National Toxicology Program
U.S. Department of Health and Human Services

# Peer-Review Draft:
# Report on Carcinogens
# Monograph on Trichloroethylene

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Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

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# FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of identified substances (i) that either are *known to be human carcinogens* or are *reasonably anticipated to be human carcinogens* and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of HHS, has delegated responsibility for preparation of the RoC to the NTP, which prepares the report with assistance from other Federal health and regulatory agencies and nongovernmental institutions. The most recent RoC, the 12th Edition (2011), is available at http://ntp.niehs.nih.gov/go/roc12.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed, or (3) removing a substance already listed in the RoC are evaluated in a scientific review process (http://ntp.niehs.nih.gov/go/rocprocess) with multiple opportunities for scientific and public input and using established listing criteria (http://ntp.niehs.nih.gov/go/15209). A list of candidate substances under consideration for listing in (or delisting from) the RoC can be obtained by accessing http://ntp.niehs.nih.gov/go/37893.

# BACKGROUND AND METHODS

Trichloroethylene (TCE, CASRN 79-01-6) is a volatile, chlorinated alkene whose major uses are as an intermediate for hydrofluorocarbon production, as a degreaser for metal parts, and as a modifier for polyvinyl chloride polymerization. Past uses of trichloroethylene include use as a solvent in the rubber industry, adhesive formulations, dyeing and finishing operations, printing inks, paints, lacquers, varnishes, adhesives, and paint strippers; in the production of agricultural chemicals such as fungicides and insecticides; as an extraction solvent for natural fats and oils; as a solvent in extracting spices, hops, and decaffeinated coffee; and as an anesthetic and analgesic in obstetrics and for minor surgical procedures.

Trichloroethylene has been listed in the Report on Carcinogens (RoC) as *reasonably anticipated to be a human carcinogen* since 2000 based on limited evidence of carcinogenicity from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals. Since that time, several cancer studies in humans have been published in the peer-reviewed literature, and the International Agency for Research on Cancer (2013) has concluded that trichloroethylene is *carcinogenic to humans* (Group 1). Trichloroethylene has been selected as a candidate substance for review for possible change in listing status in the RoC based on evidence of exposure to a significant number of persons residing in the United States and an adequate database of cancer studies.

## Monograph contents

This RoC draft monograph on trichloroethylene consists of the following components: (Part 1) the cancer evaluation component that reviews the relevant scientific information and assesses its quality, applies the RoC listing criteria to the scientific information, and recommends an RoC listing status for trichloroethylene, and (Part 2) the draft substance profile containing the NTP's preliminary listing recommendation, a summary of the scientific evidence considered key to reaching that recommendation, and data on properties, use, production, exposure, and Federal regulations and guidelines to reduce exposure to trichloroethylene. Exposure information from the substance profile in the 12$^{th}$ RoC was updated in the substance profile in this monograph and exposure information is not discussed in the cancer evaluation component.

The methods for preparing the draft RoC monograph on trichloroethylene are described in the "Trichloroethylene Protocol" (http://ntp.niehs.nih.gov/ntp/roc/thirteenth/protocols/tce_protocol12-31-13_508.pdf). As discussed in the protocol, the draft RoC monograph focuses on the relationship between exposure to trichloroethylene and non-Hodgkin lymphoma (NHL) and is histological subtypes and related cancers, and cancers of the kidney and liver. The cancer evaluation component for trichloroethylene provides information on the following topics that are relevant to understanding the relationship between exposure to trichloroethylene and the cancers listed above: chemical and physical properties (Introduction), disposition and toxicokinetics (Section 1), genetic and related effects (Section 2), quality assessment of cancer studies in humans (Section 3), kidney cancer (Section 4), NHL (and related cancers), (Section 5), and liver cancer (Section 6). Section 2 discusses genetic toxicology of trichloroethylene in humans and animals. Sections 4, 5, and 6 include both human cancer data and mechanistic data for each cancer site. The information in Section 7 is a synthesis of Sections 1 through 6.

The information reviewed in Sections 1 through 6 (except for information on exposure and properties) must come from publicly available, peer-reviewed sources.

The cancer evaluation for trichloroethylene focuses on the evaluation of the human cancer studies, animal tumor studies, and mechanistic data.

The draft profile in Part 2 of this draft monograph includes updated information on exposure to trichloroethylene, which was already identified as meeting the criteria for exposure to a significant number of persons residing in the United States in the RoC listing in 2000.

## Process for preparation of the cancer evaluation component

The process for preparing the cancer evaluation component of the monograph included approaches for obtaining public and scientific input and using systematic methods (e.g., standardized methods for identifying the literature [see Appendix A], inclusion/exclusion criteria, extraction of data and evaluation of study quality using specific guidelines, and assessment of the level of evidence for carcinogenicity using established criteria).

The Office of the Report on Carcinogens (ORoC) followed the approaches outlined in the concept document, which discusses the scientific issues and questions relevant to the evaluation of trichloroethylene carcinogenicity, the scope and focus of the monograph, and the approaches to obtain scientific and public input to address the key scientific questions and issues for preparing the cancer evaluation component of the draft monograph. The ORoC presented the draft concept document for trichloroethylene to the NTP Board of Scientific Counselors (BSC) at the June 21-22, 2012 meeting that provided opportunity for written and oral public comments and is available on the RoC website (http://ntp.niehs.nih.gov/go/37899), after which the concept was finalized and trichloroethylene was approved by the NTP Director as a candidate substance for review.

### *Key scientific questions and issues relevant for the cancer evaluation*

The key scientific issues concern the evaluation of cancer studies in humans and experimental animals, and mechanistic data. They are as follows:

#### *Questions related to the evaluation of human cancer studies*

- What is the level of evidence (sufficient, limited) for the carcinogenicity of trichloroethylene from studies in humans?
- What are the major strengths and limitations in the individual studies and how do they affect the findings?
- Are the associations between exposure to trichloroethylene and NHL and cancers of the kidney and liver observed in some studies, and in the meta-analyses, credible? Can bias, chance, or confounding be ruled out with reasonable confidence?

#### *Questions related to the evaluation of mechanistic data*

- What are the potential mechanisms by which trichloroethylene may cause NHL and cancers of the kidney and liver?
- Is there evidence that the mechanisms by which trichloroethylene causes cancer in experimental animals may not occur in humans? If so, what is the level of evidence?

- Is there mechanistic evidence in humans that would support the associations observed in some human cancer studies? If so, what is the level of evidence? Of special interest is the level of evidence for mutagenic and cytogenetic modes of action for kidney cancer.
- Is there any evidence that trichloroethylene-induced immunologic effects are related to cancer (such as lymphoma or liver cancer) development?

### *Approach for obtaining scientific and public input*

Additional scientific input was obtained for exposure, human cancer studies, and immune effects of trichloroethylene. Technical advisors are identified on the "CONTRIBUTORS" page.

Key issues identified in the concept document include (1) the need for expert input on the quality of the methods used in the epidemiological studies to assess exposure to trichloroethylene and cancer outcome, and information on trichloroethylene exposure in the studies and (2) the potential role of immune effects of trichloroethylene in human cancer. In order to receive public and scientific input on the epidemiological studies and exposure to trichloroethylene, the ORoC held a webinar titled, "Human Cancer Studies on Exposure to Trichloroethylene (TCE): Methods Used to Assess Exposure and Cancer Outcomes," on March 17, 2014. The ORoC also convened an information group of scientists, with expertise in immunology, cancer, epidemiology, or toxicology, who were asked to provide comments on the body of studies of trichloroethylene exposure and immune effects, and whether these studies are informative for evaluating potential mechanisms for trichloroethylene-related cancers in experimental animals and humans.

Public comments on scientific issues were requested at several times prior to the development of the draft RoC monograph, including the request for information on the nomination, and the request for comment on the draft concept document, which outlined the rationale and approach for conducting the scientific review. In addition, the NTP posted its protocol for reviewing the human cancer studies and studies in experimental animals for public input on the ORoC webpage for trichloroethylene (available at http://ntp.niehs.nih.gov/go/37899) prior to the release of the draft monograph. One public comment on trichloroethylene was received from the public as of the date on this document (http://ntp.niehs.nih.gov/go/37663).

### *Methods for writing the cancer evaluation component of the monograph*

The procedures by which relevant literature was identified, data were systematically extracted and summarized, and the draft monograph was written, together with the processes for scientific review, quality assurance, and assessment and synthesis of data, are described below.

The preparation of the RoC monograph for trichloroethylene began with development of a literature search strategy to obtain information relevant to the topics listed above for Sections 1 through 6 using search terms developed in collaboration with a reference librarian (see Protocol). The citations (N = 3,543) identified from these searches were uploaded to a web-based systematic review software for evaluation by two separate reviewers using inclusion/exclusion criteria, and 454 references were selected for final inclusion in the draft monograph using these criteria. Studies identified from the literature searches but excluded from the review include publications on chemicals other than trichloroethylene (or relevant structurally related compounds such as trichloroethylene metabolites and analogues or byproducts of production of

trichloroethylene), and studies involving exposure to trichloroethylene that reported results for topics not covered in this monograph (see 'Monograph contents').

Information for the relevant cancer and mechanistic sections was systematically extracted in tabular format and/or summarized in the text, following specific procedures developed by ORoC, from studies selected for inclusion in the monograph. All sections of the monograph underwent scientific review and quality assurance (QA) (i.e., assuring that all the relevant data and factual information extracted from the publications have been reported accurately) by a separate reviewer. Any discrepancies between the writer and the reviewer were resolved by mutual discussion in reference to the original data source.

Strengths, weaknesses, and study quality of the cancer studies for trichloroethylene in humans (see Appendix D) were assessed based on a series of *a priori* considerations (questions and guidelines for answering the questions), which are available in the protocol (available at http://ntp.niehs.nih.gov/go/37899). Two reviewers evaluated the quality of each study. Relevant genotoxicity and mechanistic studies were also assessed for their strengths and weaknesses.

RoC listing criteria (see text box) were applied to the available database of carcinogenicity data to assess the level of evidence (sufficient, limited, or inadequate) for the carcinogenicity of trichloroethylene from studies in humans and the level of evidence (sufficient, not sufficient) from studies in experimental animals. The approach for synthesizing the evidence across studies and reaching a level of evidence conclusion was outlined in the protocol. The evaluation of the mechanistic data included a complete discussion and assessment of the strength of evidence for potential modes of action for trichloroethylene-induced neoplasia, including metabolic activation,

**RoC Listing Criteria**

***Known To Be Human Carcinogen:***

There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

***Reasonably Anticipated To Be Human Carcinogen:***

There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, OR

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset, OR

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

cytotoxicity, genetic-related effects, and epigenetic effects. The RoC listing criteria were then applied to the body of knowledge (cancer studies in humans and experimental animals and mechanistic data) for trichloroethylene to reach a listing recommendation.

# CONTRIBUTORS

## Office of the Report on Carcinogens (ORoC), Division of the National Toxicology Program (NTP)

*Conducted technical review and evaluation and proposed the preliminary listing recommendation*

Ruth Lunn, DrPH
Drirector, ORoC

Gloria D. Jahnke, DVM, DABT
Diane L. Spencer, MS

## Integrated Laboratory Systems, Inc. (Support provided through NIEHS Contract Number HHSN273201100004C)

*Conducted technical review and evaluation*

Sanford Garner, PhD (Project leader), Principal Investigator
Stanley Atwood, MS, DABT

Andrew Ewens, PhD, DABT
Jennifer Ratcliffe, PhD, MSc
Alton Peters, MS

*Provided administrative support*

Ella Darden, BS

Tracy Saunders, BS

## Technical Advisors

Cheryl Scott, PhD
USEPA

Neela Guha, PhD
IARC

Patricia Stewart, PhD
Stewart Exposure Assessments, LLC
Arlington, VA

## TCE Webinar (March 17, 2014)

*Presenters*

Patricia Stewart, PhD
Stewart Exposure Assessments, LLC
Arlington, VA

Bernard D. Goldstein, MD
Professor Emeritus
University of Pittsburgh

Mark Purdue, PhD
National Cancer Institute

*Moderators/Discussion Leaders*

Cheryl Scott, PhD
USEPA

Neela Guha, PhD
IARC

## TCE Information Group Meeting (April 3, 2014)

Dori Germolec, PhD, Moderator
NIEHS

*Discussants*

Rafael Ponce, PhD
Amgen
Seattle, WA

Kathleen M. Gilbert, PhD
University of Arkansas
Little Rock, AR

Robert Luebke, PhD
U.S. EPA
Research Triangle Park, NC

Patricia Ganey, PhD
Michigan State University

Anneclaire De Roos, PhD, MPH
Drexel University
Philadelphia, PA

Christine Parks, PhD
Contractor to NIEHS
Research Triangle Park, NC

Mark Purdue, PhD
National Cancer Institute

**NTP and other Reviewers**

Abee Boyles, PhD

Caroline Dilworth, PhD

Steve Ferguson, PhD

Dori Germolec, PhD.

Scott Masten, PhD

Alex Merrick, PhD.

Arun Pandiri, PhD

Christine Parks, PhD

Cynthia Rider, PhD

Avima Ruder, PhD, NIOSH

Suramya Waidyanatha, PhD

Lori White, PhD

Nigel Walker, PhD

Lori White, PhD

Mary Wolfe, PhD

# Part 1

# Draft Cancer Evaluation

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**Disposition and Toxicokinetics**

**Genetic and Related Effects**

**Human Cancer Studies**

**Kidney Cancer**

**Non-Hodgkin Lymphoma (NHL)**

**Liver Cancer**

**Preliminary Listing Recommendation**

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# Introduction

Trichloroethylene is a volatile chlorinated alkene that has mainly been used as a metal degreaser. It is also used as an intermediate for hydrofluorocarbon production and as a modifier for polyvinyl chloride polymerization (CMR 2002).

A significant number of people living in the United States are or have been exposed to trichloroethylene because of its widespread presence in the environment from past and present use, particularly in some drinking-water supplies, and in the workplace. Due to its volatility, the principal route of exposure is through inhalation although absorption from dermal exposure also occurs. Exposure has been documented by direct measurements of trichloroethylene in ambient air in the general environment and in workplaces where it is used. The presence of trichloroethylene in groundwater and drinking-water supplies near sites of past use of trichloroethylene has also been confirmed. Additional information on occupational and environmental exposure to trichloroethylene is described in the draft RoC substance profile in Part 2 of this monograph.

### Chemical and physical properties

Trichloroethylene (Figure 1) is a chlorinated alkene. Table 1 contains some chemical identification information for trichloroethylene.

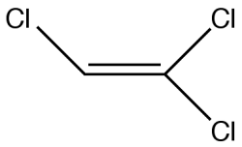


**Figure 1. Chemical structure of trichloroethylene**

**Table 1. Chemical identification of trichloroethylene**

| Characteristic | Information |
|---|---|
| Chemical Abstracts index name | 1,1,2-Trichloroethene |
| CAS Registry number | 79-01-6 |
| Molecular formula | $C_2HCl_3$ |
| Synonyms | TCE; TRI; 1,1,2-trichloroethylene; trichloroethene; ethylene trichloride; acetylene trichloride |

Source: HSDB 2012, IARC 2014.

Trichloroethylene exists at room temperature as a clear, colorless, nonflammable liquid with an ethereal odor. It is slightly soluble in water, soluble in ethanol, acetone, diethyl ether, and chloroform, and miscible in oil. Trichloroethylene evaporates easily (Dow 2008). It is relatively stable, but oxidizes slowly when exposed to sunlight in air (IARC 1976). Physical and chemical properties of trichloroethylene are listed in Table 2.

**Table 2. Physical and chemical properties of trichloroethylene**

| Property | Information |
|---|---|
| Molecular weight | 131.4 |
| Specific gravity | 1.4642 at 20°C/4°C |
| Melting point | –84.7°C |
| Boiling point | 87.2°C |
| Log $K_{ow}$ | 2.61 |
| Water solubility | 1.28 g/L at 25°C |
| Vapor pressure | 69 mm Hg at 25°C |
| Vapor density relative to air | 4.53 |

Source: HSDB 2012.

# 1 Disposition and Toxicokinetics

Disposition and toxicokinetics refer to how a chemical can enter and leave the body, what happens to it once it is in the body, and the rates of these processes. Disposition includes absorption, distribution, metabolism, and excretion while toxicokinetics refers to the mathematical description of the time course of disposition of a chemical in the body. Section 1.2 discusses the absorption, distribution, and excretion of trichloroethylene, metabolism is discussed in Section 1.3, and toxicokinetic data derived primarily from *in vitro* studies are presented in Section 1.4. These data show that there are qualitative similarities between rodents and humans. Disposition and toxicokinetic data are important because they describe various factors that affect the toxicity of a chemical. These factors include routes and rates of absorption, tissue concentrations and their temporal changes, reactive metabolites, intoxication and detoxication reactions, routes of elimination, and gender and/or species differences in these factors. The mechanistic implications of these data are discussed in subsequent sections.

## 1.1 Absorption, distribution and excretion

Trichloroethylene is a small, volatile, lipophilic compound that readily crosses cell membranes. The absorption, distribution, and excretion of trichloroethylene in humans and experimental animals has been extensively investigated and reported in several recent high quality reviews published by EPA (2011a), ATSDR (1997, 2013), and IARC (2014). Therefore, this section focuses on the principle findings from those reviews. Overall, the data indicate that trichloroethylene is well absorbed by all routes of exposure, widely distributed, and excreted either unchanged in expired air or as metabolites in the urine.

### 1.1.1 Human studies

Humans are exposed to trichloroethylene from a variety of sources and by different routes (ATSDR 1997, EPA 2011a). Occupational exposure occurs primarily by inhalation of vapors and dermal contact with vapors or liquid. Trichloroethylene is a common environmental contaminant, thus, the general population may be exposed from contact with contaminated air, food, and water. Oral absorption in humans is rapid and extensive based on clinical symptoms and measurements of trichloroethylene and its metabolites in urine and blood following accidental or intentional ingestion. However, quantitative estimates of absorption were not possible because the ingested amounts were unknown. Several controlled inhalation and dermal exposure studies have been conducted in humans. Uptake from the lungs is rapid and the absorbed dose is proportional to exposure concentration, duration, and pulmonary ventilation rate. Absorption from the lungs in subjects exposed to trichloroethylene concentrations of 9 to 200 ppm for 30 minutes to 5 hours ranged from about 40% to 70% at rest and 25% to 46% during exercise. Steady state concentrations in blood were reached within a few hours after the start of exposure. The resulting concentration in the blood after establishment of equilibrium with alveolar air is determined by the blood-to-air partition coefficient. Measured blood-to-air partition coefficients for trichloroethylene in humans ranged from 8.1 to 11.7. Dermal absorption of trichloroethylene vapors or liquid is rapid (within minutes of application) with peak concentrations in exhaled breath occurring within 15 to 30 minutes. However, a dermal flux rate of 430 ± 295 nmol/cm$^2$/minute measured in a study of volunteers exposed to neat liquid for 3 minutes indicated high interindividual variability. Poet *et al.* (2000) conducted skin absorption studies of trichloroethylene in water and soil using human volunteers (N = 3) exposed by hand

immersion or forearm patch tests. Mean permeability constants were 0.015 cm/hr (hand immersion) and 0.019 cm/hr (patch) in water and 0.0074 cm/hr (hand immersion) and 0.0043 cm/hr (patch) in soil. For the patch tests, 4% and 0.6% of the applied trichloroethylene dose was absorbed through the skin from water and soil, respectively. An *in vitro* study using surgically removed skin samples exposed to trichloroethylene in aqueous solution reported a permeability constant of 0.12 cm/hr (EPA 2011a).

Once absorbed, trichloroethylene is rapidly distributed throughout the body (EPA 2011a). Tissue samples collected at autopsy following accidental poisonings or from surgical patients exposed environmentally show that trichloroethylene is distributed to all tested tissues including the brain, muscle, heart, kidney, lung, and liver. Trichloroethylene also crosses the human placenta with ratios of concentrations in fetal:maternal blood ranging from approximately 0.5 to 2. Body distribution is largely determined by solubility in each organ and can be measured by tissue:blood partition coefficient. Partition coefficients reported for human tissues are as follows: fat (63.8 to 70.2), liver (3.6 to 5.9), brain (2.6), muscle (1.7 to 2.4), kidney (1.3 to 1.8), and lung (0.5 to 1.7). Thus, post-exposure distribution of trichloroethylene is affected by the relative amount of fat tissue in the body and accumulation of trichloroethylene in fat may prolong internal exposure.

Trichloroethylene is primarily excreted as urinary metabolites (see Section 1.2) or in expired air as the unchanged compound or carbon dioxide (EPA 2011a). Controlled inhalation studies in humans indicated that 10% to 20% is exhaled unchanged while urinary metabolites accounted for about 50% to 75% of the retained dose (Bartoníček 1962, EPA 2011a, IARC 2014, Souček and Vlachová 1960, Chiu *et al.* 2007). No quantitative estimates of $CO_2$ elimination in humans were identified. One study reported that 8.4% of the two primary metabolites (trichloroethanol and trichloroacetic acid) were eliminated in the feces (Bartoniček 1962). Elimination of unchanged trichloroethylene in the urine is minimal. Small amounts of metabolites may be excreted in sweat, milk, and saliva.

### 1.1.2 Laboratory animal studies

Trichloroethylene is well absorbed in laboratory animals by all exposure routes (ATSDR 1997, EPA 2011a). Studies in mice and rats show that absorption of orally administered trichloroethylene may approach 100%; however, other factors such as stomach contents, vehicle, and dose may affect the degree of absorption. Bioavailability from the gastrointestinal tract is higher in fasted animals and uptake is faster and more extensive when administered in an aqueous vehicle compared with an oil vehicle. Peak blood levels occurred within minutes of dosing, indicating rapid absorption. Both closed-chamber gas uptake studies and blood concentration measurements following open-chamber experiments demonstrated rapid absorption of trichloroethylene from the respiratory tract of rodents. One study reported that the fractional absorption of trichloroethylene vapors was > 90% during the initial 5 minutes in rats exposed to 50 or 500 ppm but declined to about 70% during the second hour of exposure. Studies with guinea pigs and rats indicate that trichloroethylene readily penetrates the skin. Estimated permeability constants in hairless guinea pigs were 0.16 to 0.47 mL/cm$^2$/hour (Bogen *et al.* 1992). (The authors noted that this unit is equivalent to the more commonly used unit of cm/h, but they considered it more meaningful for the permeability constant in this context.) Rat skin was shown to be significantly more permeable to trichloroethylene in water or soil than human

skin with permeability coefficients of 0.31 cm/hour in water and about 0.09 cm/hour in soil (Poet *et al.* 2000).

Detailed tissue distribution studies have been conducted in rodents using different routes of administration (EPA 2011a). These studies show that trichloroethylene is rapidly distributed throughout the body following inhalation or oral exposure. Tissue:blood partition coefficient values in rats and mice are shown in Table 1-1. The highest tissue concentrations were measured in fat; however, the fat:blood partition coefficients in rats and mice were lower than those reported for humans (63.8 to 70.2, see Section 1.2.1).

**Table 1-1. Tissue:blood partition coefficients of trichloroethylene in rats and mice**

| Species | Fat | Brain | Liver | Kidney | Lung | Heart | Muscle |
|---|---|---|---|---|---|---|---|
| Rat | 22.7−36.1 | 0.71−1.29 | 1.03−2.43 | 1.0−1.55 | 1.03 | 1.1 | 0.46−0.84 |
| Mouse | 36.4 | − | 1.62 | 2.1 | 2.6 | − | 2.36 |

Source: Adapted from EPA 2011a.

As in humans, laboratory animals primarily excrete trichloroethylene metabolites in the urine (EPA 2011a). Unchanged trichloroethylene and $CO_2$ are exhaled, and moderate amounts of metabolites are excreted in the feces. The amount of unchanged trichloroethylene exhaled increases with dose in mice and rats, which suggests saturation of metabolic pathways at high doses. In mice, 1% to 6% is exhaled unchanged at low doses but increases to 10% to 18% at high doses. Rats excrete about 1% to 3% unchanged at low doses but show a much higher increase at high doses (43% to 78%). At exposures below metabolic saturation, most of the administered trichloroethylene is eliminated as urinary metabolites.

## 1.2 Metabolism

Trichloroethylene metabolism is extensive and complex and most of the toxic effects of this compound have been linked to its metabolites (IARC 2014, EPA 2011a, ATSDR 1997). Controlled acute and subacute inhalation studies in humans at trichloroethylene concentrations up to 320 ppm show that 81% to 92% of the retained dose is metabolized (Bogen *et al.* 1988). Saturation of trichloroethylene metabolism occurs at lower doses in rats than in mice, and mathematical simulation models have predicted metabolic saturation in humans at high exposure concentrations (ATSDR 1997). Although there are sex, species, and interindividual differences in metabolism, humans and laboratory animals have in common two distinct pathways: cytochrome P450-dependent oxidation (CYP) and glutathione (GSH) conjugation (EPA 2011a). Quantitatively, the oxidative pathway predominates in all species studied. Oxidative metabolites have been linked to liver toxicity while reactive metabolites generated by the GSH pathway have been linked to kidney toxicity. Hepatic first-pass oxidative metabolism is important. In addition to the liver, other important sites of metabolism include the kidney, lung, blood, and male reproductive system (Chiu *et al.* 2006, Cummings *et al.* 2001, Lash *et al.* 2014, Lipscomb *et al.* 1996). The following sections describe the primary metabolic pathways and metabolites.

### 1.2.1 CYP-dependent oxidation

CYP-dependent oxidation occurs in humans and rodents and is illustrated in Figure 1-1. The primary urinary metabolites detected in humans and rodents include trichloroethanol,

trichloroethanol-glucuronide, and trichloroacetic acid (Lash *et al.* 2014, EPA 2011a). Chloral also is a major oxidative metabolite but has low systemic levels due to rapid transformation to other metabolites (EPA 2011a). Bradford *et al.* (2011) reported more than a fourfold difference in peak serum concentrations of trichloroacetic acid in male mice from 15 different strains administered a single oral dose of trichloroethylene. Serum concentrations of dichloroacetic acid varied more than 100 fold between strains but were about 1,000 times lower than trichloroacetic acid concentrations. *In vitro* data indicate that rodents have a higher capacity to metabolize trichloroethylene that humans, but this has not been verified *in vivo* (EPA 2011a). Knadle *et al.* (1990) reported that rat hepatocytes produced 5 to 20 times more oxidative metabolites of trichloroethylene than human hepatocytes under the same experimental conditions.

Briefly, oxidation in the liver (primarily via CYP2E1) yields a chemically unstable oxygenated trichloroethylene-P450 intermediate that rapidly forms chloral, trichloroethylene oxide, and *N*-(hydroxyacetyl)-aminoethanol. The majority of the flux is towards chloral via chlorine migration (Lash *et al.* 2014). In body water, chloral is in equilibrium with chloral hydrate. Chloral/chloral hydrate is rapidly reduced by alcohol dehydrogenase or P450 to form trichloroethanol or oxidized by aldehyde dehydrogenase to form trichloroacetic acid. Trichloroethanol production was favored in humans and experimental animals following oral chloral exposure (EPA 2011a). Trichloroethanol may be oxidized to trichloroacetic acid or form a glucuronide conjugate. Glucuronide conjugates excreted in the bile may be hydrolyzed back to trichloroethanol in the intestine and reabsorbed. *In vivo* studies in rats showed that enterohepatic circulation of trichloroethanol and subsequent oxidation was responsible for 76% of the trichloroethanol measured in blood. Although trichloroacetic acid is poorly metabolized it may undergo dechlorination to form dichloroacetic acid. Dichloroacetic acid also may form from trichloroethylene oxide, a short-lived intermediate metabolite. A few *in vivo* studies in mice have reported that dichloroacetic acid was produced to a very limited extent compared to trichloroacetic acid (Bradford *et al.* 2011, Kim *et al.* 2009a, 2009b). Trichloroethylene-oxide was the most likely source (Kim *et al.* 2009a). However, there is some uncertainty about the sources and amounts of dichloroacetic acid production *in vivo* and direct evidence for its formation from trichloroethylene exposure remains equivocal, especially in humans (EPA 2011a, Lash *et al.* 2000a). Dichloroacetic acid is difficult to detect in blood because it is rapidly metabolized to monochloroacetic acid by dechlorination or to glyoxylic acid by GST-zeta in hepatic cytosol (Lash *et al.* 2014, EPA 2011a). Glyoxylic acid is subsequently converted to oxalic acid, glycine, and carbon dioxide.

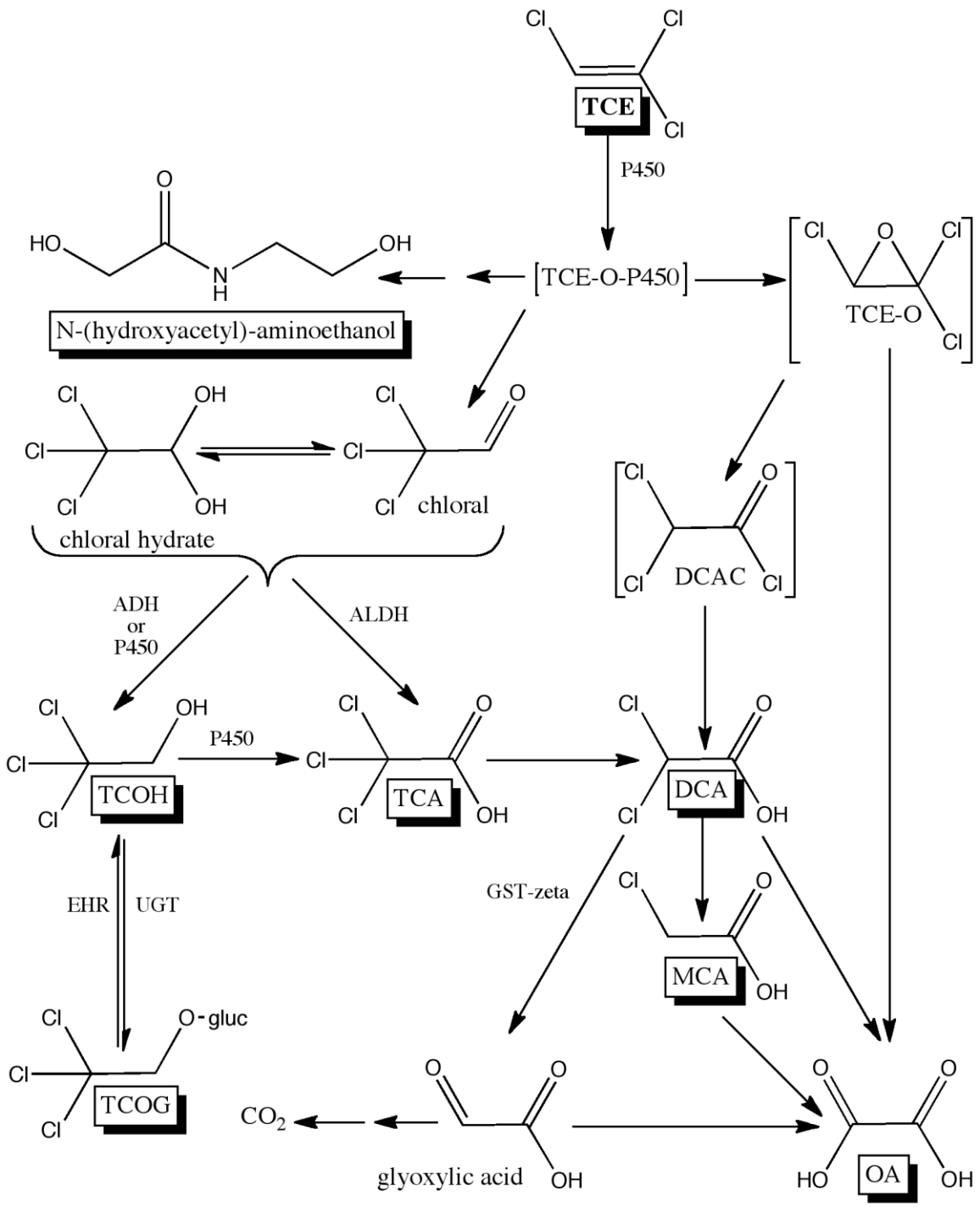


**Figure 1-1. Oxidative metabolism of trichloroethylene (TCE)**

Adapted from: (Lash *et al.* 2014, IARC 2014, EPA 2011a, Kim *et al.* 2009a)
Compounds that are recovered in urine are shown in boxes while chemically unstable or reactive compounds are enclosed in brackets. ADH = alcohol dehydrogenase, ALDH = aldehyde dehydrogenase, DCA = dichloroacetic acid, DCAC = dichloroacetylchloride, EHR = enterohepatic recirculation, GST = glutathione-S-transferase, MCA = monochloroacetic acid, OA = oxalic acid, TCA = trichloroacetic acid, TCE-O = trichloroethylene oxide, TCOG = trichloroethanol-glucuronide conjugate, TCOH = trichloroethanol, UGT = UDP-glucuronosyltransferase.

Lipscomb *et al.* (1997) determined that CYP2E1 was responsible for more than 60% of oxidative trichloroethylene metabolism in microsomes from human lymphoblastoid cell lines selectively expressing CYP1A1, CYP1A2, CYP2E1, and CYP3A4. CYP2E1 is highly expressed in human liver and testes but is expressed at very low levels in human kidney (Lash *et al.* 2014). However, CYP2E1 expression is relatively high in rat kidney (Cummings *et al.* 2001). Although CYP2E1 is the predominant high-affinity isoform for trichloroethylene oxidation in humans and experimental animals, studies with CYP2E1 knockout mice show that considerable trichloroethylene oxidation occurs in its absence (Ghanayem and Hoffler 2007). Other P450 isozymes involved in the oxidative metabolism of trichloroethylene include CYP1A1/2, CYP2B1/2, and CYP2C11/6 in rat liver and/or kidney and CYP2F4 and CYP2F2 in rat and mouse lung, respectively (Cummings *et al.* 2001, EPA 2011a, Nakahama *et al.* 2001, Tabrez and Ahmad 2013). Other human CYP enzymes that have some activity with trichloroethylene include CYP1A1/1A2, CYP2A6, and CYP3A4 (Lash *et al.* 2014, Lash *et al.* 2000a). CYP2E1 activity towards trichloroethylene is approximately 2-fold and 200-fold higher than that that of CYP1A2 and CYP3A4, respectively (Lash *et al.* 2000a). Although liver P450 content is similar across species, mice and rats have higher levels of CYP2E1 than humans (EPA 2011a). The maximal rate of CYP-dependent oxidative trichloroethylene metabolism is 2- to 4-fold higher in mice than in rats while the maximal rate in humans is 5- to more than 10-fold slower than in rats (Lash *et al.* 2014). Differences in content or expression of the various P450 isoforms could contribute to interspecies differences in susceptibility.

### 1.2.2 GSH conjugation

Trichloroethylene flux through the GSH conjugation pathway (Figure 1-2) is much less than through the oxidative pathway in humans and experimental animals; however, factors that affect the oxidative pathway indirectly affect the GSH pathway (EPA 2011a). *In vitro* studies show that inhibition of P450-mediated oxidation increases GSH conjugation. Reactive metabolites produced several steps downstream from the initial conjugation are thought to cause cytotoxicity and carcinogenicity, particularly in the kidney. Glutathione S-transferase (GST) activity is highest in the liver but appreciable activity also occurs in other tissues including the kidneys (primarily the proximal tubules) (Lash *et al.* 2014). There is some uncertainty regarding the specific GST isoforms that mediate trichloroethylene conjugation; however, Lash *et al.* (1999b) reported evidence of high- and low-activity populations among male and female volunteers exposed to trichloroethylene vapors for 4 hours. These data suggest that polymorphisms affect GSH conjugation of trichloroethylene in humans. Several studies have reported that GST polymorphisms modify the risk of renal cell carcinoma and that specific chemical exposures (including trichloroethylene) can affect the risk (Cheng *et al.* 2012, Moore *et al.* 2010, Buzio *et al.* 2003, Sweeney *et al.* 2000, Brüning *et al.* 1997); however, two recent studies reported no association (Yang *et al.* 2013, Liu *et al.* 2012b).

The initial GSH-conjugation step occurs primarily in the liver and involves GSH displacement of a chloride ion from trichloroethylene via a nucleophilic substitution reaction. Products of this reaction include *S*-(1,2-dichlorovinyl)glutathione and its isomer *S*-(2,2-dichlorovinyl)glutathione (DCVG) (Lash *et al.* 2014, EPA 2011a). Subsequent metabolism through the GSH conjugation pathway occurs primarily in the kidneys (Lash *et al.* 2014, EPA 2011a). DCVG, whether it is formed in the liver or within the kidneys, is converted to its corresponding cysteine conjugate, *S*-dichlorovinyl-L-cysteine (DCVC), by hydrolytic reactions with γ-glutamyltransferase (GGT) and

cysteinylglycine dipeptidases (CGDP) in the proximal tubular brush-border membrane. GGT and CGDP activity is much higher in the kidney than the liver in rodents and humans. These reactions also may take place in the bile or gut during enterohepatic circulation where DCVG and DCVC may be reabsorbed and further metabolized in the liver. DCVG and DCVC have been detected in blood, serum, and tissues of rodents and DCVG has been detected in the blood of humans exposed to trichloroethylene (Lash *et al.* 2014). *In vitro* studies using rodent and human liver and kidney cellular and subcellular fractions of DCVG formation from trichloroethylene show considerable differences (EPA 2011a). DCVC is a major branch point in the metabolism of trichloroethylene leading to three possible metabolites via reactions with N-acetyltransferase, cysteine conjugate β-lyase, or flavin-containing monooxygenase 3 (FMO3) and are briefly described below.

