Assessment

A consistent limitation among studies of PCE and cancer was the widespread lack of valid exposure measurements, or any other adequate indicators of potential for PCE exposure. Only one study identified and reviewed had any direct exposure measure (*Anttila*, 1995), and in this study, exposures were probably not limited to PCE. Further, important information for exposure assessment, such as duration of exposure, were not available. The majority of studies evaluated relied upon crude surrogates of exposure, allowing the inclusion of a substantial number of persons with no or mixed exposures. Surrogates of exposure included “ever” versus “never” having worked in an industry (such as dry cleaning) or general occupation with potential exposure to PCE.

While quantitative estimates of exposure may not be necessary to demonstrate the presence of an association between being a member of a working group and a cancer outcome, inaccurate classification of study subjects into “exposed” and “not exposed”

categories can have a profound impact on the estimate, and lead to erroneous conclusions.

4.1.2 Paucity of Numbers of Study Subjects

One of the major determinants of the ability of a study to correctly detect and quantitatively estimate an exposure-disease association is the size of the population studied (or in case-control studies, the number of cases and controls). Larger studies generally have greater statistical power to detect an effect if present, and measures of association based on larger numbers are more precisely estimated. Further, the prevalence of the exposure of interest can influence a study's ability to accurately estimate an effect. For example, if among a relatively large cohort of 10,000 only 1,000 or 10 % are exposed, the rate of rare diseases among the exposed group will be difficult to estimate, especially if no or only one or two cases are observed. Numerical estimates of these rates and subsequently the relative risks based on these rates will be highly unstable, and generally uninformative. Similarly, among population-based case-control studies, exposure prevalence may be as low as 3 % and the number of exposed cases (usually the limiting factor in a case-control study) will be inadequate for stable estimation of odds ratios. Many of the publications available on PCE suffer from this limitation of small numbers, especially when the results for specific cancer sites are isolated and examined.

4.1.3 Sub-division of the Literature by Cancer Sites

The problem of small numbers of study subjects within individual studies is compounded by the necessity of examining the available literature by specific cancer sites. The total epidemiological literature concerning PCE and cancer divides fairly finely across several specific and discrete cancer sites, resulting in many small bodies of literature with little evidence for any one site. Separate meta-analyses would be required for each PCE-cancer relationship; however, none of these "sub-literatures" contain adequate numbers of papers with acceptable sample sizes, exposure measurement, and avoidance of bias to properly apply meta-analytic summary techniques.

4.1.4 Study Overlap and Updates of Previous Reports

The number of apparent publications available is effectively reduced due to overlapping populations studied, or multiple reports such as mortality updates on a previously studied cohort. Among sets of related results, the most recent update or the report encompassing one or more study groups is usually selected for review. Although this decision is motivated by the larger numbers of outcomes of interest in more recent updates, it is not clear that advanced studies of occupational cohorts have the greatest sensitivity to detect an effect. If for example an effect, noted as an excess of deaths or cases of a specific outcome, occurs on average ten years following exposure, then follow-up of the cohort over 20 or 30 years may increase the number of deaths but dilute or even mask the exposure-related excess. However, without more information such as dates of actual exposure, the most appropriate period of follow-up cannot be assessed.

4.1.5 Social Context and Confounding

The specific literature on PCE exposed occupational cohorts consists of two categories: dry cleaners and other workers using various solvents including PCE. Although misclassification is likely within both categories, it is possible that dry cleaners in specific regions during certain periods, if exposed, would be exposed to PCE. Within the dry cleaning industry, actual exposure to PCE would depend on the specific equipment operating and the specific job within the shop, and some individuals would have no relevant exposure to PCE. Apart from the actual exposures, other factors likely influence the health and disease patterns of those employed within the industry. For example, in the USA, employees in dry cleaning shops are not paid well, and individuals taking these jobs are often poorly educated and of lower socio-economic status. These individuals plausibly have risk factor profiles different from the general population (or whatever referent groups are used in the studies), increasing the possible influence of confounding. Specific risk factors of concern within this context include cigarette smoking, alcohol consumption, multiple sex partners, poor diet, etc., all of which are key risk factors for specific cancers. If these factors are not validly measured

concurrently with valid measures of exposure within a study, then the study is not able to control for their confounding effects (i. e. separate the effects of the confounding factors from those related directly to PCE) and the results may be invalid. Control for effects of socio-economic factors is very difficult, and may differ by disease (e. g. cervical cancer and multiple sex partners, respiratory cancers and smoking, etc.). Most studies reviewed, however, failed to consider important potential confounding variables, including those related to social class as well as others, possibly compromising the validity of study results.