N-Acetylation of DCVC to *N*-acetyl-*S*-dichlorovinyl-L-cysteine (NAcDCVC) can occur in the liver or kidney, thus, concentrations of the acetylated metabolite can exceed that which the kidney is capable of producing on its own (EPA 2011a). NAcDCVC can be deacetylated to reform DCVC, oxidized by CYP3A to form the corresponding sulfoxide, or excreted in the urine. CYP3A expression is highly polymorphic in humans. NAcDCVC has been detected in urine samples from mice, rats, and humans, which indicates that N-acetylation of DCVC is a common metabolic pathway among these species. *In vitro* studies of DCVC metabolism indicate that *N*-acetylation to NAcDCVC is greater in rats than in mice or humans. Only NAcDCVC has been detected in the urine of experimental animals or humans, which might be due to the reactive nature of other metabolites generated from the GSH pathway.

Renal cysteine conjugate β-lyase catalyzes the formation of an unstable thiolate metabolite, *S*-dichlorovinyl-thiol (DCVT) from DCVC. This reaction has been demonstrated *in vitro* in rodents and humans with greater activity reported in rats compared to mice or humans (Green *et al.* 1997). DCVT spontaneously rearranges to form two chemically reactive and unstable compounds, chlorothioketene and chlorothionoacetyl chloride (Dekant *et al.* 1988, Goeptar *et al.* 1995, Irving and Elfarra 2012). Finally, DCVC also is a substrate for FMO3-catalyzed sulfoxidation (EPA 2011a). Although the human kidney expresses relatively low levels of FMO3 (see Section 1.3.2), the available data suggest that FMO may play a more prominent role relative to β-lyase in human kidney while the reverse occurs in rat kidney (Lash *et al.* 2014). However, none of the possible sulfoxidation products of trichloroethylene metabolism have been reported in tissues or urine *in vivo* in rodents or humans.

Strain, species, and sex differences in GSH-conjugation have been reported (Lash *et al.* 2014, EPA 2011a). Lash *et al.* (1999b) reported markedly higher amounts of DCVG formation in healthy male volunteers exposed to trichloroethylene vapors compared to females (see Section 1.3.4). In general, *in vitro* DCVG formation rates by liver and kidney subcellular fractions were higher in male rats and mice compared to females of the same species. Lash *et al.* (2006) reported that male rats formed more DCVC (considered the nephrotoxic precursor metabolite) than females. Hepatic concentrations of GSH also were reduced in male but not female rats exposed to higher doses of trichloroethylene. In mice exposed to trichloroethylene, Bradford *et al.* (2001) showed that the levels of DCVG and DCVC were much lower than oxidative metabolites and varied considerably with strain.

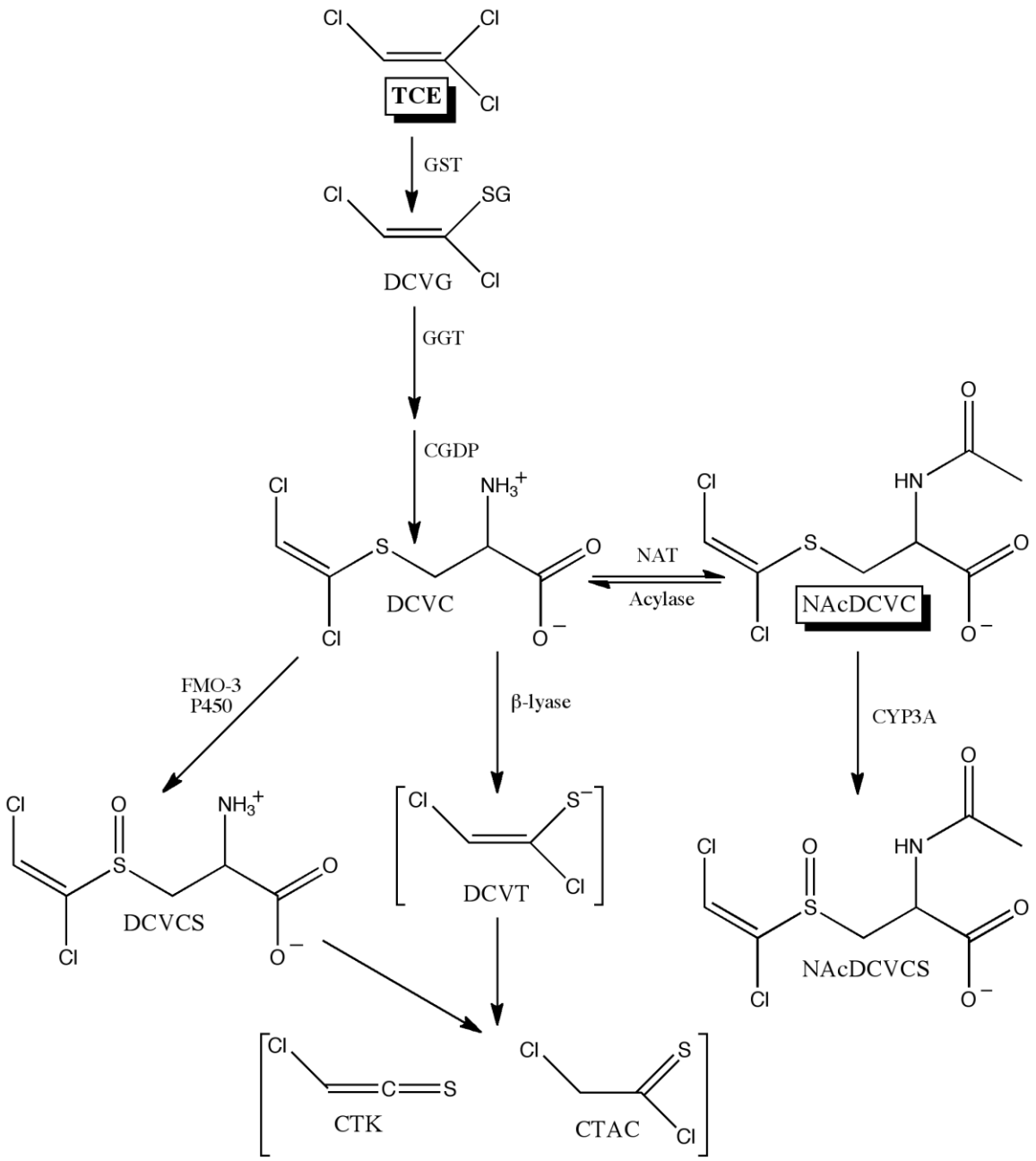


**Figure 1-2. Glutathione-dependent metabolic pathways of trichloroethylene***

Adapted from: Lash *et al.* 2014, IARC 2014, EPA 2011a, Irving and Elfarra 2012.
Compounds that are recovered in urine are shown in boxes while chemically unstable or reactive compounds are enclosed in brackets. CGDP = cysteinylglycine dipeptidases, CTAC = chlorothionoacetyl chloride, CTK = chlorothioketene, DCVC = *S*-dichlorovinyl-L-cysteine, DCVG = *S*-dichlorovinyl-glutathione, DCVCS = DCVC sulfoxide, DCVT = *S*-dichlorovinyl thiol, FMO = flavin monooxygenase, GGT = γ-glutamyl transpeptidase, GST = glutathione-S-transferase, NAcDCVC = *N*-acetyl DCVC, NAcDCVCS = *N*-acetyl DCVCS, NAT = N-acetyltransferase.

* Only 1,2-dichlorovinyl isomers shown but 2,2-dichlorovinyl isomers also produced.

### 1.2.3 Trichloroethylene metabolites

A summary of trichloroethylene metabolite formation and their systemic availability is shown in Table 1-2. Systemic availability depends on the chemical stability or reactivity of the metabolite. Metabolites that are chemically unstable or reactive are likely to spontaneously generate other chemicals through non-enzymatic rearrangement or bind with cellular proteins, lipids, and DNA near their site of formation rather than distributing via the systemic circulation.

**Table 1-2. Trichloroethylene metabolite formation and systemic availability**

| Pathway/metabolite | Tissues where formed | Human | Rodent | Systemic availability (rodents and humans) |
|---|---|---|---|---|
| **P450 oxidation** | | | | |
| TCE-O, DCAC | liver<br>lung<br>testes | yes<br>yes<br>yes | yes<br>yes<br>yes | no |
| CH/CHL | liver<br>lung<br>testes | yes<br>yes<br>yes | yes<br>yes<br>yes | yes |
| TCOH | liver<br>lung<br>GI<br>testes | yes<br>–<br>yes<br>yes | yes<br>yes<br>yes<br>yes | yes |
| TCA | liver<br>lung<br>testes | yes<br>yes<br>yes | yes<br>yes<br>– | yes |
| TCOG | liver | yes | yes | yes |
| DCA | liver<br>lung<br>testes | –<br>–<br>yes | yes<br>yes<br>– | yes<br>(low amount) |
| **GSH-conjugation** | | | | |
| DCVG, DCVC | liver<br>kidney | yes<br>yes | yes<br>yes | yes |
| DCVT, DCVCS, CTK/CTAC | kidney<br>hematopoietic | yes<br>– | yes<br>yes | no |
| NAcDCVC, NAcDCVS | liver<br>kidney | yes<br>yes | yes<br>yes | yes |

Source: Lash *et al.* 2014.
– = no data, CH/CHL = chloral/chloral hydrate, CTK/CTAC = chlorothioketene/chlorothionoacetyl chloride, DCA = dichloroacetic acid, DCAC = dichloroacetylchloride, DCVC = *S*-dichlorovinyl-L-cysteine, DCVG = *S*-dichlorovinyl-glutathione, DCVCS = DCVC sulfoxide, DCVT = *S*-dichlorovinyl thiol, NAcDCVC = *N*-acetyl DCVC, NAcDCVCS = *N*-acetyl DCVCS, TCA = trichloroacetic acid, TCE-O = trichloroethylene oxide, TCOG = trichloroethanol-glucuronide conjugate, TCOH = trichloroethanol.

## 1.3 Toxicokinetic data

The kinetics of trichloroethylene metabolism for the oxidative and GSH conjugation pathways and elimination of metabolites are described below. Since reactive metabolites are responsible for trichloroethylene toxicity, especially for the liver and kidney (EPA 2011a), it is important to understand the factors that affect the flux through each metabolic pathway.

### 1.3.1 Oxidative metabolism

The oxidative metabolites of trichloroethylene proposed to contribute to liver carcinogenicity are chloral hydrate, TCA, TCOH, and DCA (see Figure 1-1 and Section 6.2). The initial oxidative step that produces chloral hydrate is critical because this is the rate-limiting step in formation of TCA and DCA, which are the putative toxic metabolites (EPA 2011a). Mice have a greater oxidative metabolic capacity for trichloroethylene (i.e., higher Vmax) than either rats or humans (see Appendix B, Table B-1a). However, human liver microsomes generally showed a higher affinity (i.e., lower $K_m$) than rat or mouse microsomes. Thus, the lower apparent $K_m$ in humans may partially offset the lower Vmax resulting in similar clearance efficiencies (Vmax/$K_m$) compared with rodents. Rat kidney microsomes also had a much lower affinity for trichloroethylene than rat liver microsomes. $K_m$ values for TCOH formation were much lower than for TCA formation and are consistent with TCOH formation predominating over TCA formation in all three species (see Appendix B, Table B-1b). Since the metabolism of chloral hydrate to TCA and TCOH involves several enzymes and cofactors, changes in the cellular cofactor ratio or redox status in the liver could impact the relative amounts of TCOH and TCA produced. In humans, the total amount of TCA excreted may be similar to the amount of TCOH because TCA has a much longer urinary half-life.

Lipscomb *et al.* (1997) reported that $K_m$ values were not normally distributed and could be separated into three statistically distinct populations among 23 human hepatic microsomal samples (see Appendix B, Table B-1a). $K_m$ values were significantly higher (33.1, N = 13) in males than in females (21.9, N = 10) but Vmax values were not significantly different. Vmax values were normally distributed and generally correlated with increasing $K_m$ values. Lipscomb *et al.* (1998b) compared the metabolism of trichloroethylene in pooled human, mouse, and rat liver microsomes at different concentration ranges. $K_m$ values in rats showed marked differences at different concentration ranges while those for mice and humans were constant. These data indicate that several CYP isoforms with different $K_m$ values (high-, medium-, and low-affinity forms) metabolize trichloroethylene in the rat. High concentrations of trichloroethylene (1,000 ppm) inhibited CYP2E1 activity but increased CYP1A1/1A2 activity in all three species. Elfarra *et al.* (1998) reported species- and sex-related differences in kinetics of trichloroethylene metabolism. Vmax and Vmax/$K_m$ values from female mouse liver microsomes were consistently higher than values from the corresponding male mouse liver microsomes or rat and human liver microsomes. There were no sex-related differences in the rates of metabolism with rat or human microsomes. Rat and human microsomes exhibited biphasic kinetics consistent with the involvement of both low-affinity and high-affinity enzymes while mouse liver microsome kinetics were described by single values for $K_m$ and Vmax.

### 1.3.2 GSH conjugation

The GSH-conjugation pathway results in formation of reactive species several steps downstream from the initial conjugation, and some of these metabolites (particularly DCVC) are nephrotoxic (see Figure 1-2 and Section 4.2) (EPA 2011a). *In vitro* studies of trichloroethylene conjugation show considerable intra- and interspecies differences and, in some cases, contradictory results. For example, conjugation rates reported by Green *et al.* (1997) and Dekant *et al.* (1990) were orders of magnitude lower than those reported by Lash *et al.* (1999a, 1998). Green *et al.* also reported some DCVG formation in rat liver cytosol while Dekant *et al.* did not. The reasons for

the discrepancies are not completely understood but may be explained in part by different analytical methods (EPA 2011a, Lash *et al.* 2000a, Lash *et al.* 1999a).

DCVG formation was significantly higher in liver cells from male rats compared with female rats while the rates in kidney cells and subcellular fractions were comparable for both sexes. Rates of DCVG formation were significantly higher in male mouse liver microsomes and kidney cytosol compared with females but female mice had higher rates in kidney microsomes. Overall, DCVG formation was unexpectedly higher in mice than in rats. There were no significant sex-related differences in DCVG formation in humans; however, the rate of GSH conjugation in human liver spanned a range of 2.4-fold in cytosol and 6.5-fold in microsomes (Lash *et al.* 1999a). Although the data show that rates of trichloroethylene conjugation are higher in human liver and kidney subcellular fractions (with the exception of Green *et al.*) than in rats or mice (Appendix B, Table B-2), there is significant uncertainty in the quantitative estimation of DCVG formation from trichloroethylene.

Reported $K_m$ constants and Vmax values of GSH conjugation from pooled human kidney and liver cells and subcellular fractions and rat kidney proximal tubular cells (Appendix B, Table B-3) show that the liver is the primary site of GSH conjugation; however, the kidney also has significant capacity to catalyze DCVG formation. Further, conjugation of trichloroethylene in all systems, with the exception of human hepatocytes and kidney subcellular fractions, included two kinetically distinct processes (high affinity and low affinity). In human hepatocytes, DCVG formation exhibited time-, trichloroethylene concentration-, and cell concentration-dependent formation (Lash *et al.* 1999a). Maximum formation occurred with 500-ppm trichloroethylene but decreased at concentrations of 1,000 ppm and above. DCVG formation in liver and kidney subcellular fractions exhibited time-, protein concentration-, and both trichloroethylene and GSH concentration-dependent formation.

Most DCVG is converted to DCVC in a two-step process involving GGT and CGDP (see Figure 1-2). GGT activity is concentrated in the microsomal fraction of the cell and is much higher in the kidney than the liver in rodents and humans (EPA 2011a). GGT activity in rat kidney microsomes were about two-fold greater than in humans and about 20-fold greater than in mice (Lash *et al.* 1999a, 1998). Whole organ CGDP activity also was higher in the kidney than liver in all mammalian species tested (Hinchman and Ballatori 1990).

As mentioned above, three potential bioactivating pathways for DCVC are cysteine conjugate β-lyase, FMO3, and CYP3A. Limited data were available describing species differences in the activities of these metabolic enzymes. Lash *et al.* (2000a) compiled β-lyase activity and kinetic parameters ($K_m$ and Vmax) in kidney cytosol from rats, mice, and humans for several cysteine conjugates (Appendix B, Table B-4). These data show that β-lyase activity varies with substrate and laboratory but is higher in rats compared with humans or mice.

FMO3 is the predominant FMO isoform in the adult human liver and orthologues from various species were catalytically similar (Ripp *et al.* 1999). Sulfoxide formation (nmol sulfoxide/min/mg protein) was sex-dependent in mice and dogs (higher in females), but not in humans, rats, or rabbits. Sulfoxide formation was highest in rabbit liver microsomes followed by humans and rats. Data for kidney microsomes were highest for rats and were similar to values derived from rat liver microsomes. S-Oxidase activity in mouse kidney microsomes was lower

than observed in mouse liver microsomes and did not show sex-dependence. No data were available for human kidney microsomes in this study. $K_m$ and Vmax values obtained from incubating DCVC with membrane fractions of bacteria expressing human or rabbit FMO3 cDNA in the presence of NADPH were similar. In another study, DCVC sulfoxidation was detected with FMO3 but not with other isoforms (Krause *et al.* 2003). Incubations of DCVC with human liver microsomes resulted in detection of the corresponding sulfoxide but not when incubated with kidney microsomes. Expression levels of FMO1 (3.2 to 11.5 pmol/mg protein) and FMO5 (trace to 5.8 pmol/ mg protein) were higher than FMO3 levels (trace to 1.3 pmol/mg protein) in human kidney samples. There were no data on species differences in CYP3A-mediated sulfoxidation of NAcDCVC (EPA 2011a).

### 1.3.3 Comparative elimination half-lives

Reported plasma half-lives of trichloroethylene metabolites were much shorter in rodents than in humans (Lash *et al.* 2000a). Plasma half-lives of trichloroacetic acid in humans ranged from 51 to 99 hours compared with 3 to 16 hours in rodents. The plasma half-lives of trichloroethanol were about 12 hours in humans and 3 hours in mice. Reported half-lives for chloral hydrate and trichloroethanol glucuronide were 3 and 5 hours, respectively, in mice but these metabolites were not detected in humans exposed to 100 ppm for 4 hours. Lash *et al.* (1999b) reported that the elimination half-life of DCVG in blood of human volunteers was 0.74 hours in males and 0.94 hours in females. Several studies have investigated urinary elimination half-lives of trichloroacetic acid and trichloroethanol in workers exposed to trichloroethylene (reviewed by EPA 2011a). Urinary trichloroacetic acid levels exhibited marked saturation at exposure > 50 ppm while trichloroethanol did not. Reported half-lives for trichloroethanol ranged from about 15 to 43 hours compared with 40 to 58 hours for trichloroacetic acid. The elimination half-lives for both metabolites were higher in females than in males. Urinary elimination kinetics also were faster in rodents than in humans with some studies reporting complete elimination within 1 to 2 days.

### 1.3.4 Relative roles of the CYP and GSH pathways

Comprehensive mass-balance studies are unavailable in humans, but studies in rodents given 2 to 2,000 mg/kg [$^{14}$C]-trichloroethylene reported that 95% to 99% of radioactivity excreted in urine was attributed to oxidative metabolites (EPA 2011a). Genetic polymorphisms or exposure to CYP inducers or inhibitors can alter the balance between oxidation and GSH conjugation of trichloroethylene (Lash *et al.* 2014). Impacts may be more substantial at higher substrate concentrations where the Vmax may become more limiting than hepatic blood flow. Reported ratios of primary oxidative metabolites to NAcDCVC in urine ranged from 986 to 2,562:1 in rats and 3,292 to 7,163:1 in humans. Although NAcDCVC is a useful indicator of GSH conjugation, it likely represents only a small fraction of trichloroethylene flux through this pathway. The range of kinetic data for oxidation and conjugation of trichloroethylene derived from *in vitro* studies show substantial overlap (Appendix B, Table B-5) and suggest that the total flux through the GSH pathway is much more substantial than estimates derived from urinary mercapturates (< 0.1%) alone would suggest. Lash *et al.* (1999b) also reported that maximum blood concentrations of DCVG in human volunteers exposed to trichloroethylene vapors (50 or 100 ppm) were similar to those of TCA and TCOH in the same subjects; however, the area under the curve (AUC) values for the oxidative metabolites were much higher than those for DCVG. DCVG blood concentrations were higher in males (46.1 ± 14.2 nmol/mL) than in females (13.4 ±

6.6 nmol/mL) but elimination half-lives were similar. Lash *et al.* (1999a) also noted that GSH conjugation of trichloroethylene *in vitro* was inhibited by about 50% in the presence of the oxidative pathway while the addition of GSH had no effect on CYP-catalyzed formation of chloral hydrate.

## 1.4 Synthesis and summary

Trichloroethylene is a small, lipophilic compound that readily crosses biological membranes. Studies in humans and experimental animals confirm that trichloroethylene is rapidly and efficiently absorbed following oral, inhalation, or dermal exposure. Distribution from blood to tissues is determined by the blood:tissue partition coefficients, which are largely related to tissue lipid content. High concentrations, relative to blood, occur in the kidney, liver, brain, and fat. Adipose tissue may serve as a reservoir for trichloroethylene, thus prolonging internal exposure. Metabolism is complex; however, two distinct metabolic pathways have been identified that are common to all mammalian species studied: CYP oxidation and GSH conjugation. These pathways operate in parallel. Important sites of metabolism include the liver, kidneys, lungs, blood, and male reproductive system. Oxidation is the predominant pathway and CYP2E1 is the primary isoform involved. Trichloroethanol, trichloroethanol-glucuronide, and trichloroacetic acid are the primary oxidative metabolites detected in blood and urine of humans and laboratory animals. Chloral and chloral hydrate also are formed but are rapidly metabolized. The GSH conjugation pathway produces several metabolites (DCVG, DCVC, DCVCS, DCVT, NAcDCVC, NAcDCVCS, chlorothioketene, and chlorothionoacetyl chloride); however, only NAcDCVC is stable enough to be detected in urine. Trichloroethylene is eliminated unchanged or as carbon dioxide in expired breath. Metabolites are primarily eliminated in the urine with minor amounts eliminated in feces. Conjugated metabolites may be excreted in the bile and reabsorbed from the gastrointestinal tract via enterohepatic recirculation. Although metabolic pathways and metabolites detected in humans and laboratory animals are qualitatively similar, the data show substantial quantitative inter- and intraspecies variability that may explain differences in susceptibility to toxic effects. Much of the variability is due to gender-, species-, and individual-dependent differences in content and activity of key metabolic enzymes (CYP2E1 and GSTs).

*In vitro* data indicate that mice have a higher oxidative metabolic capacity for trichloroethylene than rats or humans, but the variability within species can be 2- to 10-fold. However, $K_m$ values derived from liver microsomal metabolism of trichloroethylene indicate that affinity is higher in humans than rodents. Thus, the clearance efficiency of oxidative metabolites ($Vmax/K_m$) is similar among these species when exposed to low concentrations. There is evidence that humans can be divided into statistically distinct populations based on $K_m$ values. Overall, females have a significantly higher affinity (lower $K_m$) than males. Rat and human liver microsomes exhibited biphasic kinetics (consistent with the involvement of low-affinity and high-affinity enzymes) while incubations with mouse liver microsomes were monophasic. Reported plasma and urinary elimination half-lives of oxidative metabolites were shorter in rodents than in humans.

As with oxidative metabolism, *in vitro* studies of GSH conjugation of trichloroethylene in mice, rats, and humans show considerable intra- and interspecies variability. Conjugation rates also differed by several orders of magnitude between laboratories. The reasons for the discrepancies have not been fully resolved, thus, there is considerable uncertainty in quantitative estimates

associated with this pathway. Most *in vitro* studies with subcellular fractions from the liver and kidney showed that two kinetically distinct processes (high affinity and low affinity) were involved in GSH conjugation of trichloroethylene. One study reported that the rate of GSH conjugation spanned a range of 2.4-fold in human liver cytosol and 6.5-fold in microsomes. The activities of two important enzymes in this pathway (GGT and β-lyase) were higher in rat kidney cytosol than in mice or humans; however, the rate of DCVG formation was higher in mouse liver and kidney subcellular fractions than in rats. Although oxidation clearly is the predominant metabolic pathway, the range of *in vitro* kinetic estimates for the two pathways showed substantial overlap and indicated that the total flux through the GSH pathway was higher than estimates derived solely from urinary metabolites.

# 2 Genetic and related effects

This section addresses genetic and related biological adverse effects that are possibly involved in the mode of action of trichloroethylene-induced carcinogenicity. Genotoxicity is well recognized as a characteristic of many carcinogenic chemicals and a key event for many malignant diseases. The mechanistic implications of these genotoxic effects are discussed in subsequent sections.

Trichloroethylene has been tested in short-term assays to evaluate mutagenicity and other potential genotoxic effects. The data presented in Section 2 are a compilation of evidence in studies available from authoritative reviews (IARC 1995, 2014; EPA 2011a; NRC 2006, IARC 2014) as well as a few recently published primary peer-reviewed articles. Trichloroethylene is often stabilized using a number of different chemicals, such as epichlorohydrin or 1,2-epoxybutane (both of which are potent mutagens); the presence of these stabilizers and/or the purity of trichloroethylene test substance are noted if that information is available.

While many variables in experimental design can affect the results of studies and create apparent discrepancies in responses for the same endpoint, two in particular are pertinent to trichloroethylene exposures. Trichloroethylene is a volatile liquid and, therefore, can be administered to test systems in liquid solution or in the vapor phase. Both liquid and vapor administration have been used in the studies reviewed and this may account for some discrepancies where results are mixed for certain endpoints. In addition, trichloroethylene is highly metabolized and trichloroethylene metabolites appear to be responsible for many of the biological effects reported. A wide variety of activation systems were used in the reviewed studies, including exogenous liver microsome preparations, metabolically competent cells lines, and induced and uninduced primary cells from liver, kidney, blood, and embryos. Mixed results may be a consequence of incomplete activation with some of the systems used. Moreover, in a few cases a requirement for metabolic activation was not observed, as trichloroethylene induced micronuclei and SCE in cultured CHO cells without the addition of exogenous metabolic activation (Wang *et al.* 2001, Galloway *et al.* 1987). Another potential cause for differences in results between studies includes cytotoxicity or other physiological changes to the test organism, which can affect results but is not always measured and/or reported. Finally, consideration of the positive or negative result should be based on the study design and reporting; for example, an impure test sample could result in a positive result due to contamination.

## 2.1 *In vitro* studies in bacteria

Most studies of mutagenicity in bacteria reported negative results using various standard *Salmonella typhimurium* tester strains, including TA97, TA98, TA100, TA1535, and TA1537. Trichloroethylene without stabilizers (high purity) induced a slight, but reproducible, response in a few studies, but only in TA100 with the addition of exogenous metabolic activation (S9); no response was noted in any other strain either with or without S9. Some mutagenic activity was reported in multiple *Salmonella* strains when impure trichloroethylene or trichloroethylene with stabilizers was used as the test agent. One study reported a mutagenic response but only at high levels of toxicity. A study utilizing a *Salmonella* strain competent in CYP2E1 metabolism (Emmert *et al.* 2006) reported mutagenic effects and there was a low-level (two-fold) response at a single locus ($arg_{56}$) observed in an assay using *E. coli* K12 (Greim *et al.* 1975). The results of

the latter study were considered inconclusive, however, due to the lack of information on reproducibility and dose response.

Mutagenicity studies of trichloroethylene in wastewater suggest that the parent compound or its metabolites interact with other chemicals present to enhance the genotoxicity of complex mixtures. In a study by Tabrez and Ahmad (2012), wastewater samples contaminated with trichloroethylene from two sites were mutagenic in an Ames fluctuation assay using *S. typhimurium* strains TA98 and TA100; concentrations of trichloroethylene were determined by gas chromatography analysis to be 28.4 and 8.97 mg/L. The authors reported that exposure to trichloroethylene alone at concentrations up to 1,000 mg/L in did not induce mutations. However, there was a significant increase in mutant induction when the wastewater samples plus 100 mg/L trichloroethylene (purity not reported) were tested, both with and without S9 activation. No determination of cytotoxicity was reported in this study.

Results from *in vitro* studies of trichloroethylene mutagenicity in bacteria are summarized in Appendix C, Table C-1.

### 2.2 *In vitro* studies in non-mammalian eukaryotes

Overall, there is limited evidence for genotoxic activity of trichloroethylene in fungi, and possibly plants, and this activity in most likely mediated by its metabolites. In fungi, trichloroethylene has been evaluated for gene mutation, conversion, and recombination, as well as mitotic segregation and aneuploidy. Trichloroethylene induced mutations only in actively growing cultures of the mold *Aspergillus nidulans*, indicating a requirement for metabolic activation (Crebelli *et al.* 1985). Studies in yeast *Saccharomyces cerevisiae* strains D4 and/or D7 demonstrated increased frequencies of gene conversion, recombination, or point mutation, but only in the presence of an S9 metabolic activation system, while one study reported no effects of trichloroethylene in the yeast in the presence or absence of S9 (Bronzetti *et al.* 1980, Callen *et al.* 1980, Koch *et al.* 1988). Trichloroethylene was not mutagenic in the yeast *Schizosaccharomyces pombe*, either with or without S9 activation, nor in a host-mediated assay in both uninduced and phenobarbital/benzoflavone-induced mice (Rossi *et al.* 1983).

In the study of wastewater genotoxicity described above, wastewater samples alone also induced a significant rise in chromosomal aberrations in the *Allium cepa* (onion) bulb genotoxicity test. Wastewater samples spiked with 100 mg/L trichloroethylene (purity not reported) increased the frequency of chromosomal aberrations. Since there was no effect of trichloroethylene exposure alone at up to 1,000 mg/L, this suggests that trichloroethylene and/or its metabolites might have interacted with chemicals present in the wastewater to enhance the genotoxicity. No determination of cytotoxicity was reported in this study (Tabrez and Ahmad 2012).

Results of mutagenicity in studies of non-mammalian eukaryotes are summarized in Appendix C, Table C-2.

### 2.3 *In vitro* studies in mammalian cells

Several studies have examined the potential for trichloroethylene-induced genotoxicity in mammalian systems *in vitro*.

Trichloroethylene exposure induced micronucleus formation and DNA strand breaks in primary cultures of rat and human kidney cells and in the human hepatoma HepG2 cell line (Robbiano *et al.* 2004, Hu *et al.* 2008). There was also a significant increase in micronuclei in Chinese hamster ovary (CHO) $K_1$ cells treated with trichloroethylene (Wang *et al.* 2001). A mutagenic effect was observed in mouse lymphoma cells (in the presence, but not absence, of exogenous metabolic activation S9); however, mutant induction was not reported in trichloroethylene-treated human TK6 cells, with or without S9 (Caspary *et al.* 1988).

*In vitro* trichloroethylene exposure increased the frequency of sister chromatid exchange (SCE) in mammalian cells in two of three studies reported; a short exposure time and limited dose levels, plus lack of a positive control, limits the interpretation of the results of the third study (Galloway *et al.* 1987, Gu *et al.* 1981, White *et al.* 1979). Results were mixed for trichloroethylene induction of unscheduled DNA synthesis (UDS); they were negative in rat and mouse hepatocytes except for those studies in which the purity of the test sample of trichloroethylene was unknown or reported to contain stabilizers. Cell transformation was induced by trichloroethylene in BALB/c-3T3, rat embryo cells, and Syrian hamster embryo cells (Tu *et al.* 1985, Amacher and Zelljadt 1983, Price *et al.* 1978) but did not induce chromosome aberrations in Chinese hamster ovary or lung cells or in human lymphocytes (Galloway *et al.* 1987, Sofuni *et al.* 1985, Kumar *et al.* 2009).

Kumar *et al*. 2009 evaluated the relationship of polymorphisms in several metabolism genes (CYP1A1, GSTM1, GSTT1, and GSTP1) and micronuclei and chromosomal formation by exposing lymphocytes from subjects with varying polymorphisms to trichloroethylene *in vitro*. Micronucleus formation and chromosomal aberrations were not increased irrespective of genotype (except for a few cases with high trichloroethylene concentrations) and no differences were observed according to genotype status.

Results of studies evaluating trichloroethylene genotoxicity in mammalian systems *in vitro* are summarized in Appendix C, Table C-3.

## 2.4 Nucleic acid and protein binding

Binding of trichloroethylene to nucleic acids and proteins has been studied in cell-free systems and *in vivo* in rodents. Trichloroethylene exposure results in binding to nucleic acids and protein and is likely dependent on metabolite formation, with mouse microsomes inducing a higher level of binding than rat microsomes. Incubation with $^{14}C$-labeled trichloroethylene resulted in covalent binding to salmon sperm DNA (Banerjee and Van Duuren 1978), calf thymus DNA (DiRenzo *et al.* 1982), and microsomal proteins from several mouse organs (Banerjee and Van Duuren 1978). Binding to both DNA and protein was enhanced when microsomes from phenobarbital-treated mice or rats were included in the incubations. Studies *in vivo* demonstrated binding to DNA, RNA, and proteins in both mice and rats following trichloroethylene administration. However, in one study, the detected radioactivity in DNA was due to metabolic incorporation of $^{14}C$ directly into nucleic acids, especially guanine and adenine, rather than adduct formation.

Trichloroethylene metabolism appears to be a factor in the extent of binding that occurs, as demonstrated by the enhanced binding with induced microsomes. Mouse microsomes (Miller and Guengerich 1983), and especially mouse lung microsomes (Mazzullo *et al.* 1992) were more

efficient than rat microsomes at metabolizing trichloroethylene to forms that bind nucleic acid and proteins. Studies examining binding of trichloroethylene metabolites found significant binding of trichloroethylene metabolites to DNA and protein (Miller and Guengerich 1983) and postulated that trichloroethylene oxide, which is formed as an oxidative intermediate in trichloroethylene metabolism in rodent microsomes, is the form that binds most readily to protein, and, to a lesser extent, DNA (Cai and Guengerich 2001). Phenobarbital pretreatment increased the formation of the trichloroethylene metabolites chloral hydrate and trichloroethylene oxide and increased the formation of DNA and protein adducts (Miller and Guengerich 1983).

Studies evaluating the ability of trichloroethylene to bind nucleic acids and protein are summarized in Appendix C, Table C-4.

### 2.5 *In vivo* studies in rodents

Trichloroethylene has been tested for genotoxicity *in vivo* and results were generally in agreement. Overall, there is some evidence that trichloroethylene exposure in rodents can cause DNA strand breaks and micronucleus formation. Studies on other endpoints were mainly negative.

Trichloroethylene caused strand breaks in liver in a study in rats and in two of three studies in mice; findings in kidney were positive in the mouse but inconsistent in the rat (Nelson and Bull 1988, Walles 1986, Parchmna and Magee 1982, Clay *et al.* 2008). Robbiano *et al.* (2004) reported positive findings in the rat kidney after exposure by intraperitoneal injection using trichloroethylene without stabilizer; however, no increase in strand breaks was observed after inhalation exposure using trichloroethylene of unknown purity (Clay *et al.* 2008).

Trichloroethylene exposure *in vivo* induced micronucleus formation in rat kidney cells (Robbiano *et al.* 2004), in bone-marrow erythrocytes in two of three studies in the mouse (Duprat and Gradiski 1980, Hrelia *et al.* 1994, Shelby *et al.* 1993), and in one of two studies in the rat (Kligerman *et al.* 1994, Wilmer *et al.* 2014). Trichloroethylene exposure did not increase micronucleus formation in mouse splenocytes or spermatocytes or in rat peripheral blood lymphocytes. Trichloroethylene did not induce mutations, chromosome aberrations, or UDS in any studies.

Results of studies evaluating trichloroethylene genotoxicity *in vivo* in rodents are summarized in Appendix C, Table C-5.

### 2.6 Studies in exposed human populations

There are a few studies that have examined cytogenetic endpoints in peripheral blood lymphocytes of trichloroethylene-exposed human populations, including one that evaluated chromosomal aberrations and three that measured SCEs. In addition, there are several case-control studies of renal-cell cancer that evaluated mutations in the von Hippel-Lindau (*VHL*) gene of trichloroethylene-exposed workers (see Section 4.2.2.1 and Table 4-5).

The available cytogenetic studies were limited by small numbers of exposed workers. In a group of Danish workers, Rasmussen *et al.* (1988) found statistically significant increases in chromosomal aberrations among 15 metal degreasers exposed to trichloroethylene for greater

than 20 hours per week. Conflicting findings were described for SCE induction. Although Gu *et al.* 1982 measured a statistically significant increase in SCE in 6 exposed workers, none was reported in a somewhat larger study of trichloroethylene-exposed workers (22) from Japan (Nagaya *et al.* 1989). Another study in Japan found statistically significant increases in SCE among male smokers but not among male or female non-smokers; smoking was not independently related to SCE in the study (Seiji *et al.* 1990).

Studies of the *VHL* mutation in workers occupationally exposed to trichloroethylene and diagnosed with renal-cell carcinomas are review in Section 4.2

Results of cytogenetic effects in studies on exposed workers are summarized in Appendix C, Table C-6.

## 2.7 Genotoxic effects of the metabolites of trichloroethylene

The metabolites of trichloroethylene have been tested in short-term assays to evaluate mutagenicity and other potential genotoxic effects. This section provides a summary of the available information from authoritative reviews (IARC 2014 and EPA 2011a) on several metabolites, including trichloroacetic acid (TCA), dichloroacetic acid (DCA), chloral hydrate (CH), *S*-(1,2-dichlorovinyl)-L-cysteine (DCVC), *S*-(1,2-dichlorovinyl)glutathione (DCVG), and trichloroethanol (TCOH).

Results on the genotoxic effects of trichloroethylene metabolites are summarized in Table 2.1

### 2.7.1 Trichloroacetic acid (TCA)

TCA was consistently reported as non-mutagenic in bacterial assays, both with and without exogenous metabolic activation (S9). Results from studies in mammalian cells *in vitro* and *in vivo* were mostly negative but there was some evidence that TCA could induce chromosomal damage.

TCA was tested for mutation in bacterial systems by numerous investigators, with only two studies reporting a positive response. TCA induced mutation in assays using *S. typhimurium* TA1535 with metabolic activation in an SOS DNA repair assay and in strain TA100, both with and without metabolic activation using a fluctuation assay (Giller *et al.* 1997, Ono *et al.* 1991). However, TCA did not induce mutations (with or without S9) in *S. typhimurium* reverse mutation assays, using standard or special tester strains or protocols, nor in a lambda prophage assay in *E. coli*. The acidity of TCA is an important consideration in evaluating *in vitro* test results. A report of increased chromosomal aberrations in cultured human peripheral lymphocytes exposed to TCA was considered by the authors related to a treatment-induced reduction in pH, rather than due to direct genotoxic action of the TCA (MacKay *et al.* 1995). One of two studies of gene mutation in cultured mammalian cells reported a weak mutagenic effect ( with the addition of S9) but both studies reported high cytotoxicity (Harrington-Brock *et al.* 1998, Zhang *et al.* 2010). TCA did not induce strand breaks in CHO cells, as measured by the comet assay (Plewa *et al.* 2002, 2010).

Recent studies in cultured human cells provide evidence that TCA causes chromosomal and DNA damage. Varshney *et al.* reported increased micronucleus frequency (2013a) and chromosomal aberrations (2013b) in human peripheral blood lymphocytes. TCA also induced

dose-related increases in DNA strand breaks as measured by the comet assay in human HepG2 liver carcinoma cells (Zhang *et al.* 2012).

*In vivo* studies to evaluate potential effects of TCA exposure report conflicting results for micronucleus induction and DNA single-strand breaks. TCA induced micronucleus formation in the bone marrow of mice and chickens but not in bone-marrow erythrocytes of male or female C57BL/6JfBL10/Alpk mice (Bhunya and Behera 1987, Bhunya and Jena 1996, Mackay *et al.* 1995). TCA induced dose-dependent increases in single-strand breaks in both mice and rats in liver cells in a study by Nelson and Bull (1988) but subsequent studies failed to confirm this finding (Nelson *et al.* 1989) even in the presence of liver growth induction (Styles *et al.* 1991). TCA did not induce DNA single-strand breaks in $B6C3F_1$ mice nor in F344 rats following a single treatment by oral gavage (Chang *et al.* 1992).

### 2.7.2 Dichloroacetic acid (DCA)

DCA induced mutations and DNA damage *in vitro* in some studies and was active both with and without metabolic activation. Exposure to DCA consistently gave positive results *in vivo*.

DCA was mutagenic in the bacteria *S. typhimurium* tester strains TA98 and TA100 in some studies, both with and without the addition of metabolic activation, but was consistently not mutagenic in all other strains nor in *E. coli* WP2 *uvrA* (DeMarini *et al.* 1994, Giller *et al.* 1997, Kargalioglu *et al.* 2002). Analysis of mutation spectra in TA100 indicates that DCA induces primarily GC-AT transitions in this strain. DCA also induced prophage (DeMarini *et al.* 1994) and weakly induced SOS repair (Giller *et al.* 1997) in *E. coli*.

Exposure to DCA *in vitro* resulted in statistically significant increases in HGPRT mutant frequency in $CHOK_1$ cells at a single concentration (1000 µM); it was cytotoxic at higher doses (Zhang *et al.* 2010). Harrington-Brock *et al.* (1998) reported dose-related increases in TK locus mutations and chromosomal aberrations in mouse lymphoma L5178Y/$TK^{\pm}$-3.7.2C cells treated with DCA. In contrast, Fox *et al*. (1996) found no evidence for elevated mutation levels in mouse lymphoma cells nor increased chromosomal aberrations in CHO cells after exposure to DCA. There were conflicting results for DCA-induced micronucleus formation, a significant increase in micronuclei was reported in human peripheral blood lymphocyte but not in mouse lymphoma cells (Varshney *et al.* 2013a, Harrington-Brock *et al.* 1998). Zhang *et al.* (2012) reported that DCA induced a dose-related increase in DNA damage by the comet assay after four hours of exposure in human HepG2 cells. However, treatment with DCA did not induce DNA strand breaks in cultured primary rat or mouse hepatocytes or in human CCRF-CEM lymphoblastoid cells in the DNA unwinding assay (Chang *et al.* 1992) nor in CHO or CHO-AS52 cells in the comet assay (Plewa *et al.* 2002, 2010).

*In vivo*, DCA administered in drinking water induced *lacI* mutations in $B6C3F_1$ transgenic mice in a dose-related manner at 60 weeks; the induced mutations were 33% GC-AT transitions and 21% GC-TA transversions. Fuscoe *et al.* (1996) reported increased micronucleus frequency in peripheral PCEs of male $B6C3F_1$ mice following subchronic (9 days) or chronic (> 10 weeks) exposure to DCA, but not after a 28-day exposure. Several studies have evaluated DCA for induction of single-strand breaks, with conflicting results. Nelson and Bull (1988) and Nelson *et al.* (1989) reported increased DNA strand breaks by alkaline unwinding in livers of both mice

and rats exposed to DCA for 4 hours. DCA also induced DNA strand breaks, alkali-labile sites, and crosslinking in blood leukocytes of male B6C3F$_1$ mice (Fuscoe *et al.* 1996). However, Chang *et al.* (1992) found no evidence for DNA strand breaks in male rat liver and male mouse liver, spleen, and intestinal epithelium.

### 2.7.3 Chloral hydrate (CH)

CH was positive for most of the endpoints tested *in vitro*, including mutation and DNA and chromosomal damage, regardless of the presence or absence of metabolic activation S9; however, test results for experiments *in vivo* were inconsistent.

In bacteria, CH exposure induced mutants in tester strains TA100 and TA104, with and without metabolic activation; results in other strains were negative. In the fungi *Aspergillus nidulans*, CH exposure caused aneuploidy and nondisjunction but not mitotic crossover (Crebelli *et al.* 1991, Kafer 1986, Kappas 1989). CH induced disomy and mitotic malsegregation in the yeast *S. cerevisiae* and was positive for wing-spot mutations, but negative for sex-linked lethal mutations, in *Drosophila melanogaster* ((Albertini 1990, Sora and Agostini Carbone 1987, Zordan *et al.* 1994, Beland 1999).

*In vitro* exposure to CH resulted in increased SCEs, chromosomal aberrations, cell transformation, aneuploidy, and micronuclei induction. The micronuclei were consistently kinetochore positive, indicating that they formed from whole chromosomes or larger chromosome segments rather than from chromosome fragments (Degrassi and Tanzarella 1988, Lynch and Parry 1993, Parry *et al.* 1990). CH was reported negative for the formation of DNA-protein crosslinks in rat liver nuclei and did not induce DNA single-strand breaks in rat primary hepatocytes (Keller and Heck 1988, Chang *et al.* 1992).

Results of *in vivo* studies of genotoxicity following exposure to CH were limited by few studies for some endpoints and inconsistent results for others. CH induced DNA single-strand breaks in both mouse and rat liver in one study (Nelson and Bull 1988), but not in another (Chang *et al.* 1992). CH increased the frequency of micronucleus formation in sperm and/or blood cells in rodents in many, but not all, studies. A single assay in human infants following administration of CH as a sedative prior to a hearing test reported a significant increase in micronuclei and SCE frequencies in peripheral blood lymphocytes (Ikbal *et al.* 2004). CH induced chromosomal aberrations in sperm cells in a single study (Russo *et al.* 1984), but was negative in several other studies. Aneuploidy was observed in mouse blood or sperm cells in two of the four studies reported.

A few studies have examined DNA binding of CH and adduct formation in CH-exposed tissues and DNA. Keller *et al.* 1988 demonstrated that protein from [$^{14}$C] chloral-treated rat liver nuclei had a concentration-related binding of [$^{14}$C], but did not observe DNA adducts. Studies have demonstrated an increase in malondialdehyde-derived DNA adducts and an increase in the levels of 8-oxoguanine adducts in livers of CH-exposed mice, as well as increased CH adducts in calf thymus DNA (Ni *et al.* 1995, Von Tungeln *et al.* 2002).

DNA single-strand breaks in human lymphoblast TK6 cells were induced after CH exposure *in vitro*, as measured by the comet assay, but there were no increases in micronucleus formation in peripheral human lymphocytes or TK6 cells (Liviac *et al.* 2010) or mutations in L5178Y/*TK*$^{\pm}$-

3.7.2C cells (Liviac *et al.* 2010, 2011). An increase in cytotoxicity, but not micronucleus induction, was noted in human peripheral lymphocytes after a 48-hour exposure to 25, 50, or 100 µg/mL of CH (Varshney *et al.* 2013a). CH was cytotoxic but did not result in DNA damage in the comet assay after 4-hour exposure up to 100 µM in HepG2 cells (Zhang *et al.* 2012).

#### 2.7.4 *S*-(1,2-dichlorovinyl)-L-cysteine (DCVC), *S*-(1,2-dichlorovinyl)glutathione (DCVG), and trichloroethanol (TCOH)

The number of studies evaluating the genotoxic effects of other trichloroethylene metabolites is limited. DCVC and DCVG are cysteine intermediates of trichloroethylene formed during metabolic conjugation by glutathione-S-transferase; TCOH has been identified as another metabolite of trichloroethylene. DCVC has consistently shown genotoxic effects but there are very few studies on the genotoxicity of DCVG and TCOH. DCVC and DCVG were positive in most *in vitro* and *in vivo* tests. TCOH was negative in all bacterial mutagenicity tests without exogenous metabolic activation S9, but it did increase mutant frequency in the presence of S9 at a dose > 2,500 µg/plate. It has not been evaluated in other assays.

DCVC and DCVG were positive for mutation induction in bacterial assays. Both intermediates were direct acting, i.e., induced mutations without the addition of metabolic activation, but the response was increased with the addition of kidney-derived activation systems. Additionally, the response was diminished by addition of a beta-lyase inhibitor, suggesting that beta-lyase bioactivation plays a role in the genotoxicity. DCVC induced DNA strand breaks, UDS, and increased cell transformation in a variety of cell types, including rodent kidney cells exposed both *in vitro* and *in vivo*. DCVC was mutagenic in *S. typhimurium* strain TA100 using the pre-incubation method and it induced micronucleus formation in human peripheral blood lymphocytes (Irving and Elfarra 2013, Varshney *et al.* 2013a). Studies have shown that DCVC forms covalent adducts *in vitro* with DNA and protein adducts *in vitro* and *in vivo* (Muller *et al.* 1998, Hayden *et al.* 1992, Eyre *et al.* 1995).

### 2.8 Summary of the genetic effects from trichloroethylene and its metabolites

Overall, trichloroethylene genotoxicity is caused by its metabolites. A table of summary assessments of the genotoxicity studies for trichloroethylene and its metabolites (primarily from authoritative reviews by EPA (2011a) and IARC (2014) and as discussed in this document) is provided in Table 2-1.The assessment for each endpoint in this table takes into account all the information currently available, including consideration of any methodological and/or purity issues, to provide an overall evaluation.

Mutagenicity and other genotoxic effects reported for trichloroethylene exposure *in vitro* are likely due primarily to its metabolites. For some assay results, positive findings might have been due to impurities or chemical stabilizers present in the test sample, and this was considered for the overall evaluation in Table 2-1. For example, there is little evidence that trichloroethylene is mutagenic in bacteria, and most positive findings were in the presence of mutagenic stabilizers. Trichloroethylene exposure to rodent and human cells *in vitro* induced several genotoxic effects, including micronuclei, SCE, and DNA strand breakage. Trichloroethylene was mutagenic in the mouse lymphoma assay only with the addition of metabolic activation.

There is some evidence that *in vivo* trichloroethylene exposure in rodents can induce DNA strand breaks and micronucleus formation. However, studies evaluating induction of mutation, chromosomal aberration, sister chromatid exchange, and UDS were negative.

Trichloroethylene covalently binds *in vitro* to mammalian DNA – including calf thymus, rodent, and salmon sperm DNA – and binds to proteins from several tissues of rodents and humans. Binding to DNA and protein was enhanced by metabolic activation (e.g., prepared from liver microsomes from phenobarbital-treated rodents). In addition, microsomes from the mouse induced greater total binding than those from the rat in the same study. *In vivo* experiments with trichloroethylene reported DNA binding in the liver, kidney, lung, and stomach in both rats and mice.

Metabolites of trichloroethylene resulting from both the glutathione S-transferase (GST) and oxidative pathways have been shown to induce genotoxic effects. The GST metabolite DCVG may be formed in the kidney as well as the liver; DCVC is formed in the kidney. Both are mutagenic in bacterial assays; notably there was an increased mutagenic response with the addition of kidney-derived microsomal metabolic activation. DCVC also induced gene mutation, DNA strand breaks, UDS, and increased cell transformation in a variety of cell types, including rodent kidney cells, both *in vitro* and in *vivo.* Other metabolites formed in the liver that are genotoxic include CH, DCA, and possibly TCA. The most active metabolite of these is chloral hydrate, which induced sister chromatid exchange, chromosomal aberrations, and cell transformation *in vitro*. Test results showed that CH is direct acting, i.e., similar effects were observed in the *in vitro* assays with or without the addition of metabolic activation. DCA was mutagenic and induced DNA repair (UDS); there was limited evidence that it induced DNA strand breaks and micronuclei, and possibly chromosomal aberrations. For TCA, the numbers of studies was limited but were positive for micronuclei induction *in vitro*, showed increased chromosomal aberrations DNA binding *in vivo*, but TCA was not mutagenic.

**Table 2-1. Summary assessment of genotoxicity for trichloroethylene and its metabolites[a]**

| TCE or Metabolite Endpoint | Summary of findings across studies | | |
|---|---|---|---|
| | *In vitro* (–S9) | *In vitro* (+S9) | *In vivo* |
| **TCE** | | | |
| Gene mutation | – | (–) | – |
| Gene conversion | – | ± | NT |
| Aneuploidy | + | + | |
| Recombination/gene crossover | – | (+) | |
| DNA strand break | + | NT | ± |
| UDS (DNA repair) | (–) | NT | – |
| Chromosomal aberrations | – | – | – |
| Sister chromatid exchange | + | ± | – |
| Micronucleus induction | + | NT | (+) |
| Cell transformation | ± | NT | NT |
| DNA binding | ± | + | (–) |
| Protein binding | + | NT | + |
| **TCA** | | | |
| Gene mutation | – | (–) | NT |
| DNA strand break | (–) | NT | ± |
| DNA damage (comet assay) | – | NT | NT |
| Chromosomal aberrations | ± | NT | + |
| Micronucleus induction | + | NT | ± |
| Protein binding | NT | NT | + |
| **DCA** | | | |
| Gene mutation | (+) | (+) | + |
| Aneuploidy | – | NT | NT |
| DNA strand break | – | – | (–) |
| UDS (DNA repair) | + | ± | NT |
| Chromosomal aberrations | ± | NT | NT |
| Micronucleus induction | ± | NT | (–) |
| **CH** | | | |
| Gene mutation | + | + | NT |
| Non-disjunction | + | NT | NT |
| Aneuploidy/polyploidy | + | NT | ± |
| Gene crossover | – | NT | NT |
| DNA strand break | – | NT | ± |
| DNA damage (comet assay) | + | NT | NT |

| TCE or Metabolite Endpoint | Summary of findings across studies | | |
|---|---|---|---|
| | *In vitro* (–S9) | *In vitro* (+S9) | *In vivo* |
| Chromosomal aberrations | + | + | (–) |
| Sister chromatid exchange | + | + | + |
| Micronucleus induction | (+) | – | (+) |
| Cell transformation | + | NT | NT |
| DNA binding | – | NT | – |
| DNA-protein crosslinks | – | NT | NT |
| **DCVC/DCVG** | | | |
| Gene mutation | + | + | NT |
| Mutation (loss of heterozygosity) | – | NT | NT |
| DNA strand break | + | + | ± |
| UDS (DNA repair) | + | NT | NT |
| Micronucleus induction | – | NT | NT |
| Cell transformation | + | NT | NT |
| Gene expression | + | NT | NT |
| DNA binding | + | NT | NT |
| Protein binding | + | NT | + |

Sources: IARC (2014) and EPA (2011a); summary calls include data from Tabrez and Ahmad (2012); Varshney *et al.* (2013a) and Zhang *et al.* (2012), for specific assays described in the text.

[a]Range of study assessment calls:

| | |
|---|---|
| Positive | + |
| Probably positive | (+) |
| Equivocal/mixed results | ± |
| Probably negative | (-) |
| Negative | - |

Summary calls for each endpoint were determined by integrating the findings across studies and considering methodological and/or purity issues. Rationale for conclusions is provided in the text above.

NT = not tested.

To return to text citing Table 2-1, click here.

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# 3 Human Cancer Studies

## Introduction

The cancer hazard evaluation of trichloroethylene focuses on three specific cancers: kidney, liver, and NHL and its histological subtypes and related cancers, and is discussed in Sections 4.1 (kidney), 5.1 (NHL), and 6.1 (liver). (For rationale, see Background and Methods of the monograph and the Protocol: Methods for Preparing the Draft Report on Carcinogens Monograph on Trichloroethylene ("Trichloroethylene Protocol") (http://ntp.niehs.nih.gov/NTP/roc/thirteenth/Protocols/TCE_Protocol12-31-13_508.pdf). Because many studies (primarily the cohort studies) are common for all these cancer sites, this section provides information on the studies that are relevant for cancer hazard evaluation, including an overview of the studies' methods and characteristics and an assessment of the studies' ability to inform the cancer evaluation. The steps in the cancer hazard evaluation, including the location of the discussion of these steps, are listed below.

1. Selection of the relevant literature included in the cancer evaluation (Section 3.1 and Trichloroethylene Protocol)
2. Description of the study methods and characteristics and evaluation of study quality: Cohort studies (Section 3.2, Appendix D, Tables D-1 and D-4a,b), kidney and liver case-control studies (Section 3.3, Appendix D, Tables D-2 and D-5 a,b), and NHL case-control studies (Section 3.4, Appendix D, Tables D-3 and D-6 a,b).
3. Cancer assessment: Kidney (Section 4.1), NHL and its subtypes (Section 5.1), and liver (Section 6.1).
4. Preliminary recommendation for the level of evidence of carcinogenicity (sufficient, limited, or inadequate) of trichloroethylene from human studies (Section 7).

### 3.1 Literature search strategy and selection of the relevant literature

The literature search strategy (including the databases and search terms, and other sources for identifying literature) and procedures for selecting the literature (systematic screening procedures and inclusion/exclusion criteria) are described in detail in the Protocol. Primary epidemiological studies were considered for the cancer evaluation if the study was peer reviewed, provided risk estimates (or information to calculate risk estimates) for trichloroethylene and human cancer (kidney, liver, or NHL), and provided information specific for trichloroethylene exposure at the individual level or an estimate of the proportion of exposed subjects in defined exposure groups. Studies of dry cleaners and laundry workers were excluded, as the extent of exposure to trichloroethylene is often unclear and indistinguishable from tetrachloroethylene, or other petroleum-derived solvents such as carbon tetrachloride (NRC 2006). In general, cohort or case-control studies of populations with jobs, workplaces or environmental exposures in which trichloroethylene exposure may have occurred (e.g., studies of grouped chlorinated or organic solvents, degreasing agents, metal cleaners, or jobs and occupations such as degreasing, metalworking, painting, electronics manufacturing, aircraft manufacturing) were excluded if a specific risk estimate for trichloroethylene exposure was not reported as noted above, although several were included in one or more reviews or meta-analyses of trichloroethylene (Asal *et al.* 1988, Garabrant *et al.* 1988, Harrington *et al.* 1989, Costa *et al.* 1989, Selden and Ahlborg 1991,

Sinks *et al.* 1992, Chang *et al.* 2003). In addition, descriptive studies (with no risk estimate) and geographic studies were also excluded, again because these studies were unlikely to be specific for trichloroethylene exposure, with the exception of one drinking water study (Bove *et al.* 2014). This study was included because it identified an exposed cohort and assigned individual exposure based on the household drinking water level of trichloroethylene (rather than the township level), which increased the likelihood for ever exposure to trichloroethylene.

## 3.2 Cohort Studies

### 3.2.1 Overview of the methodologies and study characteristics

Table 3.1 lists the 16 occupational cohort studies, nested case-control studies, or pooled analyses that satisfied the inclusion criteria. In general, the list includes only the latest update of the study or the most comprehensive report on a population; however, additional relevant analyses or information from previous publications are considered in the evaluation. Studies of overlapping publications are included if the overlap is not known and there are differences in methodologies (such as exposure assessment). For each of the reviewed studies, detailed data on study design, methods, and findings were systematically extracted from relevant publications, as described in the study protocol, into Appendix D Tables D-1 and D-2. The cohort and nested case-control studies can be divided into several broad occupational groups related to the exposure scenarios or occupations. Within each of these groups, studies are generally organized by publication date, although related studies (e.g., similar industries or overlapping populations) are discussed first and kept together.

#### *3.2.1.1 Nordic studies: Three incidence studies*

Several cohort studies reporting on cancer incidence were published among workers in Nordic counties. These studies include subjects with occupational exposure to trichloroethylene from diverse industries, and workers and exposed subjects were identified from broad occupational or population-based databases. Three cohort studies reported on cancer findings among workers who had urinary TCA measurements as part of trichloroethylene monitoring programs in Sweden (Axelson *et al.* 1978, Axelson *et al.* 1994), Finland (Anttila *et al.* 1995), and Denmark (Hansen *et al.* 2001). These workers were included in a pooled analysis reported by Hansen *et al.* (2013), which is reviewed rather than the individual studies because it includes all the workers from the constituent studies and uses a similar exposure assessment (although any additional information from the individual studies will be brought forward). The second cohort study is of blue-collar Danish workers at companies using trichloroethylene (Raaschou-Nielsen *et al.* 2003). Although this study may include a small proportion of workers from the Danish component of the pooled analysis, it is included in the review because the extent of the overlap is unknown, and the exposure assessment is different. The third study (Vlaanderen *et al.* 2013) includes trichloroethylene-exposed workers in the Nordic Occupational Cancer (NOCCA) study, which links occupational data reported in censuses (Sweden, Finland, Denmark, Iceland, and Norway) with their national cancer registries. The census occupational history data were linked to the NOCCA job exposure matrix (JEM) to develop semi-quantitative estimates of exposure to trichloroethylene. This large study may have included some of the same subjects as the other studies, but these were likely a very small percentage.

#### *3.2.1.2 Aerospace (rocket engine) and aircraft manufacturing workers: Five incidence or mortality studies*

Two cohort studies evaluated risk among rocket engine workers with potential exposure to trichloroethylene at the Santa Susana Field Laboratory (SSFL) in California; these studies are part of the Rocketdyne Aerospace workers cohort (Boice *et al.* 2006, Zhao *et al.* 2005). Although there is likely to be considerable overlap between the two studies, both studies are reviewed (noting potential overlap) because of differences in exposure and disease assessments and numbers of exposed workers. Boice *et al.* (2006) reported mortality findings based on a qualitative exposure assessment and Zhao *et al.* (2005) reported both mortality and incidence findings for trichloroethylene-exposed workers (intensity score greater than three) based on a semi-quantitative JEM. Two cohort studies reported mortality findings (Lipworth *et al.* 2011, Morgan *et al.* 1998) and one study (Blair *et al.* 1998/Radican *et al.* 2008) in the United States reported both incidence and mortality for aircraft manufacturing workers with potential exposure to trichloroethylene. Morgan *et al.* (1998) and Radican *et al.* (2008) used a semi-quantitative exposure assessment and Lipworth *et al.* (2011) used a qualitative exposure assessment, all of which assigned exposure using individual work history information and expert-assigned JEMs. All studies conducted both internal and external analyses.

#### *3.2.1.3 Other studies of specific industries: seven incidence or mortality studies*

Two cohort studies (Bahr *et al.* 2011, Ritz 1999) and one nested case-control study (Yiin *et al.* 2009) of uranium processing or enrichment workers which used a JEM and/or individual work histories to classify workers according to ranked exposure levels or probability of exposure, were identified that met the inclusion criteria. Bahr *et al.* (2011) evaluated cancer incidence and mortality among Kentucky uranium enrichment workers, and Ritz (1999) and Yiin *et al.* (2009) evaluated mortality among Ohio and Tennessee uranium processing workers, respectively. The remaining studies consisted of one study in each of several different manufacturing industries using trichloroethylene as a degreaser or solvent. Silver *et al.* (2014) conducted a cohort mortality analysis of New York electronics workers, based on ranked exposure scores. A small cohort study of German cardboard manufacturing workers focusing on renal-cell carcinoma (Henschler *et al.* 1995) assessed exposure using job location at the plant and surveys of plant conditions. Greenland *et al*. (1994) conducted a nested case-control study of lymphoma, and kidney and liver cancer among a cohort of workers at a Massachusetts electrical transformer manufacturing plant, using a qualitative JEM to assess exposure. Finally, Wilcosky *et al*. (1984) reported on a small nested case-control study of NHL and other cancers among a cohort of rubber manufacturing workers in which potential exposure to trichloroethylene was assessed by work in an area where trichloroethylene was authorized for use.

#### *3.2.1.4 Environmental exposure: one mortality study*

In the drinking water study, exposure to trichloroethylene was based on duration at a residence and modeled trichloroethylene concentration levels from the water supply system (Bove *et al.* 2014).

**Table 3-1. Cohort and nested case-control studies of trichloroethylene exposure.**

| Reference | Population | Exposure assessment | Cancer assessment endpoints[a] |
|---|---|---|---|
| **Nordic studies** | | | |
| Hansen *et al.* 2013 | Pooled Nordic biomonitored cohort: diverse occupations<br>N = 5,553 workers | Urine TCA surveillance | Incidence<br>External and internal analyses<br>Kidney, liver, NHL, MM |
| Raaschou-Nielsen *et al.* 2003 | Danish TCE-exposed blue-collar workers cohort: diverse occupations<br>N = 40,049 | Blue-collar workers in TCE-using companies with potential exposure to TCE | Incidence<br>External analysis<br>Kidney, liver, NHL, MM |
| Vlaanderen *et al.* 2013 | NOCCA study<br>Population-based cancer registry and occupational database linkage | Linkage of historical job information from census with national JEMs constructed from occupation data | Incidence<br>Kidney (N = 76,130), liver (N = 896), NHL (N = 69,254), MM (N= 35,534) |
| **Aerospace and aircraft manufacturing workers** | | | |
| Boice *et al.* 2006 | Los Angeles (USA) rocket engine testing workers cohort<br>N = 1,111 | Qualitative JEM | Mortality<br>External and internal analyses<br>Kidney, liver, NHL, MM, CLL |
| Zhao *et al.* 2005 | Los Angeles U(SA) aerospace workers cohort<br>N = 6,044 | Semi-quantitative JEM | Mortality/incidence<br>External and internal analyses<br>Kidney, liver, NHL + leukemia combined |
| Lipworth *et al.* 2011 | Burbank California (USA) aircraft manufacturing workers cohort<br>N = 5,443 | Qualitative JEM | Mortality<br>External and internal analyses<br>Kidney, liver, NHL, MM |
| Radican *et al.* 2008/Blair *et al.* 1998 | Utah (USA) aircraft maintenance workers cohort<br>N= 7,204 | Semi-quantitative JEM | Mortality (Radican)/ incidence (Blair)<br>External and internal analyses<br>Kidney, liver, NHL, MM |
| Morgan *et al.* 1998 | Arizona (USA) aircraft manufacturing workers cohort<br>N = 4,733 | Semi-quantitative JEM | Mortality<br>External and internal analyses<br>NHL, kidney, liver |

| | | | |
|---|---|---|---|
| **Other studies of specific industries** | | | |
| Bahr *et al.* 2011 | Kentucky (USA) uranium enrichment workers cohort<br>N = 4,792 | JEM | Mortality<br>External and internal analyses<br>NHL, liver |
| Yiin *et al.* 2009 | Tennessee (USA) nested case-control study of uranium enrichment workers<br>N = 47,941 cohort; 98 MM cases, 483 controls | Modified semi-quantitative JEM | Mortality<br>MM |
| Ritz 1999 | Ohio (USA) uranium processing workers cohort<br>N = 3,184 | Semi-quantitative JEM | Mortality<br>Internal analyses<br>Liver |
| Silver *et al.* 2014 | New York (USA) micro-electronics manufacturing cohort<br>N = 34,494 | Cumulative exposure ranking | Mortality<br>Internal analyses<br>Kidney, NHL, multiple myeloma, liver, biliary and gallbladder combined |
| Henschler *et al.* 1995 | German cardboard manufacturers cohort<br>N = 169 | Job location from individual work histories and knowledge of plant conditions. | Incidence<br>External and internal analyses<br>Kidney |
| Greenland *et al.* 1994 | Massachusetts (USA) nested case-control study of electrical manufacturers cohort<br>N = 1,821 cohort; 512 cancer deaths; 1,202 non-cancer deaths (controls) | Qualitative JEM | Mortality<br>Kidney (N =12),<br>liver (N =9),<br>lymphoma (N = 15) |
| Wilcosky *et al.* 1984 | Ohio (USA) nested case-control study of rubber manufacturing workers cohort<br>N = 6,678 cohort (controls 20% sampling) | Working in area of authorized use of specific solvents | Mortality<br>NHL (N = 9) |
| **Environmental exposure** | | | |
| Bove *et al.* 2014 | North Carolina (USA) military cohort<br>Drinking water study<br>N =154,932 | Duration of residence and modeled TCA concentration. | Mortality<br>External and internal analyses<br>NHL, kidney, liver |

CLL = chronic lymphocytic leukemia; JEM = job-exposure matrix; MM = multiple myeloma; NHL = non-Hodgkin lymphoma.

[a]Cancer endpoints of *a priori* interest only (kidney cancer, liver cancer, and NHL and its subtypes).

### 3.2.2 Evaluation of study quality and other information

This section discusses the assessment of study quality across individual studies and the utility of these studies to inform the evaluation of the potential effects of exposure to trichloroethylene and cancer endpoints. Each study was assessed (prior to evaluating the findings) for the potential for biases and other factors related to informing hazard identification according to the approach for evaluating study quality described in the protocol. (See Appendix D, Tables D-4a,b for a study-by-study assessment of potential for bias, study quality and study sensitivity.) The impact on study quality of a number of these factors, for example the analysis of cancer incidence vs. mortality, the length of follow-up, the potential for disease misclassification and the statistical power of the study, may differ according to the specific cancer endpoint being evaluated (kidney cancer, liver cancer, and NHL and its subtypes), and will be discussed separately where relevant.

#### *3.2.2.1 Selection bias*

The potential for selection bias was considered unlikely in the majority of cohort or nested case-control studies (Bove *et al.* 2014, Hansen *et al.* 2013, Lipworth *et al.* 2011, Morgan *et al.* 1998, Radican *et al.* 2008/Blair *et al.* 1998, Vlaanderen *et al.* 2013, Wilcosky *et al.* 1984, Zhao *et al.* 2005). There was the potential for bias (without consideration of a healthy worker effect) in the following studies. The German cardboard manufacturing cohort (Henschler *et al.* 1995) was initiated because of a cluster of renal cancers and included the index cases in their cohort analysis (Bloemen and Tomenson 1995, Swaen 1995, NRC 2006), which would result in an over-estimate of the risk estimate. In two of the uranium workers cohorts (Ritz 1999, Yiin *et al.* 2009), workers were selected based on having radiation monitoring data, which may result in selection bias (if trichloroethylene exposed workers without monitoring data were excluded) and potential confounding. In the nested case-control study of electrical workers by Greenland *et al.* (1994), the cohort was selected from workers participating in the pension scheme, introducing potential selection bias. In addition, the blue-collar workers included in the Nordic study by Raaschou-Nielsen *et al.* (2003) differed with respect to socioeconomic status from the referent (general) population, which may result in an over- or underestimate of expected cases, depending on the endpoint. Little information was provided to evaluate how workers were selected or excluded in the study of Kentucky uranium enrichment workers (Bahr *et al.* 2011).

There was evidence of a possible healthy worker effect in five studies, based on statistically significant decreases in all-cause mortality rates: the aerospace worker study reported by Boice *et al.* (2006), two aircraft manufacturing studies (Morgan *et al.* 1998, Lipworth *et al.* 2011), and two studies of uranium workers (Bahr *et al.* 2011, Ritz 1999) and the micro-electronic study (Silver *et al.* 2014). A healthy worker effect would bias the findings towards the null. There was also evidence for a healthy worker survival effect in the study by Bahr *et al.* (2011), which would also bias internal analyses. In addition, three of the cohorts are relatively young (Raaschou-Nielsen *et al.* 2003, Silver *et al.* 2014, Bove *et al.* 2014), suggesting that further follow-up would be informative. The loss to follow-up was minimal in the studies that reported it, but it is not reported in several studies. Internal analyses, conducted in addition to external (SMR, SIR) analyses in the majority of cohort studies (Boice *et al.* 2006, Bove *et al.* 2014, Hansen *et al.* 2013, Henschler *et al.* 1995, Lipworth *et al.* 2011, Morgan *et al.* 1998, Radican *et*

*al.* 2008, Ritz 1999, Silver *et al.* 2014, Vlaanderen *et al.* 2013, Zhao *et al.* 2005), also indirectly address the potential for selection bias.

#### *3.2.2.2 Information bias: Exposure assessment*

The quality of the exposure assessment and the potential for exposure misclassification were systematically evaluated for each study. In general, the evaluation of the exposure assessment refers to the quality of the expert assessment and/or JEM used to evaluate the frequency, confidence, and probability of exposure to trichloroethylene from specific jobs or tasks. The evaluation of the potential for exposure misclassification integrates the quality of the exposure assessment with other exposure information such as the exposure setting.

The majority of studies used qualitative exposure assessments or semi-quantitative categories of exposure based on job-exposure or job-task exposure matrices and/or estimates of exposure ranks or levels; quantitative historical exposure monitoring data, if available, were limited.

The pooled and updated Nordic study of Hansen *et al.* (2013) was based on biomonitoring data from urinary trichloroacetic acid (U-TCA) measurements, together with some ambient air monitoring data. This study most likely had high sensitivity for identifying exposed workers; however, specificity may be a concern because some workers were exposed to other chlorinated solvents that are metabolized to TCA (Anttila *et al.* 1995). In addition, because large numbers of workers may have only had one to three U-TCA measurements, the available U-TCA measurements may not represent a worker's past or future exposure to trichloroethylene. Individuals classified as unexposed workers could in fact be exposed and misclassification of intensity of exposure is possible. Furthermore, this study did not provide information on lifetime or cumulative exposure, thus limiting the analysis of exposure-response relationships.

Non-differential misclassification of exposure was a concern in the Danish blue-collar workers study (Raaschou-Nielsen *et al.* 2003), in which an estimate of the proportion of blue-collar workers in companies using trichloroethylene was used as a surrogate for trichloroethylene exposure; only an estimated 41% of workers included in the analysis were probably exposed to trichloroethylene. Air and urine monitoring data were available for only a small proportion of workers. Although these measurements were not used in the exposure assessment, they provided information on the estimated level of exposure for different calendar periods, which was used in the analysis as a surrogate for exposure intensity. There was greater confidence of exposure classification in the analyses of a subcohort considered to have higher exposure than in the entire cohort.

In the most recent population-based Nordic study (Vlaanderen *et al.* 2013) exposure was assessed by linking generic country-specific JEMs to job titles reported on census data. Individuals were assumed to have the same job between censuses. One exposure metric in this study was a product of the average exposure intensity and prevalence of exposure. For jobs with low exposure prevalence, this approach would underestimate exposure intensity and classify unexposed workers with these jobs as exposed. Misclassification of exposure for individual participants was likely to be considerable because of lack of detailed occupational information (tasks and working conditions), heterogeneity of exposure levels within and across jobs with the same job title, and overtime.

Among the five U.S. aerospace or aircraft manufacturing cohorts, the studies that used semi-quantitative job-exposure matrices based on detailed job tasks and work histories to classify exposure among individual workers by ever vs. never, and/or by categories of exposure level or duration of employment (Zhao *et al.* 2005, Radican *et al.* 2008/Blair *et al.* 1998, Morgan *et al.* 1998) were the most informative with respect to the overall quality of the exposure assessment; Zhao *et al.* (2005) classified aerospace workers as exposed if they had a trichloroethylene exposure score greater than 3, which reduced the potential for exposure misclassification. Although the quality of the exposure assessment of the Utah aircraft-manufacturing workers by Radican *et al.* (2008) was considered to be adequate, exposure assessment for some subjects with missing exposure records was based on position description, which increases the potential for exposure misclassification. A limitation of the study of Arizona aircraft manufacturing workers (Morgan *et al.* 1998) was that the exposure assessment does not appear to be calendar specific; however, there was greater confidence of actual exposure among the highest exposed workers in this study. The exposure assessments of the other two studies (Boice *et al.* 2006, Lipworth *et al.* 2011), especially the study of California aircraft manufacturing workers, were considered to be more limited because they provided little information on exposure intensity. In the study of aerospace workers by Boice *et al.* (2006), non-differential exposure misclassification was a concern in the analysis of any exposure to trichloroethylene, (which included test stand mechanics using trichloroethylene as a general utility cleaning agent) although there was greater confidence in actual exposure in the analysis restricted to exposure duration of workers engaged in test engine flushing, a task in which exposure intensity is suspected to be high. No information or analysis of exposure intensity was available for the California trichloroethylene-exposed aerospace workers studied by Lipworth *et al.* (2011); evaluation of exposure-response relationships was based only on duration, i.e., length of time in jobs with potential exposure to trichloroethylene, which may be a poor surrogate for exposure intensity.