The search process produced what appeared to be a substantial epidemiological literature on the carcinogenicity of PCE; however, upon critical assessment, this impression was simply a facade. The literature, although containing numerous published studies, was of little substance and provides limited support for scientific conclusions, and subsequently for policy and legislative decisions. Further, the weakness of the body of available literature raises some questions as to whether summarization of any parts of the literature using meta-analytical techniques is justifiable. Subjecting a body of literature to meta-analysis cannot and should not be used to remedy inherent weaknesses of the collective literature.

4.2 Key Results of the Critical Review

While all 45 of the epidemiological studies that we selected for inclusion in our meta-analysis purported to investigate similar exposure-health outcome relationships, we encountered a broad diversity of proxy measures of exposure to PCE as well as numerous specific cancer outcomes of interest. Meta-analysis of the entire body of epidemiological literature on the carcinogenicity of PCE is neither possible nor appropriate, as different cancers have different profiles of risk factors. Without applying the methods of meta-analysis, the existing body of literature can be critically reviewed and summarized, where appropriate, on a cancer-specific basis. For this report, nine
specific categories/sites of cancer were selected for detailed critical synthesis, based on a priori interest, availability of data and plausibility of an association. In addition, eight other cancer sites were briefly reviewed where some results were available.

Quantitative or meta-analytical methods were not applied to any cancer site in the critical synthesis of the literature. For a few cancers of interest, a qualitative synthesis was not possible due to limitations in the literature (discussed above), for example, cancer of the larynx. For these sites, the evidence is either too inconsistent or too sparse to support any conclusion.

For the remaining cancer sites with multiple studies available, summarization using meta-analytical methods was considered. However, for some of these the variability of results was too great to justify the use of summary measures. Heterogeneity could not be explained by study design, exposure measure or other attributes considered or the final number of studies suitable for summarization was too small and did not represent the full body of literature available for each cancer site.

Summarization of all studies ("meta-analysis") for any of these sites could not be justified, as they were of limited quality, measured exposure differently, and produced diverse results. For a few studies(e. g. esophageal cancer), a quantitative estimate was not calculated as summarization of crude estimates was felt to be far less informative than a qualitative synthesis of more refined estimates of risk (i. e. for specific subgroups more likely to have exposure to PCE or better control of confounding). Furthermore, among the studies considered for summarization, a few could not be included because of differences in the specific cancers (e. g. renal cell) studied, or the numbers necessary for summarization were not provided in and could not be derived from the published papers[1].

Therefore, the critical synthesis was conducted on qualitative level for all nine cancer sites. For some cancers (e. g. cervical cancer) an uncritical inspection of the published

[1] This raises an issue regarding the standard of how the results of epidemiological investigations in the published literature are reported. As critical reviews and meta-analyses depend on published papers as their raw materials, these papers must present at least minimal information critical to the review process, such as numbers of study subjects by all combinations of categories of outcome and exposure. Standardized criteria for publishing primary epidemiological studies should be developed and adopted.

results might suggest that a consistent association exists across studies where no true association exists. On the other hand, the inability to find homogeneity among the results of the cancer-specific literature cannot be interpreted as lack of effect, although it may be that some studies help rule out strong associations. From the extensive review and efforts to synthesize the results of the relevant studies on each cancer outcome, it appears the findings are inconsistent, a characteristic which plagues much of the recent epidemiological literature on cancer (*Hernberg*, 1998). It may be that what the studies do show is the reduction or even exclusion of the likelihood of any kind of *considerable* cancer risk.

Although some of the published studies make a limited contribution to our understanding of the role of PCE exposure as a risk factor for cancer, none is adequately strong, nor collectively is the body of evidence convincingly consistent to derive quantitative risk estimates or draw firm conclusions. However, it appears that there is little support on which to base a conclusion that occupational exposure to PCE is a strong risk factor for cancer of any site.

Nevertheless, because of a number of positive findings suggested from some of these epidemiological studies (e. g. for esophageal cancer) one cannot rule out the possibility that an association between PCE and cancer exists in humans. With considerable numbers of workers exposed to PCE, a clearer indication of human carcinogenic risk is needed than can be seen from the current body of literature. More evidence is needed to elucidate associations if they exist or demonstrate with adequate power that they do not exist.