In general, exposure misclassification was a concern in the studies of other specific industries because of low quality exposure assessments with the possible exception of the German study of cardboard manufacturing workers (Henschler *et al.* 1995). Although the exposure assessment in this study was based on job location in the plant as well as a detailed description of the work environment and considered to be of limited quality, exposure misclassification is unlikely because high levels of exposure in an open system in small work environments were likely to have occurred in the past, based on job task descriptions of and reports of illness and the odor or taste of trichloroethylene by workers. Wilcosky *et al.* (1984) classified workers based on ever working in an area of authorized use of trichloroethylene in the nested case-control study of rubber workers; however, actual use of trichloroethylene was not reported, and thus the exposure assessment was considered to be inadequate to inform the hazard evaluation.

The remaining studies used JEMs of varying quality to estimate ranked exposure level (Bove *et al.* 2014, Ritz 1999), duration (Ritz 1999), probability of exposure (Bahr *et al.* 2011), a cumulative exposure score (Yiin *et al.* 2009, Silver *et al.* 2014) or ever exposure (Greenland *et al.* 1994). The quality of the exposure assessment in two studies of uranium enrichment or processing workers using semi-quantitative assessments (Ritz *et al.* 1999a, Yiin *et al.* 2008) were considered to be somewhat better than the other studies. Ritz (1999) used a semi-quantitative exposure assessment, although not calendar year specific, to assign uranium-processing workers to two exposure categories. A modified job-exposure matrix was employed in the Tennessee

uranium workers nested case-control study by Yiin *et al.* (2009). Exposure assessment in the electronics worker cohort (Silver *et al.* 2014) used a relative cumulative exposure score, based on department-year level use of trichloroethylene and employment duration. Non-differential exposure-misclassification was a concern in this study due to lack of information on job tasks, exposure conditions, levels of use and incomplete records. Electronic workers in the nested case-control study by Greenland *et al.* (1994) were classified as ever exposed to trichloroethylene based on a generic JEM. It is difficult to evaluate the quality of the exposure assessment including the basis for the exposure probabilities categories in the study of Kentucky uranium processing workers (Bahr *et al.* 2011) because of inadequate information provided in the publication. Finally, in the cohort study of drinking water contamination (Bove *et al.* 2014), exposure misclassification for both ever exposure and exposure category (based on modeled trichloroethylene concentration by residence) was a concern, although less so for participants estimated to have higher cumulative exposure.

In all the studies, the potential for exposure misclassification was generally considered to be non-differential, and would most likely bias towards the null. In subgroup analyses, exposure misclassification between exposure groups would most likely attenuate any exposure-response relationships.

#### *3.2.2.3 Information bias: cancer ascertainment and disease misclassification*

Studies evaluating cancer incidence (or incidence and mortality) include those by Bove *et al.* 2014, Hansen *et al.* 2013, Henschler *et al.* 1995, Raaschou-Nielsen *et al.* 2003, Radican *et al.* 2008/Blair *et al.* 1998, Vlaanderen *et al.* 2013, and Zhao *et al.* 2005. Mortality-only analyses include the cohorts by Bahr *et al.* 2011, Boice *et al.* 2006, Greenland *et al.* 1994, Lipworth *et al.* 2011, Morgan *et al.* 1998, Ritz 1999, Silver *et al.* 2014, and Yiin *et al.* 2009. Disease misclassification was unlikely for kidney cancers (all renal-cell carcinomas) in the incidence cohorts, which were generally histologically confirmed, and for liver cancers, either in the mortality-only studies or the incidence analyses. Mortality analyses are less informative for kidney cancer due to high 5-year survival rates. Case-ascertainment was considered to be limited in the German study of cardboard manufacturing workers because different methods for disease diagnosis may have been used for the exposed cohort (physicians' records, abdominal sonogram) than for the general population, which could potentially bias external analyses towards an over-estimate of the risk estimate. This bias should not affect internal analyses. The quality of case-ascertainment of the Kentucky uranium enrichment workers could not be evaluated because of inadequate information on the source and completeness of vital status and cause of death data (Bahr *et al.* 2011).

In the case of NHL and its subtypes, however, changes in classification systems together with differences between studies with respect to groupings of lymphohematopoietic cancer endpoints used in analyses was of greater concern. Considerable changes in the classification systems used for these lymphomas have been made. Starting with the Revised European American Classification of Lymphoid Neoplasms (REAL) in 1994 (Harris *et al.* 1994), which was partly incorporated into the ICD Oncology Second Revision (ICD-O-2), recent substantial revisions in the classification of NHL and its subtypes have been made by the WHO in 2001 (Morton *et al.* 2007) (and again in 2008) and used in the ICD Oncology Third Revision (ICD-O-3). The 2001 and 2008 revisions were the most informative for the classification of NHL and its subtypes. The

ICD NHL classifications used in the Nordic studies (Raaschou-Nielsen *et al.* 2003, Hansen *et al.* 2013, Vlaanderen *et al.* 2013) and the older classifications used by Greenland *et al.* (1994), Morgan *et al.* (1998), Blair *et al.* (1998), Ritz (1999), Boice *et al.* (2006), Lipworth *et al.* (2011), Bahr *et al.* (2011), Silver *et al.* (2014) and Yiin *et al.* (2009) were less informative than more recent systems applied in only two studies (Zhao *et al.* 2005, Radican *et al.* 2008). In addition, death certificate data used in mortality studies (which also use underlying cause of death only, with the exception of Zhao *et al.* 2005), may be more likely to result in both missing cases and NHL misclassification than cancer registry data used in incidence studies.

#### *3.2.2.4 Study sensitivity and exposure-response relationships*

In addition to the analysis of biases and confounding, study sensitivity and analyses of exposure-response relationships also impacts the ability of a study to inform the cancer evaluation. Study sensitivity (i.e., statistical power or the ability to detect an effect), is dependent on the numbers of exposed subjects or cases and controls (which is related to the sample size and exposure prevalence), exposure level (intensity and/or duration), the degree of exposure misclassification and the length of follow-up. True relative risks will usually be lower among study populations with lower exposure (NRC 2006) and are also dependent on the biological properties of the agent. The evaluation of exposure-response relationships depends on an adequate range of exposure (in intensity or duration) among the study participants, adequate numbers of subjects in each exposure category and the confidence with which exposure groups are correctly classified.

A strength of the database is that all the studies had relatively long overall follow-up periods, although the average length of follow-up is not always clear. Three cohorts (Raaschou-Nielsen *et al.* 2003, Bove *et al.* 2014, and Silver *et al.* 2014) were relatively young, however, suggesting additional follow-up may be informative, particularly for kidney and liver cancer.

Without considering exposure levels or exposure misclassification, only the largest cohort studies (Vlaanderen *et al.* 2013, Hansen *et al.* 2013, Raaschou-Nielsen *et al.* 2003, Radican *et al.* 2008, Lipworth *et al.* 2011, and Bove *et al.* 2014) probably had adequate statistical power to observe a two-fold relative risk (see calculations by EPA 2011a, NRC 2006 for some of these studies) for ever vs. never exposed analyses, but only the two largest Nordic cohorts (Vlaanderen *et al.* and Raaschou-Nielsen *et al.*) had adequate numbers of cases in subgroup analyses, specifically for the highest trichloroethylene-exposed workers in the cohort. (The number of trichloroethylene-exposed workers in the Silver *et al.* (2014) cohort was not reported). Most studies may not have had sufficient power to detect lower risk estimates (e.g., 1.3) for ever vs. never exposure.

Although overall there are limited quantitative ambient or personal air monitoring data in the body of studies, there were reported levels of exposure for some of the Nordic studies and estimated levels of exposure for other populations. Biomonitoring data from individual studies in the pooled Nordic cohort (Hansen *et al.* 2013) indicated that exposure levels were relatively low in this study (median equivalent ambient trichloroethylene levels probably ranged between 4 and 12 ppm based on the individual studies) and only 20% of the subjects had U-TCA levels greater than 50 mg/L, which is approximately 20 ppm ambient air trichloroethylene, in the pooled analyses. Ambient air monitoring data relevant to Raaschou-Nielsen *et al.* (2003) (see Raaschou-Nielsen *et al.* 2002) indicate that exposures were higher prior to 1970 (40 to 60 ppm), 10 to 20

ppm between 1970 and 1979 and 4 ppm after 1980. Thus analyses of the subcohort of presumably higher exposed workers with employment before 1980 are considered to be more informative than analyses for the total cohort. Exposure levels, although not measured, were estimated by the JEM to be low in the large study reported by Vlaanderen *et al.* (2013). Estimated median exposure (units-yr [approximately equivalent to ppm]) for the cumulative exposure categories were 0.01 to 0.04 for the first tertile (depending on the endpoint), 0.12 to 0.13 for the second tertile, and 0.72 to 0.77 for the third tertile of cumulative exposure. However, the use of prevalence to calculate cumulative exposure complicates the interpretation of these levels. High exposure in this study was assigned to laundry workers, shoe and leather workers or mechanics.

There were few data on exposure levels among the aerospace and aircraft cohorts. Most of the available data were estimated levels for Radican *et al.* (2008). Exposure intensity from degreasing was most likely high (ranging from 200 to 600 depending on time period) and estimated cumulative exposure was likely to range from 8 to 38 ppm-yr for use as a degreasing and 5 to 15 ppm-yr for benchwork (personal communication Dr. Patricia Stewart to Dr. Ruth Lunn [June 23, 2014]). The NRC (2006) concluded that the cohort had modest numbers of highly exposed workers but most workers were exposed to approximately 10 ppm. There were few exposed cases (< 5) for kidney or liver cancer and 12 cases of NHL in the highest exposed group, and thus the study had limited statistical power to evaluate effects from high exposure to trichloroethylene. Little information is available on the other cohorts, although exposures among the highest exposure group in the study by Morgan *et al.* (1998) were estimated to be > 50 ppm. Exposure intensity was likely high among test mechanics in the aerospace worker cohort (Zhao *et al.* 2005, Boice *et al.* 2006). The study by Lipworth *et al.* (2011) was considered to have limited ability to detect an effect because exposure duration can be an insensitive metric for cumulative exposure and was likely to be low. The cohort enrolled workers employed at three facilities on or after 1960; however, trichloroethylene use ceased in 1966, and an unknown proportion of the cohort was exposed to shorter periods, although they were followed for long periods of time. Years exposed would include individuals with low and high cumulative and intensity of exposure.

In the German study of cardboard manufacturing workers, estimated peak exposure was > 2,000 ppm and long-term exposure exceeded 100 ppm (Cherrie *et al.* 2001); in addition, the workers were exposed for long periods (average 17.8 months). Thus, despite the low numbers of exposed cases, statistical power was probably adequate to detect the effect of high exposure. Exposure levels were not measured or estimated in the other studies, although large number of workers (approximately 2600) were reported as routinely exposed to trichloroethylene in the uranium cohort study by Silver *et al.* (2014; see also Fleming *et al.* 2014); in other studies, few workers appear to be exposed to trichloroethylene (Greenland *et al.* 1994) or if they were exposed, the majority were either exposed to low estimated levels (Ritz 1999), exposure probability was low (Wilcosky *et al.* 1984) or the proportion of exposed workers in the cohort or among exposed controls was not reported (Yiin *et al.* 2009). With respect to the drinking water study (Bove *et al.* 2014), the authors estimate that maximum consumption could be 3.6 mg/day from water, based on measured trichloroethylene levels, which would be the equivalent of approximately 0.07 ppm as an 8-hour TWA (assuming 100% intestinal absorption) and potentially as high as 25 ppm-yr. It is more difficult to assess levels of exposure due to unknown actual individual consumption patterns and compare with studies in which ambient exposure occurred, due to

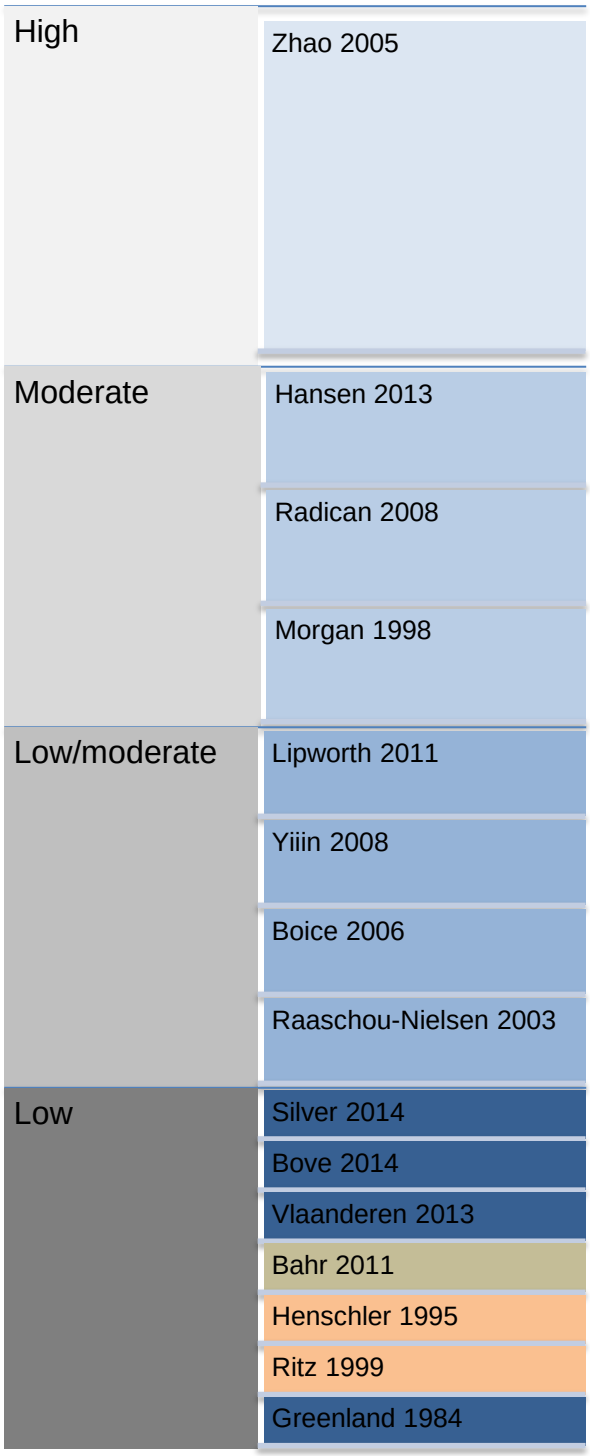
uncertainty as to whether biological effects would differ by route of exposure. In addition, the number of exposed cases in subgroup analyses was not reported.

The ability of a study to evaluate exposure-response relationships depends on the adequacy of the exposure assessment, statistical power, and range of exposure levels included in the exposure-response analysis. Of the 16 identified studies, 10 reported risk estimates for 2 or more categories of exposure (Morgan *et al.* 1998, Ritz *et al.* 1999, Raaschou-Nielsen *et al.* 2003, Zhao *et al.* 2005, Boice *et al.* 2006, Radican *et al.* 2008, Bahr *et al.* 2011, Lipworth *et al.* 2011, Vlaanderen *et al.* 2013, Hansen *et al.* 2013, Bove *et al.* 2014). However, most studies had limited ability to evaluate exposure-response relationships because of (1) lack of information on lifetime exposure (Hansen *et al.* 2013), (2) substantial concerns for exposure misclassification (Vlaanderen *et al.* 2013, Bove *et al.* 2014), (3) limited range of exposure levels because of overall low exposure levels or only two exposure categories (Morgan *et al.* 1998, Ritz *et al.* 1999, Boice *et al.* 2006, Vlaanderen *et al.* 2013), (4) adequacy of the exposure surrogate for evaluating exposure level, i.e., time since first exposure (Raaschou-Nielsen *et al.* 2003), exposure probability (Bahr *et al.* 2011) and exposure duration (Boice *et al.* 2006, Lipworth *et al.* 2011), or (5) limited statistical power because of few subjects in each exposure subgroup (most studies except for Vlaanderen *et al.* 2013). The remaining studies only reported risk estimates for one category of exposure (Wilcosky *et al.* 1984, Greenland *et al.* 1994, Henschler *et al.* 1995, Yiin *et al.* 2009, Silver *et al.* 2014).

#### *3.2.2.5 Methods for evaluating confounding*

The majority of cohort and nested case-control studies conducted age-, sex-, race- and calendar year- or period-standardized comparisons in external analyses (SMR or SIR) where appropriate and age-, sex-, race- and in some cases calendar-period-adjusted comparisons in internal analyses. Most studies did not collect information on lifestyle factors, although internal analyses were conducted in a number of studies, which can reduce the potential for confounding as well as selection bias. However, confounding is generally unlikely to strongly influence risk estimates unless there is a strong association between the potential confounder to both exposure and cancer endpoint, which has not been demonstrated for most lifestyle or demographic factors or many of the identified co-exposures. The most informative study for considering confounding was the study of aircraft workers by Zhao *et al.* (2005), which conducted analyses controlling for co-exposures. Some studies conducted separate analyses of major co-exposures (Boice *et al.* 2006, Zhao *et al.* 2005, Bove *et al.* 2014). Yiin *et al.* (2009) conducted multivariate analyses including trichloroethylene, nickel, mercury and radiation dose, although the latter was the primary focus of the study and thus detailed exposure data on trichloroethylene exposure was lacking. A discussion of confounding is presented in the cancer evaluation of each cancer endpoint, as their potential impact differs depending on the specific cancer endpoint.

**Figure 3-1. Summary of study quality: cohort studies**




Grey: study quality; highest – light grey
Study sensitivity: highest – light blue
Peach: potential bias away from the null
Tan: Other concerns

#### *3.2.2.6 Summary*

The database of cohort studies consisted of a large number of studies, many of which were considered to have adequate methodologies for evaluating potential cancer hazards. Although many of the cohorts were relatively large, most studies were still underpowered because of few exposed cases or deaths, especially in subgroups with higher exposure to trichloroethylene, to evaluate risks from the cancer sites of *a priori* interest, i.e., kidney cancer, liver cancer, and NHL, which are relatively uncommon. In addition, for some studies with adequate numbers of observed cases or deaths for kidney cancer, NHL, or liver cancer, exposure levels of trichloroethylene were low and/or exposure misclassification was a concern. Figure 3-1 depicts the overall assessment of the ability to inform the cancer evaluation based on the evaluation of study quality, potential for bias, and study sensitivity. The most informative studies (moderate- or high-quality studies) include the Nordic study of biomonitored workers (Hansen *et al.* 2013), and the aerospace and aircraft worker cohorts by Zhao *et al.* (2005), Morgan *et al.* (1998), Radican *et al.* (2008)/Blair *et al.* (1998). Overall, these studies had adequate methods to assess exposure and disease, little evidence of differential biases, and evaluated risks among subjects exposed to moderate to high levels of trichloroethylene. The study of aerospace workers (Zhao *et al.* 2005) was considered to be the most informative study because it evaluated cancer incidence, conducted detailed analysis of exposure-response relationships and adjusted for potential confounding from co-exposures. Although the biomonitoring study was relatively good for identifying individuals who were ever exposed to trichloroethylene, U-TCA may not be a good marker for lifetime exposure or exposure intensity. The

study by Morgan *et al.* was ranked lower for evaluating NHL compared with kidney and liver cancer because of fewer NHL cases compared with cases for the other endpoints.

Studies considered to have low/moderate utility, primarily because of more limited (mainly qualitative) exposure assessments and/or lower sensitivity, include the Nordic blue-collar worker study by Raaschou-Nielsen *et al.* (2003), aerospace workers by Boice *et al.* (2006), California air-craft manufacturing workers (Lipworth *et al.* 2011), and the nested case-control study of multiple myeloma among Tennessee uranium enrichment workers (Yiin *et al.* 2008). In the blue-collar worker study, the analysis of the subcohort of workers employed before 1980, when exposure levels were high, was considered to be more informative than analysis of the entire cohort. Exposure levels were presumably moderate to high in these studies; however, the study by Lipworth *et al.* (2011) only evaluated exposure duration, which most likely included workers with low levels of exposure. In addition, exposure duration was likely short in this study, which limited its sensitivity to detect an effect. There was the potential for selection bias and smoking from differences in social economic status in the exposed and reference population, leading to potential confounding from smoking in the Nordic study of blue collar workers and potential residual confounding from radiation exposure in the study by Yiin *et al.* (2008); however, overall the other limitations in all the studies (e.g. study sensitivity) was toward the null.

The population based Nordic study (Vlaanderen *et al.* 2013), the study of micro-electronic workers (Silver *et al.* 2014), the drinking water study (Bove *et al.* 2014) and the nested case-control study of electrical workers (Greenland *et al.* 1995) were considered to be limited (low quality) to inform cancer hazard evaluation primarily because of low study sensitivity (e.g., exposure misclassification, lower levels of exposures). Studies having potential differential biases (away from the null) or potential confounding from occupational co-exposures include the German cardboard manufacturers cohort study (Henschler *et al.* 1995) and the uranium enrichment workers study (Ritz 1999). The study by Bahr *et al.* (2011) had limited documentation on the selection of the cohort and exposure and disease assessments, which complicate the evaluation of its quality. Finally, there was low confidence as to whether exposure to trichloroethylene occurred in the nested case-control study by Wilcosky *et al.* (1984) in addition to other methodological concerns and it was considered to be inadequate to inform the cancer hazard evaluation.

## 3.3 Kidney or liver cancer case-control studies

### 3.3.1 Overview of the methodologies and study characteristics

Table 3.3 lists seven kidney case-control studies that satisfied the inclusion criteria; one of these studies also reported on liver cancer (Christensen *et al.* 2013). These include four studies conducted in areas with presumably higher levels and prevalence of trichloroethylene exposure using experts with knowledge of the local industry, and three studies of more widespread populations with more varying exposure potential for trichloroethylene, resulting in an overall lower average exposure levels in these populations. Two studies (Brüning *et al.* 2003, Vamvakas *et al.* 1998) were conducted on a non-overlapping consecutive series of cases and controls among the same general population in the town and immediate surrounds of Arnsberg, Germany (Vamvakas *et al.*1998) or the town and a somewhat wider surrounding area (Brüning *et al.* 2003), which has a large number of companies doing metal and electronics work.

Trichloroethylene use was widespread and one of only two principal solvents (the other was carbon tetrachloride) used in the industry. Neither study included renal-cell carcinoma (RCC) cases from the cohort study of workers at a cardboard factory from the same region (Henschler *et al.* 1995). Charbotel *et al.* (2006, 2009) conducted a case-control study of kidney cases in the Arve Valley, France, which is an area with a widespread screw-cutting industry that used trichloroethylene as a degreaser. Although population based, the French and German studies had a higher prevalence of subjects with presumably higher levels of trichloroethylene and from more homogenous industries. A multi-center study of renal-cell cancer was conducted in four countries of Central and Eastern Europe, in which occupational exposure to trichloroethylene was thought to be higher and more prevalent than in other industrial areas. Exposure was assessed in each of the different countries by a team of experts with knowledge of industries in their area (Moore *et al.* 2010). The remaining studies included population-based case-control studies in Minnesota (Dosemeci *et al.* 1999) and Germany (Pesch *et al.* 2000a) and a population-based study using both population and hospital controls in Montreal, Quebec (Christensen *et al.* 2013). The population-based study by Pesch *et al.* (2000a) included five German regions one of which (Leverkusen) was, like Arnsberg, in North Rhine-Westphalia.

For each of the reviewed studies, detailed data on study design, methods, and findings were systematically extracted from relevant publications, as described in the study protocol, into Appendix D, Tables D-2.

**Table 3-2. Case-control studies of trichloroethylene exposure: kidney or liver cancer**

| Primary reference | Study Population Total # Cases/controls | Exposure assessment | Cancer assessment |
|---|---|---|---|
| **Studies in specific areas with knowledge of local industries** | | | |
| Brüning *et al.* 2003 | Arnsberg, Germany, hospital-based 134/401 | In-person or proxy questionnaire, self- and expert assessment (JEM) | Incident and deceased RCC cases |
| Vamvakas *et al.* 1998 | Arnsberg, Germany, hospital-based 58/84 | In-person (case or proxy) questionnaire, expert assessment | Incident and deceased RCC cases |
| Charbotel *et al.* 2006, 2009 | Arve Valley, France, hospital-based 86/326 | Telephone questionnaire, expert assessment, semi-quantitative JEM | Incident and deceased RCC cases |
| Moore *et al.* 2010 | Multi-center, Central and Eastern Europe, hospital-based 1097/1476 | In-person questionnaire, expert assessment | Incident RCC cases |
| **Other studies** | | | |
| Christensen *et al.* 2013 | Montreal, Quebec (Canada), hospital- and population-based 177/533 | In-person questionnaire, expert assessment | Incident RCC and liver cancer cases |
| Pesch *et al.* 2000a | Multi-center, | In-person questionnaire, | Incident RCC cases |

| Primary reference | Study Population Total # Cases/controls | Exposure assessment | Cancer assessment |
|---|---|---|---|
| | Germany, population-based 935/4298 | expert assessment, JTEM | |
| Dosemeci *et al.* 1999 | Minnesota, (USA) population-based 438/687 | In-person questionnaire (occupation, exposures), JEM | Incident RCC cases |

JEM = job-exposure matrix; JTEM = job-task exposure matrix; RCC = renal-cell carcinoma.

### 3.3.2 Evaluation of study quality and other information

The methods for evaluation of study quality of the kidney cancer case-control studies was similar to that described for cohort studies (see Section 3.2.2). Details of the systematic assessment of potential bias, study quality, and factors related to study sensitivity and assessment of exposure-response relationships for each study are available in Appendix D, Tables D-5a,b.

#### *3.3.2.1 Selection and participation bias*

Selection bias was not a concern in the population-based case-control studies conducted in Montreal (which also used cancer controls) (Christensen *et al.* 2013), Minnesota (Dosemeci *et al.* 1999), and Germany (multi-center) (Pesch *et al.* 2000a) and the hospital-based case-control study in France (Charbotel *et al.* 2006, 2009). These studies selected cases and controls from the same population using similar inclusion criteria; controls were randomly selected and matched to the cases on age, sex, or location, if relevant. Although hospital controls may introduce selection bias if the diseases observed among controls are related to trichloroethylene exposure, several hospital-based case-control studies minimized this impact by excluding diseases related to kidney cancer (Charbotel *et al.* 2006, 2009, Moore *et al.* 2010), or restricted the inclusion of any specific disease (Moore *et al.* 2010) or cancer (Christensen *et al.* 2013) to less than 20% of the total number of diseases/tumor sites. Persons with tobacco-related diseases were excluded for controls in the multicenter European study (Moore *et al.* 2010), because the potential for selection bias could be increased if smoking or other (lifestyle or co-exposure) risk factors related to smoking are related to kidney cancer risk and to exposure to trichloroethylene. This study, however, controlled for smoking in the analyses, minimizing concern for selection bias.

In the later German case-control study (Brüning *et al.* 2003), there was the potential for selection bias (possible) because of the use of prevalent cases (selected from1992 to 2000) and residual non-cases as controls (1999 to 2000). Controls were matched to cases on sex and age and were selected from surgery and geriatric departments from the same region as cases (selected form the urology department).

The study with the most concern for potential selection bias (probable) was the earlier Arnsberg study (Vamvakas *et al.* 1998). Cases (prevalent) were not interviewed until after the selection period, and cases who died in the interim were excluded from that analysis. In contrast, unmatched controls were recruited from hospitals adjacent to Arnsberg and selected at the end of the study. Controls were also younger than cases but age was adjusted for in the analysis. This could potentially bias the findings away from the null and towards an overestimate of the risk

estimate if exposure prevalence varies by geographical location and within the time period of the study. In addition, the study was conducted during a time period of legal proceedings.

Participation rates were generally adequate between cases and controls (Vamvakas *et al.* 1998, Pesch *et al.* 2000a, Charbotel *et al.* 2006, 2009, and Christensen *et al.* 2013). Participation rates were lower among controls in the Minnesota case-control study (Dosemeci *et al.* 1999), which could reduce precision. Rates were not reported for controls and/or cases in two of the hospital-based studies (Brüning *et al.* 2003, Moore *et al.* 2010).

#### *3.3.2.2 Information bias: Exposure assessment and misclassification*

The adequacy of the exposure assessment and the potential for exposure misclassification were considered, both with respect to whether cases or controls were ever exposed, and, if exposure ranks, categories, or levels were assigned, the degree to which misclassification among exposed subjects may have occurred within those categories. Misclassification of exposure category, low levels of exposure, or similar exposure levels across exposure groups can attenuate exposure-response relationships.

Case-control studies typically rely on questionnaire data and recall of past occupational histories to assign exposure in the absence of quantitative exposure data. The assignment of exposure to trichloroethylene thus depends on detailed job or job-task description data or recall of actual exposures, which depending also on the availability of industrial hygiene data and the type and quality of the expert review or job exposure or job-task exposure matrix used, may limit exposure characterization and introduce the probability of exposure misclassification for ever/never exposure or within categories of exposure. Exposure misclassification was likely to be non-differential and to bias towards the null.

These studies used self- and/or proxy-report of work histories, jobs, or tasks using structured questionnaires and interviews, combined with expert assessment and/or JEM/job task exposure assessment (JTEM) to estimate exposure probability, frequency, or level of potential exposure to trichloroethylene. However, the quality of the assessment varied depending on the available information. The studies in France (Charbotel *et al.* 2006, 2009), and the Montreal study (Christensen *et al.* 2013) and the multi-center European study (Moore *et al.* 2010) were considered to have the high-quality assessments because they collected detailed information on job tasks, considered calendar year, and provided semi-quantitative estimates of trichloroethylene exposure. In the French (Charbotel *et al.* 2006. 2009) study, these estimates were based on ambient trichloroethylene levels for different jobs and tasks reported or estimated by other investigators in other studies (see Fevotte *et al.* 2006).

However, the likelihood of exposure, especially among individuals with higher exposure levels, is probably greater in the French (Charbotel *et al.* 2006, 2009) and European (Moore *et al.* 2010) study than in the Montreal study (Christensen *et al.* 2013) study. In contrast to Christensen *et al.* (2013), in which the subjects were employed in diverse industries and jobs, the French study was conducted in an area with more homogeneous industries and with a high prevalence of exposure to high levels of trichloroethylene. In addition, the study had a good exposure assessment so that misclassification of workers was not a concern. Although the Central and East European study was conducted in several different areas, researchers chose the study subjects from industrial areas thought to have higher exposure to trichloroethylene, used experts from the region for the

exposure assessment, and validated the assessment at a later time period (with 83% agreement in one country and 100% agreement in two countries). Additionally, investigators presented separate analyses among individuals with high confidence of exposure as an attempt to reduce the potential for exposure misclassification bias. Although the quality of the exposure assessment was considered to be adequate in the Montreal study, misclassification of exposure is still a concern because of the lower likelihood of exposure in a population-based study.

The analysis by Vamvakas *et al.* (1998), and to a lesser extent Brüning *et al.* (2003), relied more heavily on self-reported "pre-narcotic symptoms" (dizziness, nausea, headaches, and drowsiness) to indirectly characterize exposure to trichloroethylene (and tetrachloroethylene). In Vamvakas *et al.* (1998), experts integrated this information with exposure duration to assign workers to different exposure categories, whereas in Brüning *et al.* (2003), there was no expert assessment of the self-reported symptoms or exposure information. However, although self-reported exposure is usually considered to be less reliable than semi-quantitative or quantitative assessments and subjected to recall bias, exposure misclassification was not a serious concern in these studies, because of the frequency and severity of symptoms among the majority of cases in both studies as well as detailed descriptions of working conditions in the local industries, all of which suggest that most subjects were exposed to substantial levels of trichloroethylene. Interviewers were not blinded in the Vamvakas *et al.* study, and it is not clear whether the exposure assessment experts were blinded to disease status, which would have greater impact on misclassification than lack of blinding among the interviewers. In both cases, potential for differential misclassification is a concern and could lead to an overestimation of risk. Brüning *et al.* (2003) also assessed exposure to trichloroethylene using a JEM (see below).

Three studies used less detailed work information with respect to job task or a more generic job-exposure matrix (JEM) to assess exposure to trichloroethylene: the larger multi-center German study (Pesch *et al.* 2000a), the later Arnsberg study (Brüning *et al.* 2003) and the Minnesota study (Dosemeci *et al.* 1999). In the Pesch *et al.* study the job-task exposure matrix (JTEM) was considered to be more informative than the JEM exposure assessment although detailed information on job tasks was limited. The JEM used in the other two studies was based on broad occupation groups, was not calendar specific or area specific; a U.S. wide JEM was used in the Minnesota study (Dosemeci *et al.* 1999) and a British JEM was used in the German study by Brüning *et al.* (2003). These JEMs were considered to be more limited in quality than the JTEM used by Pesch *et al.* (2000a), which was developed by the study investigators although little information was provided on job tasks. Misclassification of exposure (or the use of the JEM analysis to classify exposure in the Brüning *et al.* study) is a concern in these three studies.

#### *3.3.2.3 Information bias: Disease assessment*

Renal cell carcinomas were identified from hospital files or cancer registries and appear to have been histologically or sonographically confirmed in each study, and thus there is little concern about misclassification of disease. Three studies (Brüning *et al.* 2003, Vamvakas *et al.* 1998, and Charbotel *et al.* 2006, 2009) also included a small number of deceased cases, but as the sources for both the living and deceased cases were the same, it is unlikely that any misclassification would have occurred among the latter cases. In the single study that reported on liver cancer (Christensen *et al.* 2013), incident cases (identified via hospitals) were also histologically confirmed.

#### *3.3.2.4 Study sensitivity and exposure-response relationships*

In addition to the analysis of biases and confounding, study sensitivity and the ability to analyze exposure-response relationships also impact the ability of a study to inform the cancer evaluation. As noted in the discussion of the cohort studies, study sensitivity (i.e., statistical power or the ability to detect an effect) is a function of exposure prevalence and levels, sample size, and the degree of misclassification of exposure. Subgroup analyses that examine risks among individuals with higher exposure or higher probability of exposure were considered to be more informative for cancer hazard evaluation.

Few quantitative exposure data were available for the reviewed studies although estimated exposure levels are available for several studies. In the studies conducted in the industrial regions of the Arve Valley in France (Charbotel *et al.* 2006, 2009) and the Arnsberg region of Germany (Brüning *et al.* 2003, Vamvakas *et al.* 1998), the study authors or other reviewers (Cherrie *et al.* 2001, NRC 2006) have provided estimates of exposure intensity that indicate that the study participants were exposed to high levels of trichloroethylene in both regions. In the German study, peak exposure was estimated to range from 400 to 600 ppm and overall exposure was > 100 ppm (Cherrie *et al.* 2001). In the French study, exposures of 300 to 600 ppm were estimated for some tasks. In contrast, the NRC (2006) estimated that most subjects in the multicenter study in Germany (Pesch *et al.* 2000a) had minimal contact with trichloroethylene, with concentrations up to 10 ppm.

The studies having greater sensitivity to detect an effect (if true), were the French (Charbotel *et al.* 2006, 2009) and German (Brüning *et al.* 2003, Vamvakas *et al.* 1998) studies conducted in small industrial areas because of the higher levels of exposure and/or prevalence in these regions. These studies appear to have had adequate overall numbers of workers and had higher estimated levels of exposure than the population-based studies. The statistical power for subgroup analyses conducted by Charbotel *et al.* (2006, 2009) and Vamvakas *et al.* (1998) was more limited, however. A further strength of the French study was analyses of exposure-response relationships with cumulative exposure that included an adequate range of exposure levels for trend analyses and greater confidence in the exposure assessment. The overall number of cases and controls in the Eastern and Central European study (Moore *et al.* 2010) was large, although there were fewer subjects with both high exposure and high-confidence exposure assessments. Another strength of the study was that it conducted analyses of several metrics of exposures (duration, cumulative, and intensity). The two studies of the Arnsberg area workers probably had limited ability to look at exposure-response relationships because of presumed shallow range due to widespread high exposure; Vamvakas *et al.* (1998) reported risks estimates for ranked exposure category and Brüning *et al.* (2003) evaluated categories of severity of symptoms (surrogate for exposure intensity and exposure duration). Study sensitivity in the Montreal study (Christensen *et al.* 2013), reporting on kidney and liver cancer, was limited by few cases (two for kidney and one for liver) with substantial exposure to trichloroethylene (levels unknown), and in the German multicenter study (Pesch *et al.* 2000a) was limited by lower levels of exposure. The studies by Pesch *et al.* (2000) and Christensen *et al.* (2013) combined confidence or probability as part of their exposure categories, which complicated the evaluation of exposure-response relationships. The study by Dosemeci *et al.* (1999) appeared to have sufficient statistical power (based on numbers of exposed subjects) to evaluate ever-exposed cases, but it did not report data on levels or duration of exposure.

#### *3.3.2.5 Confounding*

All of the studies adjusted for (or considered) age, sex, and smoking, and all except Vamvakas *et al.* (1998) and Christensen *et al.* (2013) adjusted for body mass index for renal-cell carcinoma. Some studies considered socioeconomic factors and, for risk estimates for liver cancer, alcohol consumption (Christensen *et al.* 2013), medical history or conditions (Vamvakas *et al.* 1998, Pesch *et al.* 2000a, Moore *et al.* 2010, Dosemeci *et al.* 1999), or other lifestyle factors (Christensen *et al.* 2013). Only the French study (Charbotel *et al.* 2006, 2009) presented additional analyses adjusting for co-exposures to other occupational carcinogens.

#### *3.3.2.6 Summary*

The major strength of the database of case-control studies was the inclusion of studies that selected populations with higher likelihood of exposure to trichloroethylene, more homogeneous industries, and used experts with knowledge of the local industries. In addition, most of the studies were able to adjust or consider potential confounding from lifestyle habits or medical history. Most studies had limited statistical power due to small numbers of subjects exposed to high levels of trichloroethylene. The studies by Charbotel *et al.* (2006, 2009) and Moore *et al.* (2010) were considered to be the most informative for the cancer evaluation because of greater confidence that most of the subjects classified as exposed were most likely exposed to substantial levels of trichloroethylene (Charbotel *et al.* 2006, 2009); in the study by Moore *et al.* (2010), analyses focused on the highest exposed individuals with high probability of exposure. Other strengths of the Charbotel *et al.* study were controlling for potential confounding from co-exposures in the analysis and evaluating exposure-response relationships for cumulative and peak exposure. The study by Brüning *et al.* (2003) was considered to be of moderate quality to inform the cancer hazard evaluation. Although the exposure assessment relied primarily on self-assessed exposure to identify workers exposed to trichloroethylene, study sensitivity was high because the presence of symptoms and qualitative job description data, strongly suggest that these workers experienced high levels of exposure. The remaining studies were considered to have low to low/moderate quality. Although the study by Christensen *et al.* (2013) also evaluated risks among individuals with substantial exposure (integration of intensity, duration, and frequency), there were few exposed cases (two cases for kidney, and one for liver cancer), which limited its ability to inform the cancer hazard evaluation. No other case-control study reported on liver cancer. The study by Pesch *et al.* (2000a), and, to a greater degree, the study by Dosemeci *et al.* (1999), were considered to be more limited because of concerns of exposure misclassification, which would most likely bias towards the null, and limit the ability to detect an effect (if present). Finally, the study by Vamvakas *et al.* (1998) should be viewed with some caution because of the potential for selection bias, which would most likely lead to an overestimate of the risk estimate. However, the likelihood of exposure to substantial levels of trichloroethylene in this study should also be considered in evaluating the degree of distortion due to selection bias on the findings in this study.

The findings from these studies and the cohort studies reporting risk estimates for kidney cancer are discussed in the cancer hazard evaluation for kidney cancer, which will integrate the study quality assessment, discuss whether chance, bias, or confounding can be ruled out for studies with positive findings, and integrate the findings from meta-analyses of these studies (see Section 4.1).

## 3.4 Case control studies of NHL and related subtypes

### 3.4.1 Overview of the methodologies and study characteristics

Table 3-3 lists six case-control studies of NHL (some of which also evaluate several subtypes, and one study specific for hairy cell leukemia [HCL], a type of NHL), and two studies specific for multiple myeloma (which is considered a type of B-cell lymphoma) that met the inclusion criteria. The studies include the International Lymphoma Epidemiology Consortium study (InterLymph) pooled case-control study (Cocco *et al.* 2013a), and population-based studies in Montreal, Quebec, Canada (Christensen *et al.* 2013), Connecticut, USA (Deng *et al.* 2013, Wang *et al.* 2009a), and Sweden (Hardell *et al.* 1994), a pooled analysis of two studies from Sweden (Persson and Fredrikson 1999), and a study of HCL in Sweden (Nordström *et al.* 1998). The InterLymph study (Cocco *et al.* 2013) includes pooled cases and controls from four large multi-center studies: the EPILYMPH study in Europe (Cocco *et al.* 2010), the ENGELA study in France (Orsi *et al.* 2010), the Multicentre Italian Study (MIS) (Miligi *et al.* 2006), and the NCI-SEER study in the United States (Purdue *et al.* 2011a). Because the InterLymph pooled analysis included all the subjects of the four constituent studies and harmonizes the exposure and disease assessment, this evaluation primarily reviews the pooled analysis. Information (e.g., such analyses of different exposure metrics) from the individual studies that was not incorporated in the pooled analysis was considered in the cancer hazard evaluation. An additional study in Germany by Seidler *et al.* (2007) was also identified, but was not reviewed because its population was included in the EPILYMPH multi-center study (Cocco *et al.* 2010), which was then included in the InterLymph pooled analysis.

For multiple myeloma, two additional studies were identified, one in Italy (Costantini *et al.* 2008, using the same population as the MIS study) and one in the United States (two of the SEER registries) (Gold *et al.* 2011), as well as the InterLymph study pooled analysis (Cocco *et al.* 2013a) and the Montreal, Quebec study (Christensen *et al.* 2013). The InteLymph pooled analysis and the Italian study (Costantini *et al.* 2008) also reported findings for chronic lymphocytic leukemia (CLL).

For each of the reviewed studies, detailed data on study design, methods, and findings were systematically extracted from relevant publications, as described in the study protocol, into Appendix D Table D-3. Studies are organized by lymphoma type and then by chronological order.

**Table 3-3. Case-control studies of trichloroethylene exposure and NHL and its subtypes**

| Primary reference | Study population Cases/controls | Exposure classification | Cancer assessment |
|---|---|---|---|
| Christensen *et al.* 2013<br>1979–1985 | Montreal, Quebec Canada<br>215/533 | In-person questionnaire, expert assessment | NHL, MM<br>ICD-9; histologically confirmed hospital cases<br>NHL 200+202 |

| Primary reference | Study population Cases/controls | Exposure classification | Cancer assessment |
|---|---|---|---|
| Cocco *et al.* 2013a<br>1991–2004 | 4 pooled studies (Cocco *et al.* 2010, Purdue *et al.* 2011a, Miligi *et al.* 2006, Orsi *et al.* 2010)<br>3,788/4,279 | Questionnaire, expert assessment | NHL and subtypes<br>WHO InterLymph consortium classification; histologically confirmed |
| Deng *et al.* 2013/Wang *et al.* 2009a<br>1996–2000 | Connecticut (USA)<br>601/7,171 | Questionnaire, JEM | NHL and subtypes<br>ICD-O-2, codes M-9590–9642, 9690–9701, 9740–9750; histologically confirmed |
| Persson and Fredrikson 1999<br>1964–1986 | Sweden<br>Pooled analysis of 2 studies (1983 and 1989)<br>199/479 | Self-reported ranked exposure | NHL<br>Hospital; histologically confirmed<br>ICD-8 used in 2nd study; NHL 200+202 (NR in 1989 study) |
| Nordström *et al.* 1998<br>1987–1992 | Sweden<br>121/484 | Self-reported occupational history | HCL<br>Cancer registry; classification and histological confirmation NR |
| Hardell *et al.* 1994<br>1974–1978 | Umea Region Sweden | Self-reported occupational history | NHL<br>Hospital histologically verified; Rappaport classification; stages and anatomical sites |
| **Multiple myeloma and chronic lymphocytic leukemia only** | | | |
| Gold *et al.* 2011<br>2000–2002 | SEER registries, Seattle Detroit<br>9,731/9,732 | In-person questionnaire, expert assessment | MM<br>SEER cancer registry; ICD-O-2/3; histologically confirmed |
| Costantini *et al.* 2008<br>1991–1993 | Regional Italy<br>263/1,100 MM<br>586/1278 (all leukemia; subtype totals NR) | In-person questionnaire, expert assessment | Hospitals<br>ICD-9; MM 203, CLL 204.1; histological confirmation NR |

CLL = chronic lymphocytic leukemia; ICD = International Classification of Diseases; HCL = hairy-cell leukemia; JEM = job-exposure matrix; NHL = non-Hodgkin lymphoma; MM = multiple myeloma; NR = not reported; SEER = Surveillance, Epidemiology and End Results program (U.S. National Cancer Institute; WHO = World Health Organization; Other LH endpoints, including all leukemia combined (ICD–9 204-208) are not included in the table.

### 3.4.2 Evaluation of study quality and other information

The methods for evaluation of study quality of the NHL case-control studies was similar to that described for cohort studies (see Section 4.2.2). Details of the systematic review of bias and factors and study sensitivity for each study are available in Appendix D, Tables D-6a,b.

#### *3.4.2.1 Selection and participation bias*

Selection bias was considered unlikely in these studies. In general, cases and controls were selected from the same underlying population using similar inclusion criteria; controls were randomly selected and age matched (and sex matched where both sexes were included) to the

controls. Non-participation rates among cases and controls were generally low (less than 10%), although in some studies the participation rate was not reported.

#### *3.4.2.2 Information bias: Exposure assessment and misclassification*

The exposure assessments in the InterLymph pooled case-control study (Cocco *et al.* 2013a), the Montreal study (Christensen *et al.* 2013), the Detroit-SEER study of multiple myeloma (Gold *et al.* 2011) and the Italian study of multiple myeloma and chronic lymphocytic leukemia (Costantini *et al.* 2008) used experts to rate frequency, confidence, intensity, and duration of exposure to trichloroethylene for each job (or task) reported in the questionnaire data, taking into consideration changes in trichloroethylene exposure over calendar periods. The InterLymph (Cocco *et al.* 2013a) and Detroit-SEER (Gold *et al.* 2011) provided quantitative ratings and the exposure assessment approaches were considered as high quality. The Detroit-SEER study used the same methods to assess exposure as the NCI-SEER study by Purdue *et al.* 2011, one of the studies in the pooled analysis in the InterLymph analysis. An advantage of these two studies was that they conducted separate analyses of individuals with high probability of exposure, which helped to mitigate concerns of exposure misclassification, especially among subjects with higher levels of exposure. The Montreal study (Christensen *et al.* 2013) and the Italian study (Costantini *et al.* 2008) provided semi-quantitative ratings of exposure.

The Connecticut study (Deng *et al.* 2013/Wang *et al.* 2009a) used a JEM to provide semi-quantitative ratings, and exposure ranks were based on broad occupational groups rather than job tasks. The quality of the exposure assessment is considered to be more limited than in studies using job and task rankings and exposure misclassification was a concern, although to a lesser degree among individuals in the higher categories of higher probability or higher intensity of exposure. The exposure assessments of the three Swedish studies were primarily based on self-reported job titles (Hardell *et al.* 1994 and Nordstrom *et al.* 1998) or ranked exposures (Persson and Fredrikson 1999) and thus were considered to be of lower quality; misclassification of exposure is likely to be substantial and is a concern.

As noted in the discussion for kidney cancer, misclassification of exposure in these studies was most likely non-differential and biased towards the null. This type of misclassification would most likely attenuate the ability to observe an exposure-response relationship. There was generally greater confidence that individuals in the highest exposure categories were actually exposed to trichloroethylene than in the lower categories, although there may be misclassification with respect to the intensity of exposure.

#### *3.4.2.3 Information bias: disease endpoints*

Histological confirmation of cases was conducted on all studies with the possible exception of the study of HCL (Nordstrom *et al.* 1998) and the Italian study of multiple myeloma (Costantini *et al.* 2008), neither of which did reported whether the cases were confirmed. As noted in the discussion of cohort studies, changes have been made in the classification systems used for these lymphomas. The WHO REAL classification (used from 2001 on; see e.g., Morton *et al.* 2007) used in the ICD Oncology Second and Third Revisions is the most recent and most informative for the revised classification of B- and T-cell lymphomas (including NHL and its subtypes). This classification system was used in the InterLymph pooled analysis (Cocco *et al.* 2013a), the Connecticut study (Deng *et al.* 2013/Wang *et al.* 2009a) and the SEER study of multiple

myeloma (Gold *et al.* 2011) (Table 4-3). Older classifications (ICD-9 and earlier) were used in the Swedish studies (Hardell *et al.* 1994, Nordstrom *et al.* 1998, and Persson and Fredrikson 1999) and the Montreal study (Christensen *et al.* 2013). Costantini *et al.* (2008) use a broader grouped classification for NHL, together with MM and CLL, from ICD-9. Overall, changes in the classification systems used would be expected to introduce heterogeneity in study comparisons because of differences in lymphoma groupings between the systems.

#### *3.4.2.4 Study sensitivity and exposure-response*

In addition to the analysis of biases and confounding, study sensitivity (i.e., statistical power or the ability to detect an effect) and the ability to analyze exposure-response relationships also impact the ability of a study to inform cancer evaluation.

Population- or hospital-based case-control studies often lack adequate power to detect an effect for NHL, as reflected by the low numbers of exposed controls (Appendix D, Table D-6b). Actual exposure levels were not reported for any studies. Some studies (Cocco *et al.* 2013a, Purdue *et al.* 2011a, and Gold *et al.* 2011) reported estimates in their exposure-response analysis. Estimated exposure levels in the highest exposure categories were > 75 or 150 ppm (Cocco *et al.* 2013a) for average exposure intensity, > 200,000 ppm-hr (Purdue *et al.* 2011a) or up to 50,000 ppm-hr (Gold *et al.* 2011) for cumulative exposure. (Purdue *et al.* was a component of the InterLymph pooled analysis.) These estimates suggest that exposure level among the highest exposed may be in the range of estimated levels reported in the cohort studies, although these should be interpreted with caution because actual ambient trichloroethylene levels were generally not available.

Although the available database included one very large study, and several medium to large studies, exposure prevalence was low to relatively low in most of the studies, ranging from less than 1% to 11% for most studies with the exception of the multiple myeloma study by Gold *et al.* (2011), which had an exposure prevalence of close to 30%. The prevalence of subjects with higher probability of exposure was even lower. In the InterLymph pooled case-control study of over 35,000 cases (Cocco *et al.* 2013a), 7% of the workers were exposed to trichloroethylene, but only 1% were classified as definitely exposed. Two studies (Cocco *et al.* 2013a, Deng *et al.* 2013/Wang *et al.* 2009a) had relatively large numbers of exposed cases and controls and most likely had adequate statistical power, although average exposure levels were not reported. A strength of both studies was that they stratified by both probability of exposure and exposure intensity level; however, in the study by Deng *et al.* (2013)/(Wang *et al.* 2009a), no subjects had high probability and medium or high intensity of exposure. In the InterLymph study, statistical power for NHL subtypes appeared to be good in evaluating risks for high exposure among all subjects although there were fewer subjects in the analyses of subjects with high probability of exposure. Finally, in the smaller studies conducted in Sweden (Hardell *et al.* 1994, Nordstrom *et al.* 1998, Persson and Fredrikson 1999) the observed prevalence of trichloroethylene exposure was less than 5% among referents, and these studies did not present analyses by exposure categories. In addition, these studies had low minimal criteria to be considered as ever exposed, based on only one-week or one-day duration of exposure, respectively, and thus some exposed individuals would typically be considered as unexposed by other investigators.

Studies evaluating exposure-response relationships (or looking at different levels of exposure) using multiple metrics of exposure (Cocco *et al.* 2013a, Gold *et al.* 2011, Deng *et al.* 2013/Wang *et al.* 2009a) were considered to be more informative for the cancer hazard evaluation. Although the exposure range was adequate in these studies and exposure levels were high in some of the studies, they had limited statistical power because of small numbers of cases and controls in each level of exposure.

#### *3.4.2.5 Confounding*

Each of the studies matched or adjusted for age, sex, birth year, or race, using conditional or unconditional logistic regression, as appropriate. Some studies (Deng *et al.* 2013/Wang *et al.* 2009a, Costantini *et al.* 2008, Christensen *et al.* 2013), and some of the component studies of the pooled analysis (Miligi *et al.* 2006, Cocco *et al.* 2010, Purdue *et al.* 2011a) also considered or adjusted for smoking, other lifestyle factors, and surrogates of socioeconomic status. Little information was available on potential occupational co-exposures, with the partial exception of Gold *et al.* (2011) who reported modest correlations (16% or less) between trichloroethylene, carbon tetrachloride, methylene chloride, and 1,1,1-trichloroethane among controls. None of the studies adjusted for co-exposures in their analysis, although the InterLymph study (Cocco *et al.* 2013a) conducted a sensitivity analysis excluding subjects exposed to benzene. Study participants in these population-based studies of NHL most likely came from diverse industries and thus it was not clear whether any specific co-exposures (other than perhaps other chlorinated or other organic solvents) would likely be correlated with trichloroethylene exposure.

#### *3.4.2.6 Summary*

Overall, the strengths of the NHL case-control study database are two studies of large populations, high-quality exposure assessment, evaluation of NHL subtypes and consideration or adjustment for potential confounding from life-style habits. The pooled analysis (Cocco *et al.* 2013a) and the SEER study on multiple myeloma (Gold *et al.* 2011) were considered to be the most informative studies because of the quality of the exposure and disease assessments, evaluation of multiple metrics of exposure, and larger numbers of exposed cases and controls, especially among individuals with higher probability or intensity of exposure. Studies by Christensen *et al.* (2013), Costantini *et al.* (2008) and Deng *et al.* (2013)/Wang *et al.* (2009a) were considered to be of low to moderate quality for the cancer hazard evaluation and were limited by one or more factors: limited statistical power, lower quality exposure assessment, or use of older disease classifications. The three Swedish case-control studies (Hardell *et al.* 1994, Nordstrom *et al.* 1998, Persson & Fredrikson 1999) were considered to be of low quality because of concerns for substantial misclassification of exposure (self-reported), used of older disease classification systems, and relatively small numbers of exposed subjects.

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# 4 Kidney Cancer

The previous sections of the cancer evaluation component contain relevant information – ADME (Section 1), genetic and related effects (Section 2), and overview and assessment of the quality of the human cancer studies (Section 3) – that are important for several of the three cancer endpoints of interest. This section builds on that information and evaluates the human cancer studies (Section 4.1) and mechanistic data (Section 4.2) specifically for kidney cancer.

## 4.1 Human cancer studies

Kidney cancer is considered to be uncommon; the age-adjusted annual kidney cancer (kidney and renal pelvis) rates (per 100,000 males or females) in the United States from 2006 to 2010 (U.S. SEER Statistics) were 21 (male) and 10.6 (female) for incidence and 5.8 (male) and 2.6 (female) for mortality. The five-year survival rate is ~70%, suggesting that incidence data may be more informative than mortality data. The studies of trichloroethylene and kidney cancer are of renal-cell carcinoma.

For each of the reviewed studies, summary data on study design, methods, and findings, systematically extracted from relevant publications as described in the study protocol, are presented in Table D-2 Appendix D. The evaluation of study quality, including methods of exposure and cancer endpoint assessment, analysis, and other relevant data, is reported in Tables D-4a,b and D-5a,b in Appendix D. Section 3 provided an overview of the study population characteristics and methods and a discussion of study quality across studies. Figure 4-1 (below) provides an overview of the conclusions from that evaluation and identifies the most informative studies based on study quality and study sensitivity.

This section summarizes and interprets the findings for kidney cancer from the individual epidemiological studies brought forward for evaluation, and integrates the evidence across studies. The key questions for evaluating the level of evidence across the body of studies is whether there is credible evidence of an association between trichloroethylene exposure and kidney cancer, and if so, could it be explained by chance, bias, or confounding. Several of the considerations developed by Austin Bradford Hill (Hill 1965) are relevant to the evaluation of the level of evidence for human carcinogenicity, including the magnitude (strength) and consistency of any observed associations across studies; evidence for exposure-response relationships and associations with appropriate latency; and the degree to which chance, bias, and confounding could plausibly explain observed associations. The level of evidence conclusion for the carcinogenicity of trichloroethylene from studies in humans is provided in Section 7.

### 4.1.1 Study findings

This cancer hazard evaluation reports on the latest update of a cohort or case-control study and meta-analyses and includes any additional relevant data (e.g., analyses or exposure information) from previous publications. The available studies that reported on kidney cancer and trichloroethylene exposure and were considered to be adequate for inclusion in the evaluation include 12 cohort or nested case-control studies and 7 population-based case-control studies. (Two cohort studies of uranium processing workers (Ritz 1999 and Bahr *et al.* 2011) did not report on kidney cancer and exposure specifically to trichloroethylene.) In addition, three recent meta-analyses were identified and are included in the evaluation. The findings of the individual

studies are discussed below and presented in Tables 4-1 and 4-2. Although the database consists of many reasonably well-conducted studies, some of which are large, in the majority of studies few workers were exposed to high levels of trichloroethylene with reasonable confidence of exposure, and thus most studies had limited statistical power to evaluate a modest risk of kidney cancer (if it exists) from exposure to trichloroethylene and exposure-response relationships. Statistical power was limited in the cohort studies, in part, because kidney cancer is uncommon or exposure levels were low in the larger studies, and in case-control studies because trichloroethylene exposure prevalence was low and exposure levels in the general population studies were most likely lower than the cohort studies. These limitations all tend to bias the findings toward the null. Meta-analyses can increase statistical power of underpowered studies, help to explain heterogeneity, and inform the cancer evaluation.

The findings of the individual studies are discussed below and presented in Tables 4-1 and 4-2.

**Figure 4-1. Summary of study quality: Kidney cancer**

Grey: Most informative (lightest) to the least informative studies (darkest).
Blue: Study sensitivity: darkest shade least sensitive.
Peach: Overall bias towards the null.
Tan: Other concerns

#### *4.1.1.1 Cohort and nested case-control studies*

The available cohort studies include three studies conducted in Nordic countries, five cohorts of aerospace and aircraft workers, a cohort study of cardboard manufacturing workers, a nested case-control study of electronic workers and a cohort of military personnel exposed to

trichloroethylene in drinking water. An overview of study quality is shown in Figure 4-1 and details are presented in Section 3 and Appendix D.

*Nordic studies*

These studies consist of a pooled analysis of biomonitored workers (Hansen *et al.* 2013), a cohort study of blue-collar workers at companies using trichloroethylene (Raaschou-Nielsen *et al.* 2003), and a large population-based cancer registry study (Vlaanderen *et al.* 2013); the studies included subjects with occupational exposure to trichloroethylene from diverse industries, and workers and exposed subjects who were identified from broad occupational or population-based databases. Both the cohort study of blue-collar workers (Raaschou-Nielsen *et al.* 2003) and the updated and pooled analysis of three cohort studies of biomonitored workers in Sweden, Finland, and Norway (Hansen *et al.* 2013) provide some evidence of an association of exposure to trichloroethylene and kidney cancer. In the former study, statistically significant increased risks (ranging from 60% to two fold) of renal cancer incidence were found among workers (SIR = 1.6, 95% CI = 1.1 to 2.4, 30 exposed cases), longer lag time (SIR = 1.0, 95% CI = 1.0 to 2.3, 25 exposed cases), and employed before 1970 (SIR = 1.9, 95% CI = 1.4 to 2.6, 41 exposed cases). Air monitoring data indicated that trichloroethylene levels were much higher (40 to 60 ppm) prior to 1970. Strengths of this study were its large size and analysis of long-term exposure using duration of exposure and calendar period as surrogates. Although the study was limited by its use of crude exposure surrogates (blue-collar workers, duration of employment), exposure misclassification was probably lower among the higher exposed subcohort than the total cohort. In the pooled analysis of biomonitored workers (Hansen *et al.* 2013), a statistically non-significant increase in risk of kidney cancer (HR = 2.04, 95% CI = 0.81 to 5.17; 9 exposed cases) was found among the highest exposed workers with urinary trichloroacetic acid (U-TCA) levels greater than 50 mg/L (estimated 20 ppm) but not among ever-exposed workers. Although this study was a large, well-conducted study, only 20% of the workers were exposed to levels greater than 20 ppm and estimated exposures for most of the workers were between 4 and 12 ppm. There was also a lack of specificity and possible misclassification of exposure, in part because some of the population was exposed to tetrachloroethylene, which is also metabolized to trichloroacetic acid (Anttila *et al.* 1995). In addition, most workers only had one to three U-TCA measurements over their entire work history and no information was available on lifetime cumulative exposure (Hansen *et al.* 2013).

No association between trichloroethylene exposure and kidney cancer was found in the large population-based study by Vlaanderen *et al.* (2013). Exposure to trichloroethylene was likely low in the study, and exposure misclassification (non-differential) was considered to be substantial because of lack of detailed occupational information (tasks, working conditions), heterogeneity of exposure levels within and across jobs with the same job title, and overtime, and use of a JEM that may not be country specific. These limitations would bias the findings towards the null.

*Aerospace or aircraft manufacturing workers*

These studies include two overlapping, but with different exposure assessments, cohorts of rocket engine workers (Boice *et al.* 2006, Zhao *et al.* 2005) and three studies of aircraft manufacturing workers in Burbank, California (Lipworth *et al.* 2011), Utah (Radican *et al.* 2008, Blair *et al.* 1998), and Arizona (Morgan *et al.* 1998). Taken together, the studies of the rocket engine workers provide evidence of an association between trichloroethylene exposure and

renal-cell cancer, with the strongest evidence coming from the Zhao *et al.* study, which was considered to be a high quality study based on a semi-quantitative exposure assessment and evaluation of exposure-response relationships for both cancer incidence and mortality in models that adjusted for co-exposure to other chemicals. In this study, the risk of kidney cancer increased with increasing cumulative exposure in both adjusted and unadjusted models (although the trend was only significant in the unadjusted model ($P = 0.023$) with risks ranging from 5-fold (unadjusted) to 7-fold (adjusted) in the highest exposure category. Statistical power was most likely reduced in the adjusted models. Similar patterns of increasing risks were also observed for kidney cancer mortality, although the magnitudes of the risk estimates were lower as might be expected since mortality is a less informative outcome measure than incidence. The study by Boice *et al.* (2006) (using a qualitative JEM) found a three-fold, non-significantly increased risk among workers with the longest exposure to trichloroethylene during engine flush and support the findings by Zhao *et al.* (2005) although this may not be independent evidence. Although exposure levels were not reported, the potential for high exposure to trichloroethylene during this task was much higher than during other tasks, such as the use of trichloroethylene as a utility solvent, according to the authors.

Among the studies of aircraft manufacturing workers, the mortality study of Arizona workers (Morgan *et al.* 1998) found non-significantly increased risks for kidney cancer among workers with the highest cumulative exposure (RR = 1.59, 95% CI = 0.68 to 3.71, 7 exposed deaths) and with high peak exposure (RR = 1.89; 95% CI = 0.85 to 4.23, 8 exposed deaths) with some evidence of increasing risks with increasing exposure. There was limited statistical power due to few exposed subjects in the high exposure categories. Exposure intensity for the highest exposed workers was estimated to be ≥ 50 ppm. Findings were null in the other two studies. Radican *et al.* (2008) found small non-statistically significant elevated risks in some subgroup analyses of the Utah workers but no evidence of an exposure-response gradient. Risks were less than unity in the internal and external analyses in the study of California workers by Lipworth *et al.* (2011). These studies had limited statistical power to detect a small excess in risk based on few workers with higher or longer exposure, and the study by Lipworth *et al.* (2011) had a higher potential for non-differential exposure misclassification. Although exposure levels were not reported, the NRC (2006) estimated that a modest number of the Utah workers (Radican *et al.* 2008) were exposed to higher levels (~ 100 ppm) but that most workers were exposed to low levels of trichloroethylene. There was evidence of a healthy worker effect in two of the aircraft manufacturing studies (Lipworth *et al.* 2011, Radican *et al.* 2008) and the aerospace worker study by Boice *et al.* (2006), which would bias external analyses towards the null. In addition, exposure duration for some workers in the Lipworth *et al.* study may have been relatively short for some workers because use of trichloroethylene was discontinued in 1966.

#### *Other mortality cohort studies*

These studies were generally considered to be of lower quality than most of the cohort studies of aerospace workers or the Nordic studies. A statistically significant high risk estimate (~ 8 to 13 fold depending on reference population rates) was observed in the study of cardboard manufacturing workers (Henschler *et al.* 1995), which may in part reflect selection and diagnostic biases because the study was designed around a cluster and cases of kidney cancer were identified using sonography (the latter would bias external but probably not internal analyses). However, the NRC (2006) estimated that the SMR would be approximately 3.2 if the three cases diagnosed in 1990 that represented the original cluster were excluded from the

analyses. There was also qualitative evidence that high exposures (estimated peak exposure greater than 2,000 ppm and long-term exposure of greater than 100 ppm) (Cherrie *et al.* 2001) occurred in this cohort. No excess risk was found in the nested case-control study of electrical workers (Greenland *et al.* 1994) which had several methodological limitations and low probability of exposure; only 10% of jobs had exposure to trichloroethylene, most of which was from indirect exposure. Bove *et al.* (2014) reported a HR of 1.52 (95% CI = 0.64 to 3.61, 11 exposed deaths) among military personnel exposed to the highest level of trichloroethylene in their drinking water. The exposure assessment was based on modeled levels and duration at residence and no information on individual water consumption was available. Although follow-up was long, the cohort was relatively young, suggesting additional follow-up might increase statistical power.

#### *4.1.1.2 Population-based case-control studies*

The case-control studies include four studies conducted in areas with presumably higher levels and prevalence of trichloroethylene exposure using experts with knowledge of the local industry, and three studies of more widespread populations.

##### *Studies in specific areas with knowledge of local industries*

As mentioned in Section 3, two non-overlapping case-control studies (Brüning *et al.* 2003, Vamvakas *et al.* 1998) were conducted in Arnsberg, Germany, which is a small geographical area with a large number of companies engaged in metal and electronics work. Trichloroethylene use was widespread and reportedly one of only two solvents (the other was carbon tetrachloride) used in the industry. This is the same geographical area as the German cardboard manufacturing cohort study of renal cancer, although cases do not overlap. A third case-control study (Charbotel *et al.* 2006, 2009) was conducted in the Arve Valley in France, which is an area with a widespread screw-cutting industry that used trichloroethylene as a degreaser. Although population based, the French and German studies have a higher prevalence of subjects with presumably higher levels of trichloroethylene and from more homogenous industries. The fourth study was a multi-center study of renal-cell cancer conducted in four countries in central and Eastern Europe, in regions in which occupational exposure to trichloroethylene was thought to be higher and more prevalent than other industrial areas. Exposure was assessed in each of the different countries by a team of experts with knowledge of industries in their area (Moore *et al.* 2010). The studies by Brüning *et al.*, Charbotel *et al.*, and Moore *et al.* are considered to have a greater ability to detect an effect because of greater confidence that most of the subjects classified as exposed were most likely exposed to substantial levels of trichloroethylene (Brüning *et al.* 2003, Charbotel *et al.* 2006, 2009) or, in the study by Moore *et al.* (2010), analyses focused on the highest exposed individuals with high probability of exposure. The studies by Charbotel *et al.* and Moore *et al.* were considered to have the best methodologies.

The study by Charbotel *et al.* (2006, 2009) is considered to be the most informative because in addition to the advantages stated above, it also evaluated exposure-response relationships and controlled for potential confounding from lifestyle factors and mineral oils, the major co-exposure in this industry, and conducted separate analyses among workers with high confidence of exposure. Kidney cancer risk increased with increasing exposure (no trend reported) with statistically significant risks (approximately 2- to 3-fold) observed among individuals with the highest cumulative exposure and high cumulative exposure together with peak exposure.

Exposure levels were considered to be high in this study, ranging up to 300 to 600 ppm for high-exposure jobs.

Strengths of the multi-center study in Central/Eastern Europe (Moore *et al.* 2010) were its large size and good exposure assessment. In this study, statistically significant risks were found among trichloroethylene-exposed individuals with high confidence exposure assessments (OR = 2.05, 95% CI = 1.13 to 3.73, 29 cases/19 controls). Risk estimates were higher among individuals with longer or higher levels of exposure (both average intensity and cumulative exposure). The authors also evaluated exposure to trichloroethylene and kidney cancer risk stratified by GSTT1 genotypes (see Section 4.2). Although there was potential selection bias due to the exclusion of controls with tobacco-related diseases, it can reasonably be ruled out, since initial regression analyses of exposure-response relationships examining smoking did not alter the ORs.

Statistically significant high risks were found for exposure to trichloroethylene and renal-cell cancer in the two German studies (Vamvakas *et al.*1998, Brüning *et al.* 2003). Although the exposure assessments were rather limited in both studies and relied on self-reported exposure, there is reasonable confidence that most workers were exposed to trichloroethylene based on detailed information on the exposure settings suggesting high exposure, the presence of narcotic symptoms and use of expert assessment (integrating frequency and severity of symptoms with exposure duration) (see Section 3). The earlier study by Vamvakas *et al.* reported a much higher risk estimate for any exposure (OR = 10.80, 95% CI = 3.36 to 34.75; 19 cases and 7 controls) than the later study by Brüning *et al.* (OR = 2.47, 95% CI = 1.36 to 4.49, 25 cases and 38 controls). The higher risk estimate in the earlier study should be viewed with some caution because of the potential for selection and other biases (see Section 3), which would most likely bias towards an overestimation of the risk. However, given the high levels of exposure to trichloroethylene, it seems unlikely that the distortion of the potential biases would nullify the observed positive association. Estimated levels of exposure were high; peak exposures were estimated to be 400 to 600 ppm and long-term exposure to be greater than 100 ppm (Cherrie *et al.* 2001, NRC 2006). The later study by Brüning *et al.* (2003) minimized some of the methodological concerns of the Vamvakas *et al.* study and thus is given greater weight in this evaluation. In the Vamvakas *et al.* study, there was little evidence of a linear exposure-response relationship, although risks were higher in both the moderate and high exposure categories compared with the lowest exposure category; exposure levels may have been somewhat homogeneous due to exposure from open systems in small spaces. In the Brüning *et al.* study, a higher risk (compared with any exposure) was found among individuals with daily narcotic symptoms (OR = 5.91, 95% CI = 1.46 to 23.99, 5 exposed cases and 4 controls), which may be a surrogate for exposure intensity. Brüning *et al.* also used a crude JEM from the UK to assess exposures in German industries, likely introducing misclassification bias, and found a two-fold increase among workers who held a job with trichloroethylene exposure compared with those who did not.

*Other studies*

These included population-based case-control studies in Minnesota (Dosemeci *et al.* 1999) and Germany (five regions) (Pesch *et al.* 2000a) and a study using both population and hospital controls in Montreal (Christensen *et al.* 2013). These studies are considered to have more limited ability to inform hazard identification because of limited statistical power (inadequate numbers of exposed subjects), low overall exposure or exposure misclassification, all of which would bias

towards the null. In the Minnesota study, risk approached statistical significance (OR = 1.96, 95% CI = 1.0 to 4.4, 22 cases) among women ever exposed to trichloroethylene but risks were close to unity among men. A small, non-statistically elevated risk was reported in the multi-center German study (Pesch *et al.* 2000a) and no increase in risk was found among subjects with substantial exposure in the Canadian study, but there were only two exposed cases (Christensen *et al.* 2013).