For this more *appropriate* research is necessary. More literature of the caliber of the available literature will not satisfy this need, much as meta-analysis of this literature cannot compensate for basic weakness in the literature. Many of the published studies were conducted under existing conditions, which themselves were inherently limiting: contexts in which no exposure measures were available; populations in which exposure prevalence is low (compounded for rarer conditions); and occupational cohorts with mixed exposures; etc.

Priority areas in which additional data are most needed include cancers of the esophagus, renal cell, and bladder. Such studies must improve on the exposure indicators used, have adequate sample sizes (especially adequate numbers of exposed persons with the cancers of interest) and concurrently consider the role of known risk factors for the cancers, especially those that might be correlated with employment in industry studied or the exposure itself. As additional, clearer epidemiological evidence is produced, it can be factored into the existing body of evidence and the conclusions regarding PCE and cancer can be reassessed.

Options for new and adequate epidemiological studies on this topic in the USA and Western Europe seem to be quite limited. Perhaps this is even impossible (i. e. finding an adequately large cohort of persons with relevant PCE exposure, individual exposure measurements, information on confounding and the capability to follow the cohort for mortality or morbidity).

However, until such additional epidemiological evidence is available, conclusions, and subsequently decisions, must rely upon existing knowledge, also from other scientific fields. Based on the *currently* available collective epidemiological evidence, however, the conclusion "occupational exposure to PCE is a risk factor for cancer of any specific site" cannot be supported from the existent epidemiological studies.

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Appendix A:

Table of Tables

Appendix B:

Table of Figures

Appendix C:
Critical Review

Critical Review Form

Date of review: _____

REFERENCE – Author(s).

Title.

Journal.

Year of publication: _____ Volume: _____ Issue: _____ pp.: _____

☐ Language: (1. English 2. Other)

Book or Book Section

Editor(s): _____ Edition: _____ Publication Firm: _____ City: _____

☐ PUBLICATION STATUS	☐ COUNTRY OF STUDY	☐ STUDY DESIGN
1. Peer Review Journal	1. North America	1. Retrospective/Prospective Cohort
2. Government Report	2. Europe	2. Case-Control
3. Abstract Only	3. Other: _____	3. Cross-sectional
4. Unpublished		4. PMR
5. Dissertation/Thesis		5. Clinical Trial
6. Other: _____		6. Ecological
		7. Other: _____

☐ STUDY OBJECTIVE: (1. Clearly stated 2. Inferred 3. Not stated or inferred)

☐ Adequate Review of the Literature ? (1 = Yes, 2 = No)

Study Population and Location: _____ (e. g. factory name, city)

Study Population included in other studies? ☐ (1 = Yes, 2 = No)

If yes, how many studies: _____

Cohort Sample Size: _____ Number of Death Certificates: _____

Case-Control Studies: Number of Cases _____ Number of Controls _____

☐ Matched Case-Control Study? (1 = Yes, 2 = No)

If matched, how many controls/cases? (enter number) _____

Controls were matched on what variables (check)

- ☐ Age group
- ☐ Gender
- ☐ Hospital
- ☐ Interviewer

Total Study Period from enrollment to end of follow-up (enter years): From _____ to _____

INCLUSION/EXCLUSION CRITERIA for study participants

Minimum work period (yrs): _____

Cutoff Year for Employment _____ e.g. before 1960

Work Area or Other Inclusion Criteria? _____

Case Selection Criteria: _____ Control Selection Criteria: _____

☐ Occupation / Industry of Study Participants:	☐ Study Outcome
1. Dry cleaning 2. Laundry 3. Dry Cleaning and Laundry 4. Other Industry _____	1. Mortality: (All cause, Specific Cancer) 2. Cander Incidence 3: Other: _____

☐ Outcome Verified by: (1. Death Certificate 2. Medical Records
3. Histological Confirmation 4. Other _____)

Cohort Studies:	Case-Control Studies:
☐ % Vital Status Known ☐ % Death Certificates obtained	☐ Case Participation Rate ☐ Control Participation Rate
1. > 95 % 2. 90-94 % 3. < 90 % 4. Not Stated 5. Does Not Apply	1. > 90 % 2. 80-89 % 3. 70-79 % 4. < 70 % 5. Not Stated 6. Does Not Apply