**Table 4-1. Trichloroethylene cohort and nested case-control studies: Findings for kidney cancer[a]**

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # cases/deaths | Internal analysis: HR, RR, SRR, or OR (95% CI) # exposed cases/deaths | Interpretation |
|---|---|---|---|---|---|
| **Nordic studies** | | | | | |
| Hansen 2013<br>(Potential overlap with Raaschou-Nielsen *et al.* 2003) | Pooled and updated Nordic cohorts Axelson *et al.* 1994, Anttila *et al.* 1995, Hansen *et al.* 2001<br>5,553 (3,776 M, 1777 F)<br>Biomonitoring (U-TCA) | All exposed subjects<br>0-yr lag<br>10-yr lag<br>20-yr lag<br><br>U-TCA (mg/L)<br>< 5<br>5–25<br>25–50<br>> 50<br>$P_{trend}$ | SIR<br>1.01 (0.70–1.42); 32<br>1.04 (0.71–1.50); 30<br>1.11 (0.67–1.73); 19 | Incidence<br><br>HRR (no lag)<br>1.0 (Ref); 9<br>1.12 (0.46–2.70); 11<br>0.81 (0.21–2.97); 3<br>2.04 (0.81–5.17); 9<br>0.19 | Low exposure levels (only 20% exposed to ≥ 20 ppm) and short duration of exposure.<br>Covariates: Age, sex, calendar period; indirect consideration of smoking and alcohol consumption<br>Strengths: Biomonitoring data; large numbers of workers ever exposed<br>Limitations: Only 2 to 3 U-TCA measurements/individual; unable to estimate lifetime or cumulative exposure<br>Limited evidence for a positive association in the highest exposed group |
| Raaschou-Nielsen 2003<br>(Potential overlap with Hansen 2013) | Danish blue-collar workers<br>40,049 M+F (approx. 70% M)<br>Working at TCE company; size of company surrogate for TCE exposure prevalence | Subcohort: higher exposed<br><br>Lag time (yr)<br>0–9<br>10–19<br>≥ 20<br><br>Duration employment (yr)<br>1–4 | SIR<br>1.4 (1.0–1.8); 53<br><br>0.9 (0.3–1.8); 6<br>1.5 (0.9–2.2); 22<br>1.6 (1.0–2.3); 25<br><br>1.1 (0.7–1.7); 23<br>1.7 (1.1–2.4); 30 | | Higher levels of TCE prior to 1970 (40–60 ppm); low levels of exposure after that time.<br>Covariates: age, sex, calendar year<br>Strengths: Large numbers of exposed cases; subcohort of subjects with higher exposure potential |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # cases/deaths | Internal analysis: HR, RR, SRR, or OR (95% CI) # exposed cases/deaths | Interpretation |
|---|---|---|---|---|---|
| | | ≥ 5<br>Yr. of 1st employment<br>Before 1970<br>1970–1979 | 1.9 (1.4–2.6); 41<br>0.7 (0.4–1.2); 12 | | Limitations: Young cohort, possible selection bias for difference in SES, external analysis only<br>Evidence for a positive association among workers with presumed highest exposure unlikely to be explained by confounding by smoking or differences in SES |
| Vlaanderen *et al.* 2013 | 5 Nordic countries Record linkage of cancer registry with census questionnaire Semi-quantitative JEM<br>M: 44,708 cases, 223,540 controls<br>F: 31,422 cases, 157,110 controls | Cumulative exposure (unit-years)<br>0<br>0.04<br>0.13<br>0.72<br>High-exposure group Cumulative<br>Men<br>Women (W)<br>Intensity × prevalence<br>Men<br>Women | | HR (incidence)<br>1.00<br>1.01 (0.95–1.07); 1,217<br>1.02 (0.97–1.08); 1,556<br>1.00 (0.95–1.07); 1,372<br>0.92 (0.77–1.09); 159<br>0.92 (0.77–1.09); 92<br>1.10 (0.97–1.25); 297<br>1.01 (0.62–0.97); 9 | Low prevalence of exposure (TCE) and exposure levels likely to be low.<br>TCE correlated with tetrachloroethylene<br>Strengths: Long follow-up, large numbers of cases<br>Limitations: Misclassification of exposure likely; JEM had poor sensitivity and did not account for heterogeneity within jobs and over time.<br>Null: No evidence of an association but study was limited by low levels and exposure misclassification |
| **Aerospace and aircraft workers** | | | | | |
| Boice *et al.* 2006<br>(Overlaps with Zhao *et al.* 2005) | Los Angeles, CA (USA)<br>Rocket engine testing workers | Ever exposed<br>*Exposure to TCE during* | SMR<br>2.22 (0.89–4.57); 7 | | Exposure occurs during text engine flush, which is likely to be high.<br>Covariates: Date of birth, year of |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # cases/deaths | Internal analysis: HR, RR, SRR, or OR (95% CI) # exposed cases/deaths | Interpretation |
|---|---|---|---|---|---|
| | 1,111 Men<br>Qualitative JEM; Individual work histories | *engine flush (test-yr)*<br>Referent (other depts.)<br>0<br>< 4<br>≥ 4<br>$P_{trend}$ | | RR (mortality)<br>1.00; 28<br>1.21 (0.33–4.35); 3<br>2.51 (0.27–23.5); 1<br>3.13 (0.74–13.2); 3<br>0.59 | hire, pay type (surrogate for SES) and exposure to hydrazine<br>Strengths: Adequate follow up<br>Limitations: Qualitative exposure assessment; few exposed deaths<br>Limited evidence for a positive association |
| Zhao *et al.* 2005<br>Overlap with Boice *et al.* 2006 | Los Angeles, CA (USA)<br>Male aerospace workers<br>6,044 (mortality)<br>5,049 (incidence)<br>Semi-quantitative JEM; individual work history | All analyses: 3 levels TCE cumulative exposure score<br>*Co-exp. Unadj.; 0-yr lag*<br>Low<br>Medium<br>High<br>$P_{trend}$<br>*Co-exp. Adj.; 0-yr lag*<br>Low<br>Medium<br>High<br>$P_{trend}$<br>Similar RR for 20-yr lag adj. model<br>*Co-exp. Unadj. 0-yr lag*<br>Low<br>Medium<br>High<br>$P_{trend}$ | | RR (incidence)<br>1.00; 6<br>1.87 (0.56–6.20); 6<br>4.90 (1.23–19.6); 4<br>0.023<br>1.00; 6<br>1.26 (0.26–6.14); 6<br>7.71 (0.65–91.4); 4<br>0.103<br>RR (mortality)<br>1.0; 7<br>1.43 (0.49–4.16); 7<br>2.03 (0.50–8.32); 3<br>0.307 | Exposure levels not reported but presumed to be high.<br>Covariates: All models – time since first employment, SES, age at event- additional analysis adjusted for co-exposure to carcinogenic chemicals.<br>Strengths: Semi-quantitative exposure assessment; multivariate analysis evaluating exposure response relationships adjusting for co-exposures<br>Limitations: Few cases in subgroup analyses<br>Evidence for a positive association. Unlikely to be explained by confounding from co-exposures. |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # cases/deaths | Internal analysis: HR, RR, SRR, or OR (95% CI) # exposed cases/deaths | Interpretation |
|---|---|---|---|---|---|
| | | *Co-exp. Adj. 20-yr lag*<br>Low<br>Medium<br>High<br>$P_{trend}$<br>No association in co-exp adj. 0-yr lag | | 1.00; 10<br>1.69 (0.29–9.70); 6<br>1.82 (0.09–38.6); 1<br>0.635 | |
| Lipworth *et al.* 2011 (update of Boice *et al.* 1999) | Burbank, CA (USA) aircraft manufacturing workers<br>5443 (approx. 80% M)<br><br>Qualitative JEM Individual work histories | TCE<br><br>TCE: years exposed<br>0<br>< 1<br>1–4<br>5+<br>$P_{trend}$ | SMR<br>0.66 (0.38–1.07); 16 | RR (mortality)<br>1.00; 33<br>0.52 (0.21–1.30); 6<br>0.42 (0.13–1.42); 3<br>0.85 (0.33–2.19); 6<br>0.20 | Exposure levels NR<br>Covariates: age, date of birth, date of hire, termination date, sex and race<br>Strengths: Long follow up, adequate number of cases and controls for ever exposure<br>Limitations: Evidence of HWE, few exposed deaths in subgroup analysis; exposure misclassification is a concern; no evaluation of exposure intensity, 70% had exposure to mixed solvent<br>Null: No evidence of association-limitations are mainly towards the null |
| Radican *et al.* 2008 (mortality to 2000)<br>Blair *et al.* 1998 (incidence | Utah (USA) aircraft maintenance workers<br>7,204 (6,153 M, 1,051 F) | Mortality<br>Ever-exposed (M & F)<br>1990 follow-up<br>2000 follow-up<br>Only 2 cases in females<br><br>Males only 2000 follow-up<br>Cumulative exp. (unit-yr) | | HR (mortality)<br><br>2.3 (0.6–8.4); 15<br>1.18 (0.47–2.94); 18 | Estimated exposure: Most workers exposed to low levels (~10 ppm), modest number of workers exposed to higher levels (~100 ppm).<br>Covariates: age, calendar year and |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # cases/deaths | Internal analysis: HR, RR, SRR, or OR (95% CI) # exposed cases/deaths | Interpretation |
|---|---|---|---|---|---|
| 1973–1990) | Semi-quantitative JEM Individual work histories | All<br>0–5<br>2–25<br>> 25<br><br>Exposure pattern<br>Low intermittent<br>Low continuous<br>Peak infrequent<br>Peak frequent<br><br>Incidence 1990 follow-up<br>None<br>0–5<br>2–25<br>> 25 | | 1.24 (0.41–3.71); 16<br>1.87 (0.59–5.97); 10<br>0.31 (0.03–2.75); 1<br>1.16 (0.31–4.32); 5<br><br>1.58 (0.52– 4.76); 15<br>1.79 (0.57–5.62); 11<br>1.04 (0.19 –5.70); 2<br>1.11 (0.31–3.96); 6<br><br>HR (incidence)<br>1.6 (0.5–5.4); 9<br>1.4 (0.4–4.7); 9<br>1.3 (0.3–4.7); 5<br>0.4 (0.1–2.3); 2 | sex<br><br>Strengths: Adequate semi-quantitative JEM, long follow-up, adequate statistical power for ever exposure<br><br>Limitations: Potential for exposure misclassification because of missing information for some workers; limited numbers of higher exposed workers<br><br>Long follow-up time (45 years) may be past induction time<br><br>Null: Small non-statistical elevated risk estimates; no evidence of an exposure response; limited statistical power |
| Morgan *et al.* 1998 | Arizona (USA)<br><br>Aircraft manufacturing workers<br><br>4,733 (2,555 M, 2,178 F)<br><br>Semi-quantitative JEM; individual work history | All TCE-exposed workers<br>Cumulative exp. Score<br>Low (2,357)<br>High (2,376)<br>Peak (med/high) vs. low/no | SMR (All)<br>1.32 (0.57–2.60); 8<br><br>0.47 (0.01–2.62); 1<br>1.78 (0.72–3.66); 7 | RR (mortality)<br>1.14 (0.51–2.58) 8[b]<br><br>0.31 (0.04–2.36); 1<br>1.59 (0.68–3.71); 7<br>1.89 (0.85-4.23); 8 | High-exposure jobs were considered to be ≥ 50 ppm<br><br>Covariates: age at hire, gender (decade of hire considered but no effect)<br><br>Strengths: Long follow-up and semi-quantitative exposure<br><br>Limitations: Evidence of a HWE; potential exposure misclassification among low/medium exposure groups; mortality analysis and few exposed cases |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # cases/deaths | Internal analysis: HR, RR, SRR, or OR (95% CI) # exposed cases/deaths | Interpretation |
|---|---|---|---|---|---|
| | | | | | Limited evidence for a positive association among the highest exposed workers. |
| **Other occupational studies** | | | | | |
| Henschler *et al.* 1995 | German cardboard manufacturing cohort<br>169 exposed<br>190 unexposed<br>Individual work history | Rates<br>1956–1993 Denmark<br>1956–1993 German<br>1956–1992 Denmark<br>1956–1992 German rates<br><br>Cases within follow-up<br>Cases outside of follow-up | SIR<br>11.15 (4.49–23.00); 7<br>13.53 (5.44–27.89); 7<br>7.97 (2.59–8.59); 5<br>9.66 (3.14–22.55); 5 | Mantel-Haenszel test<br>7.15 (NR); 7: $P = 0.005$<br>5.35 (NR); 5: $P = 0.014$<br>(no cases observed in unexposed group) | Qualitative evidence of high TCE exposure (Estimated > 2,000 ppm for peak exposure and > 100 ppm for sustained long-term exposure). Long exposure periods (17.8 months).<br>Covariates: age, sex<br>Strengths: Detailed information on plant conditions with evidence of high exposure, misclassification unlikely<br>Limitations: Possible selection bias (original cluster investigation)<br>Evidence for a positive association but likely an overestimate of the risk estimate; however, unlikely biases would nullify the association. |
| Greenland *et al.* 1994<br>(nested case-control) | Massachusetts (USA) electrical manufacturers<br>N = 12 cases (exposed controls NR) | Ever exposure | | OR (cases)<br>0.99 (0.30–3.32); NR | Limited statistical power; only 10% of jobs had exposure to TCE, most of which were from indirect exposure.<br>Covariates: Age, date of death, covariates that changed risk estimate by 20%.<br>Limitations: Small numbers of cases and controls and short |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # cases/deaths | Internal analysis: HR, RR, SRR, or OR (95% CI) # exposed cases/deaths | Interpretation |
|---|---|---|---|---|---|
| | | | | | follow-up, possible selection bias, low quality exposure assessment<br>Null: No evidence of association and numerous study limitations. |
| **Environmental exposure** | | | | | |
| Bove *et al.* 2014 | North Carolina (USA) (Camp Lejeune)<br>154,932 men and women | TCE in drinking water (µg /L-month)<br>< 1 (43%)<br>> 1–3,100 (20%)<br>> 3,100–7,700 (18%)<br>> 7,700–39,745 (20%) | | HR<br>1.0; 13<br>1.54 (0.65–3.61); 11<br>1.21 (0.47–3.09); 8<br>1.52 (0.64–3.61); 11 | Estimated mean levels (µg/L-month): TCE: 358.7 from water supply; cumulative exposure = 6,369 (median), 5,289 (mean); 20% were exposed to levels between 7,700 and 39,745<br>Covariates: sex, race, and education; other variables considered in the model (did not change risk estimates by 10%) include marital status, birth cohort, date of death, duty occupation<br>Strengths: Large cohort and adequate modeling of exposure<br>Limitations: Young cohort; no information on individual water consumption<br>Limited evidence of an association |

CI = confidence interval; F = female; HR = hazard ratio; JEM = job exposure matrix; M = male; NR = not reported; OR = odds ratio; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRR = standardized rate ratio; TCA = trichloroacetic acid; TCE = trichloroethylene; U-TCA = urine trichloroacetic acid.

[a]Within each category, studies are generally organizing by descending publication date, however, studies with some overlap or of similar industries are kept together.

[b]As reported by Scott and Jinot (2011).

**Table 4-2. Case-control studies of trichloroethylene exposure: Findings for kidney cancer.**

| Reference | Study Size (N) Exposure assessment | Exposure groups | RR or OR (95% CI) # exposed cases/controls | Interpretation |
|---|---|---|---|---|
| **Studies in specific areas with knowledge of local industries** | | | | |
| Brüning *et al.* 2003<br>(no overlap with Vamvakas *et al.* 1998) | Germany regional (Arnsberg) hospital-based<br><br>134 cases (83 M, 51 F)<br>401 hospital controls (225 M, 176 F)<br><br>Self-assessed exposure including self-reported narcotic symptoms, JEM based on CAREX database (job titles) or British JEM for grouped solvents | *CAREX Database*<br>Longest held job with TCE/Perc exposure (compared with no TCE)<br><br>Any metal greasing/degreasing<br><br>*Self-assessed TCE exposure*<br>Ever<br>Exposure + Narcotic symptoms<br>Any<br>Non-daily occurrence<br>Daily occurrence<br><br>Duration exposure (yr)<br>No exposure<br>< 10<br>10–19<br>20+<br><br>Time since 1st exp (yr)<br>No exposure<br>5–9<br>10–19<br>20+<br><br>No increasing risks with time since last exp. | OR<br>1.80 (1.01–3.20)<br><br>5.57 (2.33–13.32); 15/11<br><br>2.47 (1.36–4.49); 25/38<br><br>3.71 (1.80–7.54); 19/18<br>4.60 (1.87–11.30); 5/4<br>5.91 (1.46–23.99); 5/4<br><br>1.00; 109/363<br>3.78 (1.54–9.28); 11/14<br>1.80 (0.67–4.79); 7/13<br>2.69 (0.84–8.66); 6/7<br><br>1.00; 109/363<br>3.21 (0.28–37.38); 1/2<br>1.50 (0.28–8.10); 2/6<br>2.86 (1.49–5.49); 22/27 | Very high exposure and long exposures; estimated exposure 400 to 600 ppm during peak (hot dipping) and > 100 ppm overall (Cherrie *et al.* 2001). Approx. 50% cases >10 years' exposure.<br><br>Covariates: Sex, age, smoking; cases and controls had similar BMI<br><br>Strengths: Appears reasonable that workers with self-reported exposure had high levels of exposure and exposure to other chlorinated solvents was unlikely.<br><br>Limitations: Qualitative exposure assessment; possible selection bias<br><br>Evidence for an association that is unlikely explained by confounding |
| Vamvakas *et al.* 1998 | Germany regional hospital-based | Ever TCE exposure<br>*TCE exposure categories* | OR<br>10.80 (3.36–34.75); 19/7 | High level of exposure (see Brüning *et al.*) Mean duration of exposure: |

| Reference | Study Size (N) Exposure assessment | Exposure groups | RR or OR (95% CI) # exposed cases/controls | Interpretation |
|---|---|---|---|---|
| | 58 RCC cases<br>84 hospital controls<br>Expert assessment based on severity of pre-narcotic symptom and exposure duration using occupational history data from interviews | No TCE exposure<br>Low TCE exposure<br>Medium TCE exposure<br>High TCE exposure | 1.00; 39/77<br>6.61 (0.50–87.76); 2/2<br>11.92 (2.55–55.60); 9/3<br>11.42 (1.96–66.79); 8/2 | 16 years cases, 7 years controls.<br>Covariates; age, gender, smoking, blood pressure, and diuretic intake<br>Strengths: High level of confidence that workers had high level of exposure and exposure to other chlorinated solvents was unlikely<br>Limitations: Potential selection bias (differential) away from the null<br>Evidence of a positive association. Potential for biases would lead to an over-estimate of the risk estimate but unlikely to nullify the positive association. Confounding by co-exposure not likely. |
| Charbotel *et al.* 2006, 2009 | Arve Valley, France<br>86 RCC cases<br>326 hospital controls | *2006 analysis*<br>Non-exposed (ever)<br>Ever exposed<br><br>*High confidence (Model 1)*<br>Cumulative dose<br>Non-exposed<br>Low<br>Medium<br>High<br><br>*Cumulative exp. + peaks*<br>Non-exposed<br>Low/medium no peaks<br>Low/medium + peaks<br>High no peaks<br>High + peaks | OR<br>1.00; 44/188<br>1.88 (0.89–3.98); 16/37<br><br><br><br>1.00<br>0.85 (0.10–7.41); 1/8<br>1.03 (0.29–3.70); 4/13<br>3.34 (1.27–8.74); 11/16<br><br><br>1.00; 44/188<br>0.90 (0.27–3.01); 4/18<br>1.34 (0.13–14.02); 1/3<br>2.74 (0.66–11.42); 4/8<br>3.80 (1.27–11.40); 7/8 | High intensity of exposure and high exposure prevalence. Screw cutting industry. Estimated TCE intensities for high exposure jobs were 300–600 ppm.<br>Covariates: (Model 1) sex, age, smoking, BMI; (Model 2) sex, age, cutting oils, petroleum oils, and/or other mineral oils. No significant difference between cases and controls in a number of medical history-related factors<br>Strengths: Good exposure assessment and consideration of co-exposures.<br>Limitations: Small number of |

| Reference | Study Size (N) Exposure assessment | Exposure groups | RR or OR (95% CI) # exposed cases/controls | Interpretation |
|---|---|---|---|---|
| | | *All workers*<br>High cum. dose (Model 1)<br>High cum. dose (Model 2)<br>High + peak (Model 1)<br>High + peaks (Model 2)<br><br>*2009 analysis: combined effects TCE & cutting oil (Model 2)*<br><u>Cutting oil/TCE</u><br>No/No<br>Yes/No<br>No/Yes<br>Yes/< 50 ppm<br>Yes/≥ 50 ppm | <br>2.16 (1.02–4.60); 16/37<br>1.96 (0.71–5.37)<br>2.73 (1.06–7.07); 8/14<br>2.63 (0.79–8.83)<br><br><br><br>1.00; 46/200<br>2.39 (0.52–11.03); 3/6<br>1.62 (0.76–3.44); 15/46<br>1.14 (0.49–2.66); 12/47<br>2.70 (1.02–7.17); 10/1 | exposed cases and controls in subgroup analyses<br><br>Evidence of an association with TCE unlikely explained by confounding. |
| Moore *et al.* 2010 | Central/Eastern Europe<br><br>Hospital based<br><br>1999–2003<br><br>1,097 cases RCC<br>1,476 hospital controls<br><br>Expert assessment based on occupational data from interviews. | *High confidence assessments*<br>No TCE exposure<br>Ever TCE exposure<br><u>Years TCE Exposure</u><br>< 13.5<br>≥ 13.5<br>$P_{trend}$<br><u>Hours TCE Exposure</u><br>< 1080<br>≥ 1080<br>$P_{trend}$<br><u>Cumulative (ppm-yr)</u><br>< 1.58<br>≥ 1.58<br>$P_{trend}$<br><u>Average intensity (ppm)</u><br>< 0.076<br>≥ 0.076<br>$P_{trend}$ | OR<br>1.00<br>2.05 (1.13–3.73); 29/19<br><br>1.89 (0.84–4.28); 15/10<br>2.25 (0.95–5.29); 14/9<br>0.02<br><br>1.22 (0.48–3.12); 9/9<br>2.86 (1.31–6.23); 20/10<br>0.01<br><br>1.77 (0.64–4.80); 9/7<br>2.23 (1.07–4.64); 20/10<br>0.02<br><br>1.73 (0.75–4.02); 13/10<br>2.41 (1.05–5.56); 16/9<br>0.02 | Intensity and prevalence of occupational exposure have been higher in central and eastern Europe than other industrial areas.<br><br>Covariates: Age, sex, center; residence, smoking, BMI, and history of hypertension considered but did not affect risk estimate<br><br>Strengths: Analysis of high confidence assessment reduces potential for exposure misclassification. Large number of exposed cases and controls in overall and subanalysis<br><br>Limitations: Potential for selection bias.<br><br>Evidence for a positive association unlikely explained by biases or |

| Reference | Study Size (N) Exposure assessment | Exposure groups | RR or OR (95% CI) # exposed cases/controls | Interpretation |
|---|---|---|---|---|
| | | *TCE exposure stratified by GSTT1*<br>*GSTT1 null*<br>No<br>Yes<br><br>Duration (years)<br>Hours<br>Cumulative exposure<br>Average exposure<br>*GSTT1 Active*<br>No<br>Yes<br><br>Duration (years)<br>Hours<br>Cumulative exposure<br>Average exposure | <br><br><br>1.0 reference<br>0.93 (0.35–2.44)<br>$P_{trend}$<br>0.41<br>0.95<br>0.75<br>1.0<br><br>1.0 reference<br>1.88 (1.06–3.33); 23<br>$P_{trend}$<br>0.03<br>0.02<br>0.01<br>0.02 | confounding. Higher risks of cancer among subjects with an active GSTT1 allele compared with subjects with GSTT1 null genotype is consistent with proposed mechanism of carcinogenicity. |
| Christensen *et al.* 2013 | Montreal, Québec (Canada)<br>Population- and hospital-based<br>1975–1985<br>177 male RCC cases<br>RCC 533 population-based controls<br>1999 cancer controls<br>Expert assessment of occupational data from interviews | <br>Ever exposure<br>Substantial exposure | OR (95%CI) #cases/#cancer controls/#population controls<br>0.9 (0.4–2.4); 5/63/15<br>0.6 (0.1–2.8); 2/34/9 | Exposure prevalence to TCE very rare; ≤ 2% of cancer controls or population controls had substantial exposure and 3% had any exposure<br>Covariates: age, census tract, median income, ethnicity, self vs. proxy respondent, smoking, alcohol assumption, coffee use<br>Strengths: Adequate quality of exposure assessment<br>Limitations: Low exposure prevalence resulting in low statistical power<br>Null: No evidence of an association |

| Reference | Study Size (N) Exposure assessment | Exposure groups | RR or OR (95% CI) # exposed cases/controls | Interpretation |
|---|---|---|---|---|
| | | | | but study had low statistical power |
| Pesch *et al.* 2000a | Germany<br>Cancer registry study<br>935 (570 M, 365 F) RCC cases<br>4,298 (2,650 M, 1,648 F) registry control<br>JEM and JTEM | *JTEM*<br>Men<br>No exposure<br>Medium TCE exposure<br>High TCE exposure<br>Substantial TCE exposure<br><br>Women<br>No exposure<br>Medium TCE exposure<br>High TCE exposure<br>Substantial TCE exposure | (Controls not reported)<br>OR<br>1.00<br>1.3 (1.0–1.8); 68<br>1.1 (0.8–1.5); 59<br>1.3 (0.8–2.1); 22<br><br>OR<br>1.00<br>1.3 (0.7–2.6); 11<br>0.8 (0.4–1.9); 7<br>1.8 (0.6–5.0); 5 | Prevalence of substantial TCE exposure was low among cases and varied by type of JEM.<br>Covariates: age, center, and smoking. Cases and controls did not differ in BMI, education, age, region, and smoking status and analgesics use.<br>Strengths: Adequate number of exposed cases and controls<br>Limitations: Potential for exposure misclassification<br>Limited evidence for a possible association |
| Dosemeci *et al.* 1999 | Minnesota (USA)<br>Registry-based<br>1988–1999<br>438 living cases RCC (273 M, 165 F); 687 population controls<br>Qualitative JEM based on occupational data from interviews | Men<br>Women<br>Total | 1.04 (0.6–1.7); 33 (controls NR)<br>1.96 (1.0–4.4); 22 (controls NR)<br>1.30 (0.9–1.9); 55 (controls NR) | Exposure prevalence to TCE among controls was 13%.<br>Covariates: age, sex, smoking, BMI, hypertension, use of diuretics or hypertension drugs<br>Strengths: Adequate number of exposed cases and controls<br>Limitations: Exposure assessment only considered current and usual jobs, no assessment of intensity or duration of exposure.<br>Limited evidence of an association among women but not men; unclear why the association is sex specific. |

BMI = body mass index; Cum. = cumulative; Exp. = exposure; JEM = job exposure matrix; JTEM = job task exposure matrix; NR – not reported; OR = odds ratio; ppm = parts per million; RCC = renal cell carcinoma; RR = relative risk; TCE = trichloroethylene.

### 4.1.2 Meta-analyses: kidney cancer

Meta-analyses have been recommended as an approach to analyze the body of epidemiological studies of trichloroethylene (NRC 2006) in order to provide a synthesis of data and to partly overcome the limitations of individual studies due to low statistical power. Several meta-analyses of kidney cancer and trichloroethylene exposure have been conducted (Wartenberg *et al.* 2000, Kelsh *et al.* 2010, EPA 2011a/Scott and Jinot 2011, Karami *et al.* 2012a). This evaluation is limited to the recent meta-analyses by the EPA (EPA 2011a/Scott and Jinot 2011), Karami *et al.* (2012a) and Kelsh *et al.* (2010). The EPA and Karami *et al.* meta-analyses primarily analyzed cohort and case-control studies with specific exposure to trichloroethylene reviewed in this monograph although Karami *et al.* (2012a) also included two studies (Asal *et al.* 1988, Harrington *et al.* 1989) that were not considered to be specific for trichloroethylene and thus were excluded from this evaluation. The meta-analysis by Kelsh *et al.* also included a larger number of studies not specific for trichloroethylene that were excluded from this monograph (see Table 4-3). Both the EPA (Scott and Jinot 2011) and Karami *et al.* (2012) meta-analyses pre-dated the pooled and updated Nordic cohort study (Hansen *et al.* 2013), the population-based Nordic study by Vlaanderen *et al.* (2013), the Montreal case-control study by Christensen *et al.* (2013), and the drinking water study by Bove *et al.* (2014). The EPA meta-analysis (Scott and Jinot 2011) included an earlier update (Boice *et al.* 1999) of the cohort study of aircraft manufacturing workers in Burbank, CA, whereas the later update (by Lipworth *et al.* 2011) was included in the analysis by Karami *et al.* (2012). An earlier update of the Montreal Canadian study or the component studies (in the case of the pooled analysis) were included in both meta-analyses and the only new study populations are those reported by Vlaanderen *et al.* (2013) and Bove *et al.* (2014).

The EPA meta-analyses (EPA 2011a, Scott and Jinot 2011) included systematic data extraction of eight cohort and seven case-control studies (including one nested case-control study) in which potential trichloroethylene exposure was documented and risk estimates for kidney cancer and trichloroethylene exposure were calculated (Table 4-3). Studies with evidence of a low potential for exposure to trichloroethylene were excluded. Fixed and random effects models, tests for heterogeneity and publication bias, and sensitivity analyses (to examine the impact of individual studies and selection of alternative relative risk selections on meta-relative risk estimates) were used to calculate summary meta-relative risks using, where provided, adjusted or crude risk estimates from internal analyses rather than external (SMR or SIR) estimates. In addition, separate meta-analyses were conducted for the highest exposure groups (either by duration and/or intensity) within trichloroethylene-exposed populations (reported in 13 of the 15 constituent studies). In these highest exposure subgroups, non-differential misclassification of exposure would be expected to be less than among the whole group, bearing in mind that actual levels and lengths of exposure might have differed considerably across studies.

Karami *et al.* (2012) used similar inclusion/exclusion criteria to the EPA and considered an overlapping body of studies, but with the inclusion of cohort studies by Boice *et al.* (2006) (rather than Zhao *et al.* 2005, with which it overlaps) and Lipworth *et al.* (2011) and, as noted, the case-control studies by Asal *et al.* (1988) and Harrington *et al.* (1989). Initial examination of the cohort study of German cardboard manufacturers (Henschler *et al.* 1995) and the case-control study by Vamvakas *et al.* (1998) introduced the greatest heterogeneity and so were excluded from some analyses. Only the data for analyses excluding these studies, which are more closely

comparable with the EPA analysis, are reported in Table 4-3 below. Since Kelsh *et al.* (2010) included a number of studies that were considered non-specific for trichloroethylene exposure, the results should be interpreted with caution.

**Table 4-3. Meta-analyses of kidney cancer and trichloroethylene exposure**

| Reference | Study design (# studies) | mRR (95% CI) All | mRR (95% CI) Highest exposure | Comments |
|---|---|---|---|---|
| EPA 2011a/Scott-Jinot 2011 | Combined cohort and case-control studies (15 for any exposure, 13 for high exposure) | 1.27 (1.13–1.43) | 1.58 (1.28–1.96) | Random effects model<br>Low sensitivity to removal of individual studies or selection of alternative RRs<br>Little evidence of heterogeneity or publication bias |
| EPA 2011a/Scott-Jinot 2011 | Cohorts (8) | 1.16 (0.96–1.40) | NR | No sig. diff. between cohort and case-control mRRs<br>No heterogeneity in cohorts, low to moderate heterogeneity in case-control studies |
| EPA 2011a/Scott-Jinot 2011 | Case-control (7) | 1.48 (1.15–1.91) | NR | |
| Karami *et al.* 2012a | TCE-exposed cohort + case-control studies (18) | 1.32 (1.17–1.50)[a] | NR | Random effects model<br>Little evidence of heterogeneity and publication bias;<br>Higher mRR among incidence vs. mortality studies |
| Karami *et al.* 2012a | TCE-exposed cohorts (9)<br><br>*Exp.-Response*<br>Long duration vs. Short duration (3)<br><br>Subset of U-TCA studies (3) | 1.26 (1.02–1.56)[a]<br><br><br><br><br>1.03 (0.59–1.78) | <br><br><br>1.52 (1.08–2.13)<br>0.90 (0.56–1.45) | Little evidence of heterogeneity or publication bias |
| Karami *et al.* 2012a | TCE-exposed case-control studies (9)<br><br>*Exp.-Response*<br>High intensity vs. Low intensity (6) | 1.35 (1.17–1.57)[a] | <br><br><br>1.68 (1.23–2.30)<br>1.49 (1.02–2.17)[a] | Little evidence of heterogeneity or publication bias |
| Kelsh *et al.* 2010 | TCE-exposed cohorts (8)<br><br>*Exp.-Response*<br>Long duration vs. | 1.34 (1.07–1.67)[a] | <br><br><br>1.24 (0.69–2.23)<br>1.50 (0.89–2.26) | Little evidence of heterogeneity or publication bias |

| Reference | Study design (# studies) | mRR (95% CI) All | mRR (95% CI) Highest exposure | Comments |
|---|---|---|---|---|
| | Short duration[b] (7)<br><br>High cum. exp. vs. Low cum. exp.[b] (3) | | <br><br>1.39 (0.75–2.59)<br>1.29 (0.68–2.47)[a] | |
| Kelsh *et al.* 2010 | TCE-exposed case-control (6) | 1.33 (1.02–1.73) | See above | Little evidence of heterogeneity or publication bias |

mRR = meta-relative risk; NR = not reported; RR = relative risk; U-TCA = urine trichloroacetic acid
See Appendix D for a list of the studies include in the meta-analyses.
[a]Excluding studies by Henschler *et al.* 1995 and/or Vamvakas *et al.* 1998.
[b]Combined cohort and case-control studies

The overall results of the three meta-analyses were broadly comparable, with some variation partly depending on which specific studies were included. Both cohort and case-control studies, separately and combined, yield robust and statistically significant but modest increases in meta-relative risks (mRRs) for kidney cancer in the two most recent and comparable meta-analyses, ~ 1.3 (for case-control and cohort combined), with little evidence of heterogeneity and publication bias, and with slightly higher statistically significant mRRs among the case-control studies than the cohort studies. Importantly the mRR was robust and not sensitive to removal of individual studies or selection of alternative RRs. Investigation of the highest exposure groups in the EPA analysis of the combined cohort and case-control studies (EPA 2011a, Scott and Jinot 2011), yielding a statistically significant mRR of 1.58, provides some evidence of higher risk among more highly exposed workers. This was similar to the mRRs for higher exposure calculated in the separate cohort and case-control analyses by Karami *et al.* (2012a), but slightly higher than those reported by Kelsh *et al.* (2010) (which, as noted, included some different studies). However, the data were insufficient to distinguish which metric of exposure (among the studies categorized as "high" exposure) is more clearly associated with an increase in the risk of kidney cancer mRRs.

#### *4.1.2.1 Evaluation of potential confounding by occupational co-exposures or other risk factors*

Section 3 discussed the adequacy of the methods used in the cohort (Section 3.1) and case-control studies (Section 3.2) for evaluating potential confounding from occupational co-exposures and non-occupational factors. However, that assessment was not specific for kidney cancer. This section builds on that assessment, integrating it with other relevant information and evaluating whether confounding can explain the increased risks of kidney cancer observed in many of the studies.

#### *4.1.2.2 Occupational co-exposures*

With respect to occupational agents, IARC (Cogliano *et al.* 2011) and/or the Report on Carcinogens (NTP 2011) have identified X-radiation as a known kidney carcinogen in humans and concluded that there was limited evidence of carcinogenicity for arsenic, cadmium, and printing processes. Few of the cohort and nested case-control studies provided qualitative or quantitative data on potential co-exposures or adjusted (or considered) for them in statistical analyses. The potential co-exposures include a wide range of other chemical or physical agents,

principally the chlorinated solvents tetrachloroethylene and 1,1,1-trichloroethane in both the Nordic and aerospace and aircraft studies and cutting fluids such as mineral and petroleum oils, hydrazine, benzene, chromates, and PAHs in the aerospace and aircraft industries, although the most common co-exposures among the group of studies are probably chlorinated solvents and cutting oils such as mineral and petroleum oils. The workers in the Nordic studies had diverse occupations, and thus the types, patterns, and levels of co-exposures to other agents are likely to vary across the different industries and time periods. In most studies, it is not clear if or how strongly exposures to other occupational agents were correlated with exposure to trichloroethylene. Moreover, none of these substances has been identified as a known or suspected kidney carcinogen in humans to date although some are carcinogenic in animals. IARC (2014) recently concluded that there was little overall evidence of an association of exposure to tetrachloroethylene with kidney cancer in humans. No independent epidemiological data on 1,1,1-trichoroethane and kidney cancer were identified.

The two studies of aerospace workers, which found a positive association between trichloroethylene exposure and kidney cancer, adjusted for exposure to known co-exposures. Zhao *et al.* (2005) directly adjusted for co-exposures (mineral or petroleum oils) in their internal analysis of trichloroethylene and kidney cancer risk, and Boice *et al.* (2006) adjusted for hydrazine exposure.

Case-control studies were more limited on information for potential occupational co-exposures. However, as in the Nordic studies, workers were from diverse industries, with varying types and patterns of co-exposures. Only one study (Charbotel *et al.* 2006, 2009) adjusted for co-exposures (to petroleum and cutting oils); risks for trichloroethylene exposure were still elevated but slightly attenuated (from 2.23 to 1.96) and an elevated risk (although not statistically significant) was observed among workers without exposure to mineral oils in combined analyses. There is no independent evidence that mineral oils are associated with kidney cancer.

#### *4.1.2.3 Lifestyle and other potential confounders*

Non-occupational risk factors for kidney cancer include tobacco smoking, obesity (BMI), diabetes, hypertension (diuretics), and X-radiation (see e.g., Chow *et al.* 2010, Cogliano *et al.* 2011). It is not clear whether any of these would be associated with trichloroethylene exposure but tobacco smoking may be the most likely risk factor.

The majority of cohort and nested case-control studies conducted age-, sex-, race- and calendar-year or period-standardized comparisons in external analyses (SMR or SIR) where appropriate and age-, sex-, race- and in some cases calendar-period-adjusted comparisons in internal analyses. In addition, all of the studies, except for the Danish blue-collar worker study, conducted internal analyses, which would mitigate potential confounding from lifestyle factors. Each of the case-control studies, in addition to matching or adjusting for demographic variables including age, sex, and residential location, examined or adjusted for BMI and/or measures of hypertension, with the exception of Christensen *et al.* (2013) and Vamvakas *et al.* (1998). There was no clear evidence of confounding by these variables in the studies that examined or adjusted for them. Some studies also considered socioeconomic factors (Christensen *et al.* 2013), medical history or conditions (Vamvakas *et al.* 1998, Pesch *et al.* 2000a, Moore *et al.* 2010, Dosemeci *et al.* 1999), or other lifestyle factors (Christensen *et al.* 2013).

Across the body of studies, potential confounding from smoking can reasonably be ruled out. Smoking is a relatively weak risk factor for renal cancer (~1.4 for current smoking in meta-analyses data), and the NRC (2006) estimated that it most likely would only account for ~10% increase in risk if smoking differences were 20% higher among trichloroethylene-exposed populations. Although most of the cohort studies did not adjust for smoking, lung cancer rates among the trichloroethylene-exposed workers appear to be unremarkable, with the exception of significantly elevated risks (~ 40%) for men and women in the Danish blue-collar cohort (Raaschou-Nielsen *et al.* 2003); however, this likely explains less than 6% of the excess risk from trichloroethylene (EPA 2011a). The EPA (2011a) also found no association with lung cancer and trichloroethylene in a meta-analysis of studies (OR ~ 1 for all studies and also for high trichloroethylene exposure).

Overall, there was little evidence to suggest that confounding by occupational co-exposures explains the observed increases in kidney cancer, which have been reported in populations with different industries and lifestyle factors and in different regions.

#### 4.1.3 Forest plot methods

Forest plots were constructed using risk estimates for kidney cancer and ever exposure (Figure 4-2) or the highest exposure category (Figure 4-3) and grouping the studies by study quality ranking or broad group of estimated exposure (high exposure risk estimates only) (Figure 4-4). Cohort and case-control studies were presented together because the meta-analyses did not report statistically significant differences for the meta-relative risks between the two study designs.

*High exposure category:* For each study, risk estimates (SMR, SIR, RR, HR, or OR) were extracted for the highest estimated exposure group (intensity or cumulative exposure), if reported. In the cohort study by Lipworth *et al.* (2011), duration was used because risk by exposure level was not reported. In some cases, surrogates for exposure intensity were used. Calendar year was used as a surrogate in one cohort study (Raaschou-Nielsen *et al.* 2003) because additional data suggested that average exposures were highest in the earliest calendar period (prior to 1970). In the case-control study of renal-cell carcinoma by Brüning *et al.* (2003), prevalence of narcotic symptoms was used as a surrogate by the authors to indicate the highest exposed workers.

*Study quality:* Studies were ranked into categories: high; moderate; low with potential bias most likely towards the null; and low with potential bias most likely towards a positive effect (overestimate of the risk estimate). Studies with low or low/moderate study quality in Figure 4-2 were combined into one category. This broad ranking was based on consideration of selection bias and information bias (quality of exposure and disease characterization and likely degree of exposure or disease misclassification), and on study sensitivity (as a function of statistical power, estimated exposure levels, and length of follow-up). (See Sections 3.2.2.6, 3.3.2.6 and 3.4.2.6 and Appendix D, and Figure 4.1) for detailed summaries of study quality.)

*Ranked estimated exposure:* For each study the risk estimate and 95% CI for the highest exposure level were plotted as described above. The studies reported different metrics of exposure, including intensity (or surrogate for intensity), cumulative exposure, and duration. Some studies used an exposure category that integrated confidence or probability with intensity or duration (Pesch *et al.* 2000a, Christensen *et al.* 2013b). Although there were very few data on

actual exposure levels, some authors or reviewers have estimated exposure for either jobs or cumulative exposure or intensity for individuals, and this information was used to group the studies in three broad exposure level groups. (See Tables D-4a, and D-5a for estimated exposure level and ranked exposure group). The exposure group (high to very high, moderate to high, low) is for the estimated exposure level for the exposure metric reported in that study, e.g. studies reporting risk estimates for exposure for cumulative exposure are ranked according to the estimated cumulative exposure for that study.

#### 4.1.4 Integration across studies

There is credible evidence of an association between exposure to trichloroethylene and renal-cell cancer risk based on consistent findings of increased risks of kidney cancer across studies of different designs, different geographical areas, and different occupational settings (see Figures 4-2 to 4-3) and evidence of exposure-response relationships. The most convincing evidence for an association between kidney cancer incidence and exposure to trichloroethylene comes from the three most informative (high quality) studies (Charbotel *et al.* 2006, 2009, Moore *et al.* 2010, Zhao *et al.* 2005), and two studies with moderate or moderate to low quality, a Nordic cohort of blue-collar workers in companies using trichloroethylene (Raaschou-Nielsen *et al.* 2003), and a case-control study from an area in Germany with known trichloroethylene exposure (Brüning *et al.* 2003), all of which found statistically significant elevated risks of kidney cancer among workers with the highest exposure to trichloroethylene (see Figure 4.3). These findings are supported by weaker associations (in analyses of high or ever exposure to trichloroethylene) found in most of the other studies considered to be of moderate study quality (Hansen *et al.* 2013, Morgan *et al.* 1998), and some studies considered to have low to moderate study quality (Dosemeci *et al.* 1999, Pesch *et al.* 2000a,) or low quality (Bove *et al.* 2014, Silver *et al.* 2014). Limitations in most of these studies would most likely bias towards the null, and the fact that the studies were considered to be of lower quality does not detract from the positive evidence. Statistically significant increased risks were also found in two German studies located in a geographical area known to have industries with exposure to high levels of trichloroethylene: a cohort study of cardboard manufacturing workers (Henschler *et al.* (1995), and a case-control study by Vamvakas *et al.* (1998). Both of these studies have potential biases that would most likely lead to an overestimate of the risk estimate although it is unlikely that the biases nullify the large excess risk found in these studies. Figure 4-3 plots the risk estimate for high exposure group from each study and groups the studies according to broad groups of estimated exposure. The highest risks were found among studies with very high or high to moderate exposure to trichloroethylene and findings were more heterogeneous among studies with low estimated exposure.

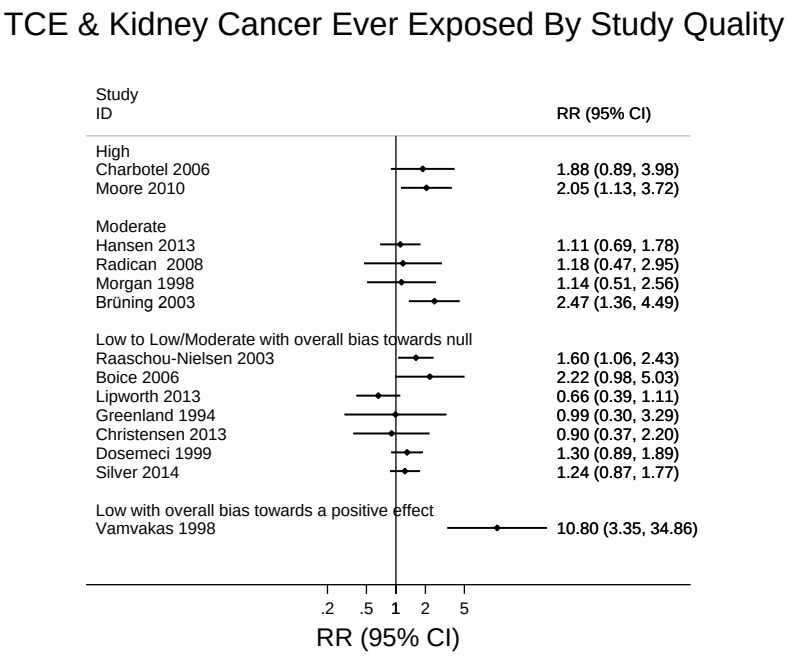
Meta-analyses are useful for evaluating potential heterogeneity between studies or types of studies and also for summarizing the results of underpowered studies. The most recent meta-analyses (Scott and Jinot 2011, Karami *et al.* 2012a) provide strong evidence for an association between trichloroethylene exposure and kidney cancer. Both analyses found statistically significant meta-relative risks of similar magnitudes, i.e., 1.27 (95% CI = 1.13 to 1.43) by Scott and Jinot (2011) and 1.32 (95% CI = 1.17 to 1.50) by Karami *et al.* (2012a). Importantly, the mRR was robust and not sensitive to removal of individual studies or selection of alternative RRs. There was no evidence of publication bias or heterogeneity across studies (which did not include the studies by Vamvakas *et al.* and Henschler *et al.*, which have the high risk estimates) or publication bias in both meta-analyses. Although a higher mRR was found for cohort studies

than case-control studies, the subgroup risk estimates for case-control and cohort studies did not significantly differ from each other.

There was evidence for positive exposure-response relationships or higher risks in more highly or longer exposed groups in both cohort and case-control studies with several exposure metrics. Risks increased with increasing exposure intensity or cumulative exposure in the cohort study of aerospace workers (Zhao *et al.* 2005), the French case-control study, which was primarily of workers in the screw-cutting industries (Charbotel *et al.* 2006, 2009), the European study (Moore *et al.* 2010), and the Nordic study of blue-collar workers (Raaschou Nielsen *et al.* 2003), using calendar year of first exposure as a surrogate for exposure level. Other studies found higher risk among individuals with longer exposure to trichloroethylene (Moore *et al.* 2010) or employment duration (Raaschou Nielsen *et al.* 2003). The meta-analyses also provide evidence for exposure-response relationships between trichloroethylene exposure and kidney cancer. The EPA meta-analysis found a higher mRR for higher-exposure groups (1.6) across studies compared with the risk for ever exposure across studies (1.3) (Scott and Jinot 2011). Karami *et al.* (2012a) found higher mRRs for high (vs. low) intensity exposure and long (vs. short) duration of exposure in separate analyses of cohort and case-control studies.

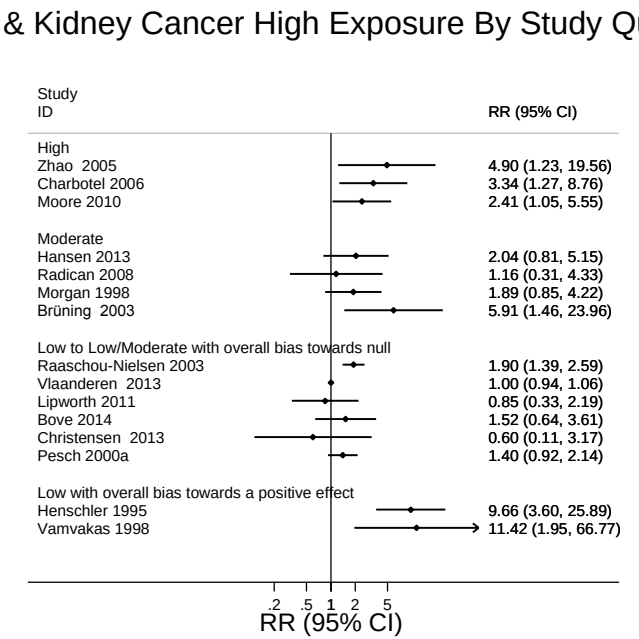
The findings across studies are unlikely to be explained by biases. Although selection bias cannot be ruled out in the studies by Henschler *et al.* (1995) and Vamvakas *et al.* (1998), these studies were not included in the meta-analyses, and thus do not affect the overall conclusion. Confounding from smoking and other lifestyle factors can also be reasonably ruled out across studies. Increased risks were found in case-control studies, which adjusted for these factors. Almost all the cohort studies conducted internal analyses, which can mitigate concerns about lifestyle factors, and the lack of an association with exposure to trichloroethylene and lung cancer in these studies argues against confounding by smoking, which is not strongly associated with renal cancer. Potential selection bias and confounding from smoking in the study of blue-collar worker does not explain all of the excess risk of kidney cancer associated with trichloroethylene exposure. Although information on occupational co-exposures is missing in most of the studies, the identified co-exposures were neither known nor suspected renal carcinogens. In addition, some of the positive studies found increased risks after controlling for (primarily mineral oils) or considering exposure to known occupational co-exposures; co-exposures were not likely to confound the German studies (Henschler *et al.* 1995, Brüning *et al.* 2003, Vamvakas *et al.* 1998). Most of the other positive studies were from diverse industries with varying levels and patterns of co-exposures. Exposure to chlorinated solvents other than trichloroethylene and mineral oils may be the most common exposures across industries, and these are not known or suspected renal carcinogens. Thus, no identified risk factors for renal cancer are likely to explain the increased risks found in these studies.

**Figure 4-2. Forest plot-1: Kidney cancer and ever exposure**



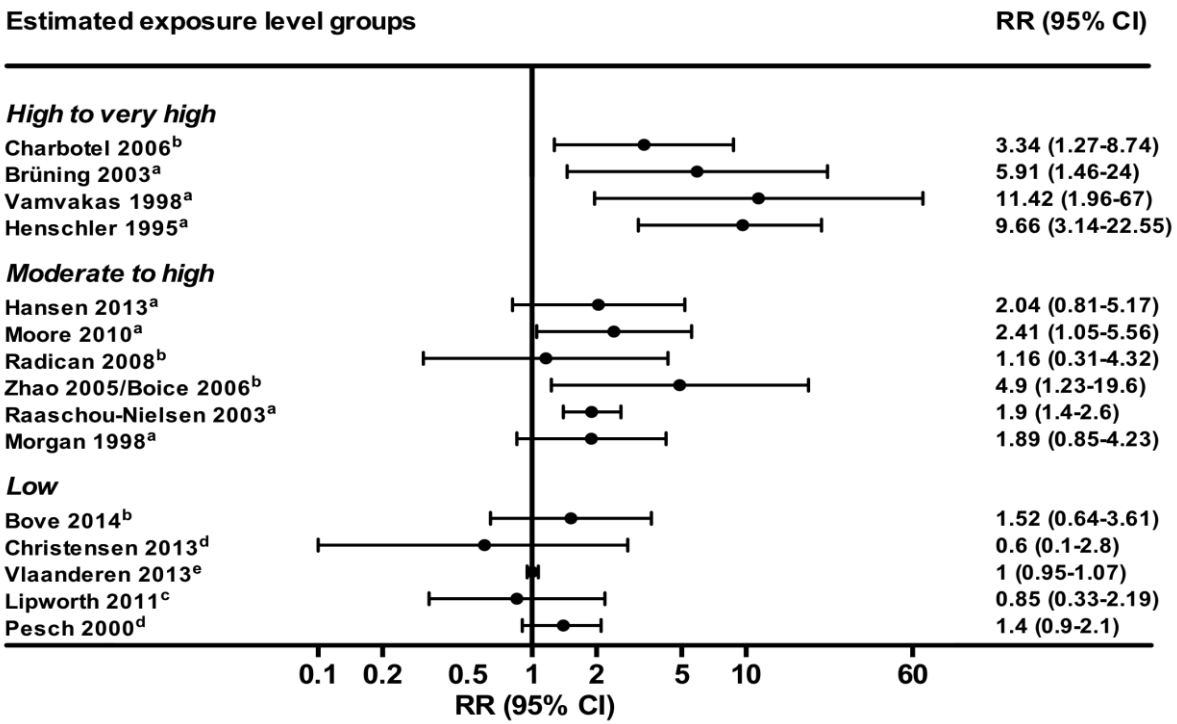

Relative risk and 95% CI for ever exposure to TCE and kidney cancer by study quality according Section 4.1.3. Studies by Bove *et a*l. (2014) and Vlaanderen *et al*. (2013) are not graphed because they did not report relative risk for ever exposure but they are reported in Figure 4-3.

**Figure 4-3. Forest plot-2: Kidney cancer and high exposure**




Relative risk and 95% CI for high exposure to TCE and kidney cancer by study quality according to Section 4.1.3. Studies by Greenland *et al.* (1994), Dosemeci *et al.* (1999), and Silver *et al.* (2014) are not graphed because they did not report a risk estimate for high exposure. Findings for these studies are reported in Table 4-1 and in Figure 4-2.

**Figure 4-4. Forest plot-3: Kidney cancer and estimated exposure level**




Relative risk and 95% CI for high exposure to TCE and kidney cancer and estimated exposure level as described in Section 4.1.3. Different metrics of exposure were graphed. a = exposure intensity, b = cumulative exposure, c = exposure duration, d = categories including confidence of probability of exposure with level and/or duration, and e = cumulative exposure measures that included exposure prevalence. Studies by Greenland *et al.* (1994), Dosemeci *et al.* (1999), and Silver *et al.* (2014) are not graphed because they did not report a risk estimate for high exposure. Findings for these studies are reported in Table 411 and Figure 4-2.

## 4.2 Mechanistic data for kidney carcinogenicity

EPA (2011a,b) and IARC (2014) recently reviewed the mechanistic data for trichloroethylene. The findings from these reviews and other mechanistic data are presented here. Relevant primary literature is cited if the study was not included in these reviews, or if specific data or further details of the study were needed for clarification.

### 4.2.1 Hypothesized modes of action

Hypothesized modes of action for kidney carcinogenicity include genotoxicity of glutathione (GSH)-derived metabolites, cytotoxicity and regenerative proliferation, peroxisome proliferation activated receptor α (PPARα) activation, $\alpha_{2u}$-globulin-related nephropathy, and formic acid-related nephrotoxicity (EPA 2011a). The key events associated with each of these hypothesized modes of action are listed in Table 4-4 and discussed in the following sections.

**Table 4-4. Hypothesized modes of action and key events for kidney tumors**

| Mode of action | Key events |
|---|---|
| Genotoxicity | 1. GSH-conjugation-derived metabolites produced *in situ* or delivered systemically to kidney.<br>2. Genotoxic effects induced by metabolites in kidney (e.g., mutations, DNA damage, DNA strand breaks, micronuclei) that advance acquisition of multiple critical traits contributing to carcinogenesis. |
| Cytotoxicity and regenerative proliferation | 1. GSH-conjugation-derived metabolites produced *in situ* or delivered systemically to kidney.<br>2. Cytotoxicity and compensatory cell proliferation.<br>3. Clonal expansion of initiated cells. |
| PPARα activation | 1. Oxidative metabolites produced in the liver activate PPARα in the kidney.<br>2. Alterations in cell proliferation and apoptosis.<br>3. Clonal expansion of initiated cells. |
| $\alpha_{2u}$-Globulin-related nephropathy (relevant only in male rats) | 1. Oxidative metabolites cause hyaline droplet accumulation and an increase in $\alpha_{2u}$-globulin resulting in nephrotoxicity.<br>2. Subsequent cytotoxicity, necrosis, and sustained regenerative tubule-cell proliferation.<br>3. Development of intraluminal granular casts from sloughed cellular debris associated with tubule dilation and papillary mineralization.<br>4. Foci of tubule hyperplasia in the convoluted proximal tubules.<br>5. Renal tubule tumors. |
| Formic acid-related nephropathy | 1. Oxidative metabolites produced in the liver lead to increased formation and urinary excretion of formic acid.<br>2. Increased formic acid causes cytotoxicity in the kidney.<br>3. Compensatory cell proliferation.<br>4. Clonal expansion of initiated cells. |

Source: Adapted from EPA 2011a.

### 4.2.2 Evaluation of the experimental support for the hypothesized modes of action

The toxicology of trichloroethylene has been extensively studied, and the data indicate that metabolites are responsible for most of the toxic effects. As discussed in Section 1.2, trichloroethylene is metabolized in the liver by two separate pathways, cytochrome P450-dependent oxidation (Figure 1-1) and GSH conjugation (Figure 1-2). These metabolic pathways act in parallel and may compete for trichloroethylene as a substrate, thus, factors that affect the relative flux of trichloroethylene through each pathway (e.g., metabolic saturation,

polymorphisms, enzyme induction/inhibition) can alter the toxic response. Both oxidative (trichloroethanol and trichloroacetic acid) and GSH-conjugation metabolites (DCVG, DCVC, and related metabolites) have been associated with various nephrotoxic effects; however, the experimental data indicate that metabolites derived from the GSH-conjugation pathway are more important for nephrotoxicity. The role of oxidative metabolites, if any, is comparatively small. This section reviews the experimental data and level of support for the hypothesized modes of action for kidney carcinogenicity in humans and laboratory animals.

#### *4.2.2.1 Genotoxicity*

Genotoxicity is a well-established cause of carcinogenicity. The key events include (1) GSH-conjugation-derived metabolites produced *in situ* or delivered systemically to the kidneys, and (2) mutagenic and genotoxic effects induced by these metabolites in the kidneys advance the acquisition of multiple critical traits contributing to carcinogenesis (EPA 2011a). These key events are discussed below.

Disposition and toxicokinetic data (reviewed in Section 1) show that metabolites from the GSH-conjugation pathway are formed in the liver and kidneys. Metabolites formed in the liver are delivered to the kidneys through the systemic circulation. *In vitro* studies using liver and kidney cells from humans and rodents and subcellular fractions incubated with trichloroethylene also have shown formation of GSH-derived metabolites. These metabolites include DCVG, DCVC, NAcDCVC, and other metabolites derived from subsequent β-lyase, flavin-containing monooxygenase 3 (FMO3), or CYP3A metabolism within the liver or kidneys (see Section 1.2.2, Figure 1-2). The data also show that levels of some of the metabolites (e.g., NAcDCVC) may accumulate in the kidney due to *in situ* production and systemic delivery from the liver.

Studies in humans provide support for the importance of the GSH conjugation pathway in renal cancer development in humans. Three studies, using different types of analyses (or statistical analyses), specifically investigated GST polymorphisms and renal-cell cancer among humans exposed to trichloroethylene (Brüning *et al.* 1997a, Wiesenhütter *et al.* 2007, Moore *et al*. 2010). The Central and Eastern European case-control study by Moore *et al.* (2010) (see Sections 3 and 4.1) was considered to be the most informative study to evaluate potential effect modification of GST genotypes and trichloroethylene exposure because of larger numbers of exposed kidney cancer cases and controls, study design (calculated ORs for trichloroethylene exposure stratified by GSTT1 genotype), and evaluation of exposure-response relationships. Positive associations ($P_{trend} < 0.05$) with kidney cancer were found for all trichloroethylene exposure metrics (any exposure, duration, average and cumulative exposure) among subjects with GSTT1 active genotypes but not with inactive genotypes (see Table 4.2). Moore *et al.* also found statistically significant interaction between trichloroethylene exposure (ever versus never) and minor alleles in single nucleotide polymorphisms (SNPs) spanning the renal cysteine β-lyase (*CCBL1*) gene region. The other two studies had limited methods for evaluating potential effect modification. Brüning *et al.* (1997a) reported that having a GSTT1 or GSTTM1 active genotype increased the risk of renal cancer in a small study of cases and controls, both of which had been exposed to high concentrations of trichloroethylene, from a highly industrial region in Germany (see Section 3 for a description of occupational exposure in this area, Arnsberg). EPA (2011a) noted that the frequency of GSTM1 in the controls was lower than that of background European populations. In a later study, using cases and controls from the hospital-based case-control study by Brüning

*et al* (2003) (see Sections 3 and 4.1), and an additional control group, Wiesenhütter *et al.* (2007) reported that frequency of GSTT1, GSTM1, and NAT1 polymorphisms was similar among cases and controls, and among trichloroethylene-exposed cases and non-exposed cases. Genotype distribution in exposed controls versus non-exposed controls was not reported and there appear to be some errors in the reporting of the frequency of the GSTT1 genotypes of exposed and non-exposed cases.

Although trichloroethylene was not mutagenic without metabolic activation in most standard bacterial assays, several metabolites derived from the GSH-conjugation pathway are genotoxic (see Section 2). Positive genotoxicity data for GSH–derived metabolites were reported from multiple *in vitro* and *in vivo* assays. DCVG, DCVC, and NAcDCVC were mutagenic in the Ames test, and kidney-specific genotoxic effects were reported in experimental animals. DCVC induced dose-dependent increases in unscheduled DNA synthesis in porcine kidney tubular epithelial cells and Syrian hamster embryo fibroblasts. Other genotoxic effects of DCVC included DNA strand breaks in the kidneys of rats and rabbits (oral exposure), and micronuclei in primary kidney cells from humans and rats. A single study in Eker rats, which are prone to the development of renal tumors, showed no increase in tumor incidence or in *VHL* mutations in trichloroethylene-exposed animals compared with controls (Mally *et al.* 2006).

Only one study was identified that investigated the genotoxic effects of trichloroethylene in the mouse kidney (Douglas *et al.* 1999). Mutations were not increased in the kidney of *lacZ* transgenic mice exposed to trichloroethylene vapors for 12 days (EPA 2011a). However, these results are not highly informative as to the role of mutagenicity in trichloroethylene-induced kidney tumors given the uncertainties of the mouse model in the production of genotoxic GSH conjugation metabolites and the low carcinogenic potency of trichloroethylene in the mouse kidney. Although renal tumors were not increased in mice, this is not an unusual finding compared with results for other genotoxic kidney carcinogens. Five of seven direct-acting genotoxic carcinogens also induced kidney tumors in rats but not in mice. Since kidney tumors are rare in rodents, and given that the incidence of kidney tumors was low in rats, it is not unreasonable that a small difference in potency in mice compared with rats would not be detected in chronic bioassays. Toxicokinetic data (see Section 1.3.2 and Appendix B) did not indicate that GSH conjugation and subsequent renal metabolism were lower in mice compared with rats; however, there is substantial uncertainty in the total flux through this pathway. Therefore, the lack of a detectable response in mice does not rule out a genotoxic mode of action.

Inactivation of the *VHL* tumor suppressor gene from base-change mutations, silencing, or small deletions is thought to be an early and causative event in human renal clear-cell carcinomas (EPA 2011a). Mutations in the *VHL* gene from exposure to trichloroethylene were evaluated in four case-control studies (Brüning *et al.* 1997b; Brauch *et al.* 1999, 2004; Charbotel *et al.* 2007) and one case series study (Moore *et al.* 2011) of renal-cell carcinomas (Table 4-5). Moore *et al.* (2011) reported that *VHL* inactivation, either through genetic alterations or promoter methylation in tumor DNA, occurred in more than 86% of the 470 sporadic clear-cell renal cancer cases examined. In addition, some researchers have reported differences between trichloroethylene-exposed and nonexposed renal-cell carcinoma patients in the frequency of somatic mutations in the *VHL* gene (Brauch *et al.* 1999, Brauch *et al.* 2004, Brüning *et al.* 1997b). The two studies by Brauch *et al.* reported multiple mutations in the *VHL* gene and increased frequencies with trichloroethylene exposure. Additionally, Brauch *et al.* (2004) reported that trichloroethylene-

exposed patients were diagnosed with renal-cell carcinoma at a younger age than non-exposed patients. Brauch *et al.* (1999) reported that 39% of clear-cell renal carcinomas from trichloroethylene-exposed individuals contained a hot-spot mutation (C to T transition) in the *VHL* gene at nucleotide 463 that caused a substitution of serine for proline at amino acid 81 (P81S). Overall, *VHL* mutations were found in about 75% of the exposed patients and there was an association between the number of mutations and the severity of trichloroethylene exposure. *VHL* mutations also were frequently accompanied by loss of heterozygosity. However, other researchers have not found a higher incidence of *VHL* mutations in trichloroethylene-exposed patients with renal clear-cell carcinomas compared with nonexposed patients (Charbotel *et al.* 2007, Moore *et al.* 2011). The Moore *et al.* (2011) study reported that most of the renal-cell carcinomas were clear-cell renal carcinoma, while < 10% of the cancers were non-clear-cell renal carcinoma. One study was unable to assess a change in mutations from trichloroethylene exposure, because no unexposed control was included (Brüning *et al.* 1997b). Of those cases with mutations in the *VHL* gene, mutations occurred more frequently in exon 1 (Brauch *et al.* 1999, Moore *et al.* 2011), exon 2 (Brüning *et al.* 1997b), and nucleotide 454, which is considered a hotspot (Brauch *et al.*1999, 2004). DeSimone *et al.* (2013) compared the activity of the trichloroethylene-associated P81S *VHL* mutation with cells expressing normal *VHL* and another *VHL* mutant (R167Q). Their data indicated that the P81S *VHL* mutation initiated pleiotropic effects that selectively influenced tumor behavior in a mutation-specific manner. These effects provided a selective growth advantage through metabolic pathway diversification, suppression of apoptosis, and alteration of DNA damage response.

Further data are needed to determine the validity of *VHL* mutations as a legitimate biomarker for trichloroethylene-induced renal tumors (EPA 2011a). If valid, these data suggest that a specific mutational spectrum may be associated with trichloroethylene-induced kidney tumors and adds biological plausibility for a mutagenic mode of action. There are currently no data to determine if there is a possible link between trichloroethylene metabolites and these events. Recent studies also suggest that multiple genes are involved in renal clear-cell carcinoma; therefore, the inconsistent results with respect to *VHL* mutations do not constitute negative evidence for a mutagenic mode of action. Overall, the data clearly show that human and rodent kidneys are exposed to GSH-derived metabolites following exposure to trichloroethylene and that these metabolites are capable of causing genetic damage. Thus, the data are sufficient to conclude that a mutagenic mode of action is likely operative in trichloroethylene-induced kidney tumors.

**Table 4-5. Studies of *VHL* mutation in trichloroethylene-exposed human subjects with renal-cell carcinoma**

| Reference<br>Country | Study Type<br>Population | Exposure Estimate<br>Method | Findings<br>Incidences | Comments |
|---|---|---|---|---|
| Brüning *et al.* 1997<br>Germany | Case-control<br>23 exposed | Semi-quantitative<br>Work history and acute exposure symptoms | **Unable to assess mutation differences**<br>23/23 mutated in exposed<br>30% in exon 1<br>44% in exon 2<br>26% in exon 3 | No unexposed controls or increase in mutations with higher exposure |
| Brauch *et al.* 1999<br>Germany | Case-control<br>44 exposed<br>107 controls | Low/medium/high<br>Occupational hygienist | **Increased mutations**<br>33/44 mutated in exposed<br>54% in exon 1<br>39% at nucleotide 454<br>32% of mutations were multiple mutations<br>42/73 mutated in control<br>0% of mutations were multiple mutations | Number of mutations increased with higher levels of estimated exposure |
| Brauch *et al.* 2004<br>Germany | Case-control<br>17 (exposed)<br>21 (unexposed) | Low/medium/high<br>Occupational hygienist | **Increased mutations**<br>14/17 mutated in exposed<br>39% at nucleotide 454<br>50% of mutations were multiple mutations<br>2/21 mutated in control | RCC cases exposed or unexposed to trichloroethylene<br>Exposure decreased the age of diagnosis |
| Charbotel *et al.* 2007<br>France | Case-control<br>69 cases of RCC | Low/medium/high<br>Expert-evaluated questionnaire | **No mutation differences**<br>2/23 mutated in exposed<br>2/25 mutated in control | Low rate of mutation and no difference in mutations with exposure<br>Potential for exposure misclassification |
| Moore *et al.* 2011<br>Europe | Case series<br>470 sporadic clear cell RCC cases | Levels of exposure not reported<br>Expert interview | **No mutation differences**<br>415/470 mutated in clear cell renal carcinoma<br>37% in exon 1<br>30% in exon 2<br>26% in exon 3 | Level of exposure not reported.<br>Only 1 unexposed case had mutation at nucleotide 454.<br>Non-clear-cell renal carcinoma were < 10% of RCC. |

Source: IARC 2014.
RCC = renal-cell carcinoma.

#### *4.2.2.2 Cytotoxicity and regenerative proliferation*

The key events for cytotoxicity and regenerative proliferation are: (1) formation of cytotoxic GSH-conjugated metabolites of trichloroethylene either within the kidney or delivered systemically to the kidney, (2) nephrotoxicity leading to compensatory cellular proliferation and an increased mutation rate, and (3) tumor formation through clonal expansion of initiated cells. Although the available data currently are insufficient to establish a causal link between trichloroethylene-induced nephrotoxicity and sustained regenerative cellular proliferation and carcinogenicity, there is substantial evidence that trichloroethylene and/or its metabolites are nephrotoxic (EPA 2011a). The experimental evidence includes the following: (1) increased urinary excretion of nephrotoxicity markers in humans (especially evident from chronic occupational exposure to high concentrations), (2) near 100% incidence of proximal tubule toxicity in rats and mice in chronic bioassays at the highest doses tested, (3) proximal tubule toxicity in rodents following trichloroethylene exposure via inhalation or injection, (4) kidney toxicity in rodents exposed to DCVC and other GSH-conjugated metabolites, (5) toxicokinetic data showing that DCVC is formed in the kidney following exposure to trichloroethylene, and (6) data that demonstrate that nephrotoxic metabolites formed in the liver are delivered through the systemic circulation to the kidney.

Nephrotoxic trichloroethylene metabolites derived from the GSH-conjugation pathway are formed in the kidney and are delivered from the liver to the kidney via the systemic circulation (Irving and Elfarra 2012). Some nephrotoxic effects also have been reported for trichloroethanol and trichloroacetic acid (oxidative metabolites of trichloroethylene) in rats. Chronic exposure to trichloroethanol caused tubular degeneration in rats but there was no evidence of karyomegaly or cytomegaly (EPA 2011a, Green *et al.* 2003). Overall, trichloroethanol did not induce the same pathology as trichloroethylene or DCVC. Trichloroacetic acid administered to rats caused an increase in the kidney-weight to body-weight ratio but did not cause histopathologic changes in the kidney. However, trichloroacetic acid has been associated with peroxisomal proliferation in the kidney (discussed below). Both trichloroethanol and trichloroacetic acid may contribute to trichloroethylene-induced nephrotoxicity through formic acid formation (discussed below), but the overall contribution is likely very small compared with the GSH-derived metabolites (EPA 2011a).

Urinary biomarkers of early renal dysfunction include glutathione-S-transferase $\alpha$, glutathione-S-transferase $\pi$, $\beta_2$-microglobulin, $\alpha_1$-microglobulin, retinol binding protein, N-acetylglucosaminidase (NAG), kidney injury molecule-1, albumin, and total protein (Green *et al.* 2004, Vermeulen *et al.* 2012). Several studies have reported an increase in urinary markers of proximal tubule injury in workers repeatedly exposed to high concentrations of trichloroethylene over an extended period (Bolt *et al.* 2004, Brüning *et al.* 1999a,b) or following acute intoxication (Brüning *et al.* 1998). Peak exposures were estimated to have frequently exceeded 500 ppm based on reported narcotic symptoms (drunkenness, dizziness, headache, and drowsiness). The workers also reported that they frequently had to leave the work area to recover in fresh air. Two of these studies also reported that there were significantly more cases of tubular damage (measured by increased $\alpha_1$-microglobulin in the urine) among renal-cell carcinoma patients exposed to high levels of trichloroethylene over many years compared with nonexposed patients

with renal-cell carcinoma or exposed controls (Bolt *et al.* 2004, Brüning *et al.* 1999a). Vermeulen *et al.* (2012) investigated nephrotoxicity among 80 Chinese factory workers (mean duration of employment 2 years) exposed to trichloroethylene concentrations (22.2 ppm ± 35.9) below the Occupational Safety and Health Administration permissible exposure limit of 100 ppm (8-h TWA). Urinary levels of kidney injury molecule-1 were significantly elevated in exposed workers compared with controls and an increase in glutathione-S-transferase π was borderline statistically significant. Other markers of kidney toxicity (NAG and glutathione-S-transferase α) were not significantly different. This was the first study to show that relatively low occupational exposures to trichloroethylene could induce kidney toxicity.

An earlier study by Green *et al.* (2004) did not find evidence of exposure-related kidney damage in 70 workers exposed to relatively low trichloroethylene concentrations (mean = 32 ppm, range = 0.5 to 252 ppm). There was a significant dose-dependent increase in urinary glutathione-S-transferase α activity; however, the levels were not significantly increased compared with controls. Although NAG and albumin levels were significantly higher in the exposed workers compared with controls, the levels of these markers were not correlated with either the magnitude or duration of exposure and could be explained by chance or by exposure to some unidentified agent. *In vitro* studies with primary cultures of human proximal tubular cells show that DCVC caused necrosis at high concentrations (> 100 μM) and increased cell proliferation and apoptosis at lower concentrations (Lash *et al.* 2005). These effects were associated with changes in expression of proteins that regulate apoptosis, cellular growth, differentiation, and stress response. A study by Xu *et al.* (2008) indicated that mitochondrial dysfunction was an early, obligatory step in DCVC-induced cytotoxicity in cultured human proximal tubular cells. Overall, the data support the hypothesis that chronic tubular damage is a precondition for the nephrocarcinogenic effects of trichloroethylene in humans.

DCVC was nephrotoxic in rats, mice, guinea pigs, rabbits, cats, and dogs (EPA 2011a). DCVC may be metabolized to other nephrotoxic metabolites by FMO3, β-lyase, or NAT (see Figure 1-2). Mice appear to be more sensitive to the acute nephrotoxic effects than rats but are less susceptible to renal carcinogenesis. Studies reviewed by EPA (2011a) reported that mice administered a single dose of 1 mg/kg DCVC developed proximal tubule cell damage, and karyomegaly was noted following repeat doses of 1 mg/kg/day for 10 days. Higher doses in mice resulted in more severe damage including desquamation and necrosis of the tubular epithelium. In rats, no histological changes were observed following single doses up to 10 mg/kg or 10 daily doses of 0.5 to 5 mg/kg. Single doses in rats of 25 mg/kg or 50 mg/kg resulted in cellular debris in the tubular lumen and slight degeneration and necrosis, respectively. Irving *et al.* (2013) investigated the nephrotoxicity of NAcDCVCS, NAcDCVC, and DCVCS in male Sprague-Dawley rats following a single i.p injection (230 μmol/kg b.w.). Nephrotoxic effects occurred at 24 hours post treatment for all three compounds. NAcDCVCS and NAcDCVC had similar effects causing necrosis in the proximal tubules in the outer medulla and adjacent inner cortex but were less nephrotoxic than DCVCS on an equimolar basis. DCVCS caused acute proximal tubular necrosis in the cortex but not in the medulla. Based on a comparison of kidney lesions of rats dosed with trichloroethylene or DCVC, the data suggest that these compounds also may play a role in trichloroethylene-induced nephrotoxicity.

Subchronic and chronic studies in rats and mice exposed to DCVC via drinking water consistently report pathological and histological effects in the kidney and show a progression

from tubular necrosis and shedding of pyknotic cells into the lumen during the first few days to increased prominence of karyomegaly and cytomegaly in tubular cells after several weeks of exposure (EPA 2011a). Effects were noted at doses as low as 1 to 2 mg/kg/day and did not show a difference in sensitivity between rats and mice. In a recent study, Shirai *et al.* (2012) administered DCVC to male BALB/c mice orally or by i.p. injection for 13 weeks at 1, 10, and 30 mg/kg/day. Dose-related effects in the kidney were reported that progressed from weak tubular dilation, but no necrosis or fibrosis, at the low dose to renal tubular degeneration characterized by moderate tubular necrosis and marked interstitial fibrosis at the high dose.