☐ STUDY EXPOSURE:

1. Perchloroethylene (PCE)	4. Mixed Solvents, PCE not mentioned
2. Mixed PCE and Trichloroethylene (TCE)	5. Other: _____
3. PCE and Other Mixed Solvents	6. Not specified

☐ EXPOSURE ASSESSMENT CLASSIFICATION: (1. Quantitative/semi quantitative 2. Qualitative)

☐ EXPOSURE MEASURE

1. Personal IH date
2. Area IH data
3. Industry Classification
4. Job Title
5. Personal Report (interview)
6. Union Membership
7. Blood Samples
8. Usual Occupation/Industry from death certificate
9. Other: _____

☐ COMPARISON POPULATION

1. Internal Group (unexposed workers)
2. Other Industry Controls
3. General Population (National)
4. General Population (State)
5. General Population (Regional)
6. Hospital Controls
7. Not Defined
8. Other: _____

ANALYSIS

☐ Methods well described? (1. Yes, 2. No) (e.g. derivation of risk estimates)

COMMENTS: _____

WHAT WAS (WERE) THE ESTIMATES OF EFFECTS?

☐ RISK ESTIMATE:

1. Relative Risk
2. Odds Ratio
3. SMRatio
4. PMRatio
5. PCMR
6. Other: _____
7. None

DO THESES ESTIMATES INCLUDE: (Check each below: 1. Yes, 2. No)

☐ Point Estimate	☐ Confidence Intervals _____ %
☐ Standard Errors	☐ p-values
☐ Variance	☐ Mean / Median
☐ Estimates of Power	☐ Other

WHAT WAS (WERE) THE PRIMARY OUTCOME(S) OF THE ANALYSIS? (Check below: 1. Yes, 2. No)

☐ OVERALL MORTALITY
☐ TOTAL CANCER MORTALITY
☐ TOTAL CANCER INCIDENCE

☐ SPECIFIC CANCER MORTALITY:
☐ SPECIFIC CANCER INCIDENCE:

FILL IN DATA BELOW

Outcome	No. Cases Observed	Expected	Person-Years	Point Estimate	Confidence Interval Lower Limit	Confidence Interval Upper Limit	P-value
☐ Overall Mortality							
☐ Total Cancer Mortality							
☐ Total Cancer Incidence							
☐ **Specific Cancers**							
☐ Incidence or ☐ Mortality							
☐ LIVER							
☐ BLADDER							
☐ KIDNEY							
☐ RENAL							
☐ PANCREAS							
☐ CERVIX							
☐ LUNG							
☐ BREAST							
☐ BRAIN							
☐ PROSTATE							
☐ ESOPHAGUS							
☐ LYMPHATIC/ HEMATOPOIETIC							
☐ CHD							
☐ OTHER							

☐ POTENTIAL CONFOUNDERS MEASURED: (Check ech blow: 1. Yes, 2. No)

☐ Age	☐ Smoking
☐ Gender	☐ Alcohol Consumption
☐ Body Mass Index (Quetelex Index)	☐ Education
☐ Race	☐ Other _____

Discussion Section

(CONSIDER THE FOLLOWING: WERE THE METHODS AND ALTERNATE EXPLANATION OF RESULTS ADEQUATELY ADDRESSED; WAS THERE DISCUSSION OF OTHER STUDIES?)

POTENTIAL FOR BIAS:

☐ Selection Bias ☐ Information Blas

1. Unlikely
2. Possible
3. Likely

DUE TO

MISCLASSIFICATION OF CASES

MISCLASSIFICATION OF EXPOSED/NOT EXPOSED

APPROPRIATE USE OF CONTROL GROUP

CODING OF MORTALITY – UNDERLYING/NON-CONTRIBUTING CAUSES?

LOST OF FOLLOW-UP OUTCOMES

☐ **OVERALL STUDY QUALITY ASSESSMENT** (1. VERY GOOD/GOOD 2. FAIR 3. POOR)
(CONSIDER STUDY DESIGN, STUDY SIZE, EXPOSURE ASSESSMENT, PARTICIPATION/FOLLOW-UP, OUTCOME, AND OTHER PARAMETERS)

☐ **APPROPRIATE FOR META-ANALYSIS?** (1. YES, 2. NO)

ADDITIONAL INFORMATION REQUIRED: _____

Appendix D:

Database Structure