The histological and morphological changes in the tubular cells observed in studies with DCVC were similar to those reported in chronic studies with trichloroethylene (NTP 1988, 1990). The NTP studies were conducted with five rat strains and one mouse strain and reported high incidences of cytomegaly of the proximal tubules (82% to 100%) in dosed groups of males and females of all strains and species. Cytomegaly was more severe in male rats than female rats and more severe in rats than in mice, but it was not observed in the unexposed control or vehicle control groups. Lash *et al.* (1998) reported that the greater sensitivity of trichloroethylene-induced kidney toxicity in male rats compared with females was correlated with the rate of DCVG formation. However, species-dependent differences in nephrotoxicity and carcinogenicity between rats and mice were not correlated with rates of DCVG formation and suggested that other enzymes (e.g., β-lyase, NAT, GGT, or deacetylase) may be responsible for the lower susceptibility in mice.

Cytotoxicity alone is insufficient for tumor formation because all cytotoxins clearly are not carcinogenic. Further, nephrotoxicity occurred at much lower doses and was observed at near 100% incidences in all dose groups while renal tumors occurred only in rats in the high-dose group (NTP 1988, 1990). Multiple factors may contribute to cytotoxicity including oxidative stress, alterations in calcium ion homeostasis, mitochondrial dysfunction, protein alkylation, cellular repair processes, and alterations in gene expression (Lash *et al.* 2000b). Each of these factors may have ancillary consequences related to tumor induction that are independent of cytotoxicity *per se* (EPA 2011a). El Aram *et al.* (2014a,b) reported that dichloroacetic acid and trichloroacetic acid were nephrotoxic in rats and that the kidney damage could be prevented by antioxidants. However, it is not known whether cytotoxicity is causally related to carcinogenesis or is merely a marker for a different, key causal event. Although experimental data currently do not demonstrate a causal link between nephrotoxicity/sustained cellular proliferation and renal tumors, the data are consistent with the hypothesis that cytotoxicity and regenerative proliferation contribute to trichloroethylene-induced kidney tumors, either independently or in combination with a mutagenic mode of action. The more biologically plausible mode of action likely involves a combination of mutagenicity and cytotoxicity. That is, sustained regenerative cellular proliferation likely promotes the selection, survival, and clonal expansion of mutated cells in the tubular epithelium.

#### *4.2.2.3 PPARα activation*

Tubular epithelial cells are relatively rich in peroxisomes and trichloroacetic acid and dichloroacetic acid, oxidative metabolites of trichloroethylene, are PPARα agonists (EPA 2011a, Lash *et al.* 2000b, Rusyn *et al.* 2014). However, renal peroxisomes are generally less responsive than hepatic peroxisomes to peroxisome proliferators and humans are markedly less responsive

to peroxisome proliferation than rodents. Only one study was identified that investigated peroxisome proliferation in kidneys of rats and mice exposed to trichloroethylene (Goldsworthy and Popp 1987). Trichloroethylene induced peroxisome proliferation in the liver and kidneys of rats and mice; however, similar levels were observed in both species. Thus, there was no correlation between induction of peroxisome proliferation in the kidneys and species-specific renal carcinogenicity. Another study investigated the role of trichloroacetic acid in carcinogenesis and peroxisome proliferation in liver and kidneys of rats and mice exposed to tetrachloroethylene, which can be metabolized to trichloroacetic acid (Odum *et al.* 1988). Due to differences in toxicokinetics, male mice were exposed to higher levels of trichloroacetic acid than male rats, and peroxisome proliferation was observed only in male mouse liver. The data did not support a role of trichloroacetic acid and peroxisome proliferation in the carcinogenicity of tetrachloroethylene in the male rat kidney. Although some metabolites of trichloroethylene are peroxisome proliferators, the available data are insufficient to support peroxisome proliferation as a mode of action for trichloroethylene-induced kidney tumors (EPA 2011a).

#### *4.2.2.4 $\alpha_{2u}$-Globulin-related nephropathy*

$\alpha_{2u}$-Globulin-related nephropathy is characterized by the rapid accumulation of protein droplets containing $\alpha_{2u}$-globulin (hyaline droplets) in lysosomes in the P2 segment of the proximal tubule and is specific to male rats (IARC 1999, Lash *et al.* 2000b, Swenberg and Lehman-McKeeman 1999). A number of chemicals, including several halogenated organic solvents, are known to cause hyaline droplet nephropathy. Goldsworthy *et al.* (1988) investigated $\alpha_{2u}$-globulin nephropathy in both male and female F344 rats exposed to trichloroethylene, tetrachloroethylene, or pentachloroethane to determine if the effects were male rat specific. There was no increase in renal $\alpha_{2u}$-globulin concentrations or cell replication in male or female rats exposed to trichloroethylene but some effects were consistent with $\alpha_{2u}$-globulin nephropathy in male rats for the other compounds tested. Trichloroethylene nephrotoxicity has been observed in rats and mice of both sexes and in humans, and kidney tumor incidences were elevated (although not always statistically significant) in both male and female rats. Thus, the data do not support the hypothesis that $\alpha_{2u}$-globulin nephropathy is a factor in trichloroethylene-induced kidney carcinogenesis in rats.

#### *4.2.2.5 Formic acid-related nephrotoxicity*

Some investigators have suggested that since the nephrotoxic metabolite DCVC is formed in very small amounts it fails to explain the male rat specific renal carcinogenicity of trichloroethylene and have proposed that trichloroethylene nephrotoxicity may be caused by formic acid (Green *et al.* 1998, 2003). The sequence of events for formic acid-related nephropathy is the same as for GSH-conjugated metabolite-induced cytotoxicity discussed above but is related to oxidative metabolites (trichloroacetic acid and trichloroethanol). Formic acid is not a metabolite of trichloroethylene but may accumulate as an indirect consequence of vitamin $B_{12}$ and folate depletion caused by trichloroethylene exposure (Dow and Green 2000). Male Fischer rats exposed to trichloroethylene, trichloroacetic acid, or trichloroethanol via gavage, drinking water, or inhalation for one day to one year excreted large amounts of formic acid in urine (Green *et al.* 2003, 1998, Dow and Green 2000). No kidney damage was reported in rats following acute exposures (1 to 5 daily doses) or subacute exposures of 15 to 28 days (oral and inhalation). In contrast, male rats exposed to trichloroethanol at 500 to 1,000 mg/L for 52 weeks developed kidney damage characterized by increased urinary NAG, protein excretion, basophilic

tubules, tubular damage, increased cell replication, and focal proliferation of abnormal tubules (Green *et al.* 2003). However, the characteristics of trichloroethanol-induced nephrotoxicity did not account for the full range of effects observed after exposure to trichloroethylene or DCVC (EPA 2011a). Studies with trichloroacetic acid did not report histopathologic changes in the rat kidney. Yaqoob *et al.* (2013) also reported that male and female rats exposed to low doses of trichloroethylene for 3 days excreted formic acid in the urine but did not develop nephropathy. The induced formic aciduria was less pronounced in female rats and was less in male Wistar rats compared with male F344 rats. Yaqoob *et al.* (2014) compared the renal toxicity of trichloroethylene and trichloroethanol administered to male F-344 rats for 12 weeks to determine whether the GSH pathway or formic aciduria were responsible for nephrotoxicity. Although their findings did not clearly identify the pathway responsible for renal toxicity, the data provided some support for the GSH conjugation pathway.

Although rats chronically exposed to trichloroethanol excreted significantly larger amounts of formic acid and developed tubular degeneration, there were important dissimilarities in the characteristics of the nephrotoxicity compared with rats exposed to trichloroethylene or DCVC (EPA 2011a). Histological changes associated with trichloroethylene and DCVC included karyomegaly, cytomegaly, and flattening and dilation of the tubular epithelium. These effects did not occur in rats exposed to trichloroethanol. Furthermore, no specific evidence links the particular nephrotoxic effects caused by trichloroethanol/formic acid to carcinogenesis. Thus, the data do not support the hypothesis that cytotoxicity mediated by oxidative metabolites via increased formic acid production is a major contributor to trichloroethylene-induced kidney carcinogenesis.

#### 4.2.3 Summary

The mode of action for trichloroethylene-induced kidney cancer is not completely understood but the available data strongly support a mutagenic mode of action mediated by GSH-conjugated metabolites. There is substantial experimental evidence that those metabolites are genotoxic and nephrotoxic and are both formed in and delivered to the kidney following exposure to trichloroethylene. Factors that increase the proportion of trichloroethylene undergoing GSH conjugation (e.g., CYP enzyme inhibition or saturation, polymorphic expression of metabolizing enzymes) would be expected to increase kidney toxicity. Although there is some evidence that chronic tubular damage might be a precondition for the nephrocarcinogenic effects of trichloroethylene in humans, tubular toxicity has not been established as a necessary precursor or causal event for carcinogenesis. However, the data are consistent with the hypothesis that cytotoxicity and regenerative proliferation contribute to trichloroethylene-induced kidney tumors, most likely in combination with a mutagenic mode of action. Mutagenic and cytotoxic modes of action are relevant to humans. Other hypothesized modes of action for kidney carcinogenicity have inadequate or limited experimental support.

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# 5 Non-Hodgkin Lymphoma (NHL)

Previous sections of the cancer hazard evaluation component contain relevant information – ADME (Section 1), genetic and related effects (Section 2), and overview and assessment of the quality of the human cancer studies (Section 3) – that are important for the three cancer endpoints of interest. This section builds on that information and evaluates the human cancer studies (Section 5.1) and mechanistic data (Section 5.2) specifically for non-Hodgkin lymphoma (NHL) and other related B-cell lymphohematopoietic cancers.

## 5.1 Human cancer studies

This review of NHL includes other B-cell lymphohematopoietic cancers thought to be related to NHL, including multiple myeloma (now renamed plasma-cell lymphoma), chronic lymphocytic leukemia (CLL), and hairy-cell leukemia (HCL). Other subtypes, such as diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, have also been studied in large cohorts. NHL and its related subtypes are relatively uncommon, with NHL comprising about 4.3% of all new cancer cases per year in the United States. The U.S. incidence rate for NHL is approximately 19.7 cases per 100,000 per year (2006 to 2010 rates; http://seer.cancer.gov/statfacts/html/nhl.html) compared with 6.4 deaths per 100,000 per year, due to an almost 70% 5-year survival rate, so that studies reporting incidence are more informative than mortality studies. In addition, misclassification of NHL may be greater on death certificates than in cancer registries. Multiple myeloma is a rare cancer; the U.S. incidence and mortality rates for multiple myeloma are approximately 6 per 100,000 and 3.4 per 100,000 per year, respectively, (http://seer.cancer.gov/statfacts/html/mulmy.html), again suggesting that the studies reporting incidence rates are more informative than those reporting only mortality rates. For CLL, incidence and mortality are approximately 16,000 cases and 4,600 deaths per year, respectively, in the United States, and the onset of disease increases markedly with age, with an average age at diagnosis of 72 years.

As noted in Section 3, classification systems for NHL and its subtypes have changed considerably over the past twenty years, so that comparisons of incidence rates over time should take into account such changes. In the available studies, NHL was classified by ICD-7, 8, 9 or 10, ICD-O-2 or 3, or the InterLymph classification (Cocco *et al.* 2013), with some studies, using more recent classifications, reporting on B-cell lymphoma subtypes, primarily DLBCL, follicular lymphoma, multiple myeloma, CLL, or HCL.

Details on the study design, methods, and findings are available in Appendix D (see Tables D-1 and D-3). The evaluation of study quality, including study design, methods of exposure and cancer endpoint assessment, analyses and other relevant data, is reported in Appendix D (see Tables D-4a,b and D-6a,b) and discussed in Section 3. Figure 5-1 provides an overview of the conclusions from that evaluation and identifies the most informative studies based on study quality and study sensitivity. This section summarizes and interprets the findings for NHL and related B-cell lymphomas from the individual epidemiological studies brought forward for evaluation, and integrates the evidence across studies, applies the RoC listing criteria to the body of evidence, and reaches a preliminary recommendation for the level of evidence for NHL and related B-cell lymphomas using the same criteria as described for the evaluation of kidney cancer in Section 4.

**Figure 5-1. Summary of study quality: NHL**

Grey: Most informative (lightest) to the least informative studies (darkest).
Blue: Study sensitivity: darkest shade = least sensitive.
Peach: Overall bias towards the null.
Tan: Multiple types of bias or other limitations.
Morgan (1998) was rated somewhat lower for NHL than kidney or liver cancer because of fewer expected and exposed cases.

### 5.1.1 Study findings

The available studies reporting on trichloroethylene exposure in association with NHL and related cancers that were considered for inclusion in the cancer evaluation include 11 cohort or nested case-control studies and 7 case-control studies (of independent populations). Two meta-analyses were also identified and contributed to the evaluation.

The database consists of many reasonably well-conducted studies; however, similar to kidney cancer, NHL is a relatively uncommon cancer, and the majority of the cohort studies had limited statistical power to evaluate a modest risk from exposure to trichloroethylene and to evaluate exposure-response relationships.

The findings of the individual studies are discussed below and presented in Tables 5-1, 5-2, and 5-3

### 5.1.2 Cohort and nested case-control studies

The available cohort studies and nested case-control studies reporting on NHL, multiple myeloma, or CLL include the following:

- Three studies conducted in Nordic countries (Raaschou-Nielsen *et al.* 2003, Hansen *et al.* 2013, Vlaanderen *et al.* 2013),
- Four studies of U.S. aircraft workers (Morgan *et al.* 1998, Boice *et al.* 2006, Radican *et al.* 2008/Blair *et al.* 1998, Lipworth *et al.* 2011),

- Two studies of uranium processing workers (Bahr *et al.* 2011, Yiin *et al.* 2009),
- One study of micro-electronic workers (Silver *et al.* 2014), and
- One study of U.S. military personnel exposed to trichloroethylene in drinking water (Bove *et al.* 2014).

Several of these studies also reported data for multiple myeloma (Raaschou-Nielsen *et al.* 2003, Boice *et al.* 2006, Radican *et al.* 2008/Blair *et al.* 1998, Lipworth *et al.* 2011, Hansen *et al.* 2013, Silver *et al.* 2014) or specifically for CLL (Boice *et al.* 2006, Lipworth *et al.* 2011). Several studies reported only on combined categories of NHL and leukemia (Zhao *et al.* 2005) or lymphoma (Greenland *et al.* 1994), and Ritz (1999) only reported data for all lymphohematopoietic cancers combined, and so these studies are excluded from this section.

#### *5.1.2.1 Nordic studies*

As discussed previously, workers and exposed subjects in these incidence studies (Hansen *et al.* 2013, Raaschou-Nielsen *et al.* 2003, Vlaanderen *et al.* 2013) were identified from broad occupational or population-based databases and with a wide range of occupations and likely co-exposures. All of these studies reported cancer incidence. Modest increases in overall risk for NHL in external analyses were observed among men (SIR = 1.55, 95% CI = 1.06 to 2.20; 32 cases) in the biomonitoring study (Hansen *et al.* 2013) and among those considered to have higher exposure in the blue-collar workers study (SIR = 1.7, 95% CI = 1.1 to 2.4, 31 exposed cases, 20-year lagged) (Raaschou-Nielsen *et al.* 2003). In internal analyses by Hansen *et al.* (2013), the highest risk was found among workers in the second highest exposure group but the risk estimate was lower in the highest exposure group. This study had limited ability to evaluate exposure-response relationships because of lack of information on lifetime exposures and possible misclassification of exposure intensity. Among blue-collar workers (Raaschou-Nielsen *et al.* 2003), risks did not increase by employment duration or presumed exposure level (as assessed by date of first employment). No increases in NHL risk were observed in the population-based study by Vlaanderen *et al.* (2013), which might have included subjects with a broader range of exposures and with a greater probability of exposure misclassification. It is not clear whether a linear exposure-response pattern would be predicted if the proposed mechanism involves immunomodulation.

No increases in the risks of multiple myeloma were observed in all three Nordic studies (Hansen *et al.* 2013, Raaschou-Nielsen *et al.* 2003, Vlaanderen *et al.* 2013).

#### *5.1.2.2 Aircraft manufacturing workers*

Four mortality studies of aircraft manufacturing workers (Morgan *et al.* 1998, Boice *et al.* 2006) Radican *et al.* 2008, and Lipworth *et al.* 2011) reported findings for NHL. The study of Utah aircraft workers (Radican *et al.* 2008) also included incidence data in an earlier update (Blair *et al.* 1998). The mortality study by Radican *et al.* had a 10-year longer follow-up and reported about two times as many NHL deaths as cases reported in the incidence study. There is some evidence of modest statistically non-significant increases in mortality for NHL (~30%) and multiple myeloma among workers ever exposed to trichloroethylene in two studies (Radican *et al.* 2008, Lipworth *et al.* 2011); however, no clear patterns of increasing risk with cumulative exposure or exposure pattern (Radican *et al.* 2008) or exposure duration (Lipworth *et al.* 2011) were reported. Most of the exposed cases were in the low-exposure group in the latter study. No association between trichloroethylene exposure and NHL was found in the smaller study by

Morgan *et al.* (1998) based on three deaths, in the study of aerospace workers (Boice *et al.* 2006) based on only one death, or with cancer incidence in the earlier update of the Utah aircraft manufacturing worker cohort (Blair *et al.* 1998).

#### *5.1.2.3 Other studies*

The remaining four studies had more limited sensitivity for informing these endpoints. Bahr *et al.* (2011) reported a statistically significant increase in mortality in external analyses but these were inversely related to higher exposure categories in internal analyses. In the study of micro-electronic workers, HRs for 5-modified exposure years were 0.87 (95% CI = 0.5 to 1.35) for NHL and 1.18 (95% CI = 0.70 to 1.99) for multiple myeloma (Silver *et al.* 2014), but this study had a limited exposure assessment and was a relatively young cohort. No association was found for multiple myeloma and trichloroethylene exposure in the nested case-control study of Tennessee uranium enrichment workers (Yiin *et al.* 2009). Lastly, small increases in NHL and multiple myeloma were observed in some exposure categories in the drinking water mortality study (Bove *et al.* 2014), which was also a young cohort and was limited by indirect measures of trichloroethylene exposure.

### 5.1.3 Population-based case-control studies

Table 5-2 reports findings for NHL and Table 5-3 reports findings on NHL-related subtypes. Four population-based case-control studies in different geographical locations, including Montreal (Christensen *et al.* 2013), Connecticut (Deng *et al.* 2013/Wang *et al.* 2009), and two in Sweden (Hardell *et al.* 1994, Persson and Fredrikson *et al.* 1999), and one pooled analysis, the InterLymph study (Cocco *et al.* 2013), reported data on NHL. Two of these studies (Cocco *et al.* 2013, Deng *et al.* 2013/Wang *et al.* 2009) also reported on the NHL subtypes DLBCL and follicular lymphoma. Three other case-control studies reported on multiple myeloma (Gold *et al.* 2011, Costantini *et al.* 2008, and Cocco *et al.* 2010, one of the constituent studies of the pooled analysis), and two studies reported on CLL (Cocco *et al.* 2013, Costantini *et al.* 2008). One study reported on the NHL subtype HCL (Nordstrom *et al.* 1998).

The InterLymph study included pooled cases and controls from four large multi-center studies: the EPILYMPH study in Europe (Cocco *et al.* 2010), the ENGELA study in France (Orsi *et al.* 2010), the MIS study in Italy (Miligi *et al.* 2006), and the NCI-SEER study in the United States (Purdue *et al.* 2011a). Because the pooled analysis included all the subjects of the individual studies and harmonized the exposure and disease assessment, this evaluation primarily reviews the pooled analysis. Importantly, the authors did not observe between-study heterogeneity. Findings from analyses on different exposure metrics from the NCI-SEER study (Purdue *et al.* 2011) as well as findings for multiple myeloma from the EPILYMPH study (Cocco *et al.* 2010) are also included in the evaluation.

The major advantage of the recent case-control studies was greater statistical power, especially for evaluating NHL histological subtypes. The pooled InterLymph study (Cocco *et al.* 2013) and the SEER study on multiple myeloma (Gold *et al.* 2011) were considered to be the most informative studies because of the quality of the exposure and disease assessments, evaluation of multiple metrics of exposure, and larger numbers of exposed cases and controls, especially among individuals with higher probability or intensity of exposure. The other studies were more limited in their ability to inform cancer evaluation (Christensen *et al.* 2013, Costantini *et al.*

2008, Deng *et al.* 2013)/Wang *et al.* 2009), especially the three Swedish case-control studies (Hardell *et al.* 1994, Nordstrom *et al.* 1998) because of small numbers of exposed cases and controls, lower quality exposure assessments, and concerns for exposure misclassification or the use of older disease classifications (see Figure 5-1, Section 3, and Appendix D).

*NHL*

The InterLymph pooled analyses (Cocco *et al.* 2013) found a moderate increase in NHL risk for all exposed subjects (OR = 1.4, 95% CI = 0.9 to 2.1, 50 exposed cases vs. 38 exposed controls); Fisher combined probability test, $P = 0.004$. Among subjects with a high probability of exposure, there was evidence of an exposure-response relationship with duration ($P_{trend} = 0.009$) and intensity ($P_{trend} = 0.059$) of trichloroethylene exposure; risk estimates in the highest exposed categories were approximately two- to three-fold higher than in the lowest categories but were not statistically significant. The most informative of the constituent studies, the U.S. SEER analysis (Purdue *et al.* 2011), had the advantage of a high-quality and detailed exposure assessment and reported on additional exposure metrics. Increased risks were observed with multiple metrics, but most notably a positive trend with average exposure ($P_{trend} = 0.02$, OR = 1.1, 95% CI = 1.02 to 1.21 for each 99 ppm-hr/week increase, and 7.9, 95% CI = 1.8 to 34.3 for > 360 ppm-hr per week) and for cumulative exposure ($P_{trend} = 0.08$, OR = 1.10, 95% CI = 0.99 to 1.22 per each 65,520 ppm-hr and 3.3, 95% CI = 1.1 to 10.01 for greater than 234,000 ppm-hr). Estimated (not measured) exposures for a proportion of the workers were high (> 234,000 ppm-hr cumulative exposure and 99-ppm average intensity of exposure), which increased the ability of the study to detect an effect.

Findings in the remaining case-control studies were somewhat inconsistent. The U.S. study of women (Deng *et al.* 2013/Wang *et al.* 2009) reported increases in NHL risk for women with medium or high intensity of exposure (OR = 2.2, 95% CI = 0.9 to 5.4, 13 exposed cases). In addition, the risk associated with trichloroethylene exposure was higher (and statistically significant) among women with the AT or AA polymorphism of the IL2A_07 genotype than the TT polymorphism; most of this difference was observed in the DLBCL subtype rather than the follicular lymphoma subtype. Hardell *et al.* (1994) reported a high risk for NHL among trichloroethylene-exposed subjects (OR = 7.2, 95% CI = 1.3 to 4.2, 4 exposed cases), this point estimate was inconsistent with the findings of the other case-control and cohort studies and raises the possibility of biases or confounding, particularly considering the minimum requirement to be classified as exposed was less than one week of continuous exposure. The other Swedish study by Persson & Fredrikson (1999) found an OR of 1.2 (95% CI = 0.5 to 2.4, 16 exposed cases) for ever exposure to trichloroethylene. In the Montreal study (Christensen *et al.* 2013), ORs were 1.0 (95% CI = 0.3 to 3.5, 3 exposed cases) for substantial exposure and 1.2 (95% CI = 0.5 to 2.9, 7 exposed cases) for ever exposed.

*Multiple myeloma, follicular-cell lymphoma, chronic lymphocytic leukemia, diffuse large B-cell lymphoma and hairy-cell leukemia*

The most informative of the three studies reporting on multiple myeloma, a case-control study using SEER cancer registry data (Gold *et al.* 2011), found a statistically significant exposure-response relationship for multiple myeloma ($P_{trend} = 0.02$), with a risk of 2.3 (95% CI = 1.1 to 5.0, 18 exposed cases) in the highest cumulative exposure category. The estimated highest exposure cumulative exposure category was 6,593 to 49,500 ppm-hr. This study used the same detailed exposure assessment as Purdue *et al.* (2011). There was little evidence of an association

with multiple myeloma in the other two studies, the EPILYMPH study (Cocco *et al.* 2010), and the Italian multi-center study by Costantini *et al.* (2008).

The InterLymph analysis found evidence of statistically significant association with two NHL subtypes, follicular lymphoma and CLL; Fisher combined probability tests were 0.015 for follicular cell lymphoma and 0.005 for CLL. No association was found for any NHL subtypes in the EPILYMPH study (Cocco *et al.* 2010) but positive associations were found for CLL in the NCI-SEER study (Purdue *et al.* 2011). In the case-control study among Connecticut women (Deng *et al.* 2013/Wang 20009), elevated risks were found for both DLBCL among genetically susceptible women, and an exposure-response relationship was found for DLBCL but not follicular-cell lymphoma. The Swedish study of HCL (Nordstrom *et al.* 1998) using similar methodologies as Hardell *et al.* (1994) observed a small (1.5) increase in this endpoint, based on 9 cases.

**Table 5-1. Cohort and nested case-control studies and trichloroethylene exposure: Findings for NHL[a]**

| Reference | Study name<br>Population #<br>Exposure assessment | Exposure groups | External or additional analyses<br>SMR, SIR (95% CI)<br># cases/deaths | Internal analysis<br>RR, SRR, HR or OR (95% CI)<br># exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| Hansen *et al.* 2013 (Potential overlap with Rasschou-Nielsen *et al.* 2003) | Pooled and updated Nordic cohorts Axelson *et al.* 1994, Anttila *et al.* 1995, Hansen *et al.* 2001<br>5553 (3776 M, 1777 F)<br>Biomonitoring (U-TCA) | *Hansen* et al. *2013*<br>Men<br>Women<br><br>Men & women<br>Lag analysis (yr)<br>0<br>10<br>20<br>U-TCA (mg/L)<br>< 5<br>5–25<br>25–50<br>> 50<br>$P_{trend}$ | *ICD-7*: 200, 202<br>*SIR*<br>1.55 (1.06–2.20); 32<br>0.63 (0.23–1.37); 6<br><br>1.26 (0.89–1.73); 38<br>1.21 (0.83–1.71); 32<br>1.11 (0.68–1.72); 20 | ICD-7:200,202<br>*HRR incidence (no lag)*<br>1.0; 12<br>1.16 (0.53–3.09); 14<br>1.56 (0.63–3.81); 8<br>0.66 (0.21–2.03); 4<br>0.79 | Low exposure levels (only 20% exposed to ≥ 20 ppm) and short duration of exposure<br>Covariates: Age, sex, calendar period; indirect consideration of smoking and alcohol consumption<br>Strengths: Biomonitoring data, which is a sensitive marker for ever exposure; large numbers of workers ever exposed.<br>Limitations: Misclassification of levels of exposure likely; only 2 or 3 U-TCA measurements/individual and unlikely to represent lifetime or cumulative exposure; low statistical power for evaluating modest risks<br>NHL: Limited evidence for a positive association in males; no association at higher exposures; study had limited ability to evaluate exposure-response relationship |
| Raaschou-Nielsen *et al.* 2003 (Potential overlap with | Danish blue collar workers<br>40,049 M+F (approx. 70% M) | *Higher TCE exposure subcohort*<br><br>*Ever exposed*<br>Lag time (yrs)<br>0–9 | *ICD-7: 200, 202*<br>*SIR*<br>1.5 (1.0–2.0) 65<br><br>1.8 (0.9–3.1); 12 | NR | Higher levels of TCE prior to 1970 (40–60 ppm); low levels of exposure after that time<br>Covariates: age, sex, calendar |

| Reference | Study name<br>Population #<br>Exposure assessment | Exposure groups | External or additional analyses<br>SMR, SIR (95% CI)<br># cases/deaths | Internal analysis<br>RR, SRR, HR or OR (95% CI)<br># exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| Hansen *et al.* 2013) | Working at a company using TCE | 10–19<br>≥ 20<br>Duration employment (yrs)<br>1–4<br>≥ 5<br>Yr. of 1st employment<br>Before 1970<br>1970–1979 | 1.3 (0.8–2.0); 22<br>1.7 (1.1–2.4); 31<br><br>1.5 (1.1–2.1); 35<br>1.6 (1.1–2.2); 30<br><br>1.6 (1.1–2.3); 35<br>1.5 (1.0–2.1); 30 | | year<br>Strengths: Large numbers of exposed cases<br>Limitations: Young cohort, possible selection bias for difference in SES, external analysis only<br>NHL: Evidence of an association |
| Vlaanderen *et al.* 2013 | Population-based of 5 Nordic countries, linkage of cancer registry with census questionnaire<br>M: 44,708 cases, 223,540 controls<br>F: 31,422 cases, 157,110 controls<br>Semi-quantitative JEM | *Cumulative exp. (median unit-yr)*<br>0<br>0.04<br>0.13<br>0.72<br>*High exposure group (median)*<br>Cumulative (0.83 unit-yr)<br>Intensity × prevalence (0.04 unit) | | *ICD-7: 200, 202*<br>*HR incidence*<br>1.00<br>1.01 (0.95–1.07); 1,213<br>0.93 (0.88–1.00); 1,183<br>0.97 (0.91–1.03); 1,211<br><br>0.95 (0.84–1.06); 353<br>0.96 (0.84–1.09); 269 | Low prevalence of exposure (TCE) and exposure levels likely to be low<br>Covariates: Age, sex, country<br>Strengths: Long follow-up, large numbers of cases<br>Limitations: Misclassification of exposure likely; JEM had poor sensitivity and did not account for heterogeneity within jobs and over time<br>TCE exposure correlated with tetrachloroethylene exposure<br>Null: No evidence of an association- study was limited by low levels and exposure misclassification |
| **Aerospace and aircraft workers** | | | | | |
| Boice *et al.* 2006<br>(Overlaps | Los Angeles (USA) | Ever exposed to TCE | *ICD-9; 200-2010*<br>*SMR*<br>*(0.01–1.18) 1* | | Exposure occurs during text engine flush, which is likely to |

| Reference | Study name<br>Population #<br>Exposure assessment | Exposure groups | External or additional analyses<br>SMR, SIR (95% CI)<br># cases/deaths | Internal analysis<br>RR, SRR, HR or OR (95% CI)<br># exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| with Zhao *et al.* 2005) | rocket engine testing workers<br>1,111 Men<br>Qualitative JEM; Individual work histories | | | | be high.<br>Covariates: Date of birth, year of hire, pay type (surrogate for SES) and exposure to hydrazine<br>Strengths: Adequate follow up<br>Limitations: Qualitative exposure assessment; one exposed death<br>Number of cases inadequate for evaluation |
| Lipworth *et al.* 2011 (update Boice *et al.* 1999) | Burbank, CA (USA) aircraft manufacturing workers<br>N = 5,443 (approx. 80% M)<br>Individual work histories (JEM) | TCE cohort (ever exposed)<br>*TCE: years exposed*<br>0<br>< 1<br>1–4<br>5+<br>$P_{trend}$ | *ICD (time of death) SMR*<br>1.31 (0.97–1.73); 50 | *ICD (time of death) RR mortality*<br>1.00; 50<br>0.84 (0.48–1.47); 18<br>1.10 (0.59–2.04); 14<br>1.02 (0.55–1.90); 15<br>> 0.20 | Exposure levels not reported; exposure duration likely to be short<br>Covariates: Age, date of birth, date of hire, termination date, sex and race<br>Strengths: Long follow-up, adequate number of cases and controls for ever exposure<br>Limitations: Evidence of HWE, few exposed deaths in subgroup analysis; exposure misclassification is a concern; no evaluation of exposure intensity, 70% had exposure to mixed solvents.<br>Limited evidence of an association, no exposure-response with duration |

| Reference | Study name<br>Population #<br>Exposure assessment | Exposure groups | External or additional analyses<br>SMR, SIR (95% CI)<br># cases/deaths | Internal analysis<br>RR, SRR, HR or OR (95% CI)<br># exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| Radican *et al.* 2008 (mortality to 2000)<br>Blair *et al.* 1998 (incidence 1973–1990)<br>Note: mortality only updated by Radican) | Utah (USA) aircraft maintenance workers<br>N = 7,204 (5,153 M, 1,051 F)<br>Individual work histories (JEM) | *Ever-exposed (M & F)*<br>1990 follow-up: mortality<br>2000 follow-up: mortality<br><br>Mortality; 2000 follow-up<br>Cumulative exp. (unit-yr)[a]<br>All<br>0–5<br>2–25<br>> 25<br><br>Exposure category<br>Low intermittent<br>Low continuous<br>Peak infrequent<br>Peak frequent<br><br>*Incidence (1990) follow-up*<br>Cumulative exp (unit-yr)<br>None<br>0–5<br>2–25<br>> 25 | *ICDA-8, ICD-9, 10 200, 202, or C82-8*<br><br>*Internal analysis*<br>*HR mortality*<br>Women<br>1.18 (0.49–2.85); 9<br>1.48 (0.47–4.66); 4<br>0<br>1.30 (0.45–3.77); 5<br><br>1.39 (0.48–4.03); 5<br>1.03 (0.23–4.68); 2<br>3.45 (0.96–12.37); 3<br>1.27 (0.47–3.45); 6<br><br>less than 3 exposed cases | *ICDA-8, ICD-9,10: 200, 202, or C82-85*<br>*HR mortality*<br>2.0 (0.9–4.5); 28<br>1.36 (0.77–2.39); 46<br><br>*Internal analysis*<br>*HR mortality*<br>Men<br>1.56 (0.72–3.35); 37<br>1.83 (0.79–4.21); 18<br>1.17 (0.42–3.24); 7<br>1.50 (0.61–3.69); 12<br><br>1.50 (0.67–3.34); 25<br>1.74 (0.76–3.97); 20<br>1.90 (0.69–5.24); 7<br>1.57 (0.67–3.69); 16<br><br>*RR incidence*<br>0.5 (0.2–1.7); 5<br>0.9 (0.3–2.6); 8<br>0.7 (0.2–2.6); 4<br>1.0 (0.4–2.9); 7 | Estimated exposure: Most workers exposed to low levels (~10 ppm), modest number of workers exposed to higher levels (~100 ppm)<br>Covariates: Age, calendar year and sex<br>Strengths: Adequate semi-quantitative JEM, long follow-up, adequate statistical power for ever exposure<br>Limitations: Potential for exposure misclassification because of missing information for some workers; limited power due to low numbers of higher exposed workers<br>Cannot rule out confounding from other co-exposures<br>Limited evidence; HRs greater than one but little evidence of an exposure- response relationship |
| Morgan *et al.* 1998 | Arizona aircraft manufacturing workers<br>N = 4,733 (2,555 M, 2,178 F)<br>Semi-quantitative JEM; individual | All TCE exposed workers<br>*Cumulative exp. score*<br>Low (2,357)<br>High (2,376)<br>Peak (med/high) vs. low/no | ICD 7-9: 200<br>SMR<br>0.96 (0.20–2.81); 3<br><br>1.79 (0.22–6.46); 2<br>0.50 (0.01–2.79); 1 | ICD 7-9: 200<br>RR mortality<br>1.36 (0.35–5.21) 3<br><br>2.25 (0.46–11.09); 2<br>0.81 (0.10–6.49); 1<br>1.31 (0.28–6.08); 2 | High exposure jobs were considered to be ≥ 50 ppm<br>Covariates: age at hire, gender (decade at high considered but no effect)<br>Limitations: Inadequate statistical power because of few |

| Reference | Study name<br>Population #<br>Exposure assessment | Exposure groups | External or additional analyses<br>SMR, SIR (95% CI)<br># cases/deaths | Internal analysis<br>RR, SRR, HR or OR (95% CI)<br># exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| | work history | | | | cases and ICD for NHL does not include 202<br>Null: Small increase in risk but few cases |
| **Other occupational studies** | | | | | |
| Silver *et al.* 2014 | New York State (USA) micro-electronics manufacturing workers<br>3,113 TCE exposed<br>Semi-quantitative JEM | 5 modified exposure years (exposure duration modified by exposure potential) | NR | *ICD time of death*<br>*HR*<br>0.87 (0.57–1.35) NR | Exposure levels NR. Only 13.9% of cohort exposed.<br>Covariates: Paycode and sex, age; variables considered in analyses but did not change risk estimate were birth cohort, time since last exposure (healthy worker survival), hire era, and employment duration prior to 1966<br>Limitations: Evidence of HWE. Exposure classification based on potential exposure and duration and only one cumulative exposure variable reported in analysis. Limited information on comparison and # of exposed cases NR. Young cohort with only 17% deaths<br>Null: No increased risk but limited study sensitivity |
| Bahr *et al.* 2011 | Kentucky (USA) Uranium enrichment workers | TCE exposure probability category<br>0<br>0–1<br>2–3 | ICD NR<br>SMR<br>3.20 (0.39–11.57); 2<br>1.85 (0.85–3.52); 9<br>1.70 (0.88–2.97); 12 | ICD NR | No information on exposure levels.<br>Covariates: Age, sex, race (unclear) |

| Reference | Study name<br>Population #<br>Exposure assessment | Exposure groups | External or additional analyses<br>SMR, SIR (95% CI)<br># cases/deaths | Internal analysis<br>RR, SRR, HR or OR (95% CI)<br># exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| | 5,535 (M)<br>Generic JEM | 0–3<br>4–5<br>Total<br>TCE exposure category<br>1<br>2<br>3<br>Total | 1.76 (1.09–2.69); 21<br>1.05 (0.52–1.88); 11<br>1.49 (1.02–2.10); 32 | SRR mortality<br>1.0<br>1.31 (0.47–3.65)<br>0.75 (0.27–2.12)<br>0.99 (0.40–2.4) | Limitations: Unclear descriptions of methods and findings; limited statistical power; evidence of HWE hire and survival bias.<br>Limited ability to evaluate. |
| **Environmental exposure** | | | | | |
| Bove *et al.* 2014 | North Carolina (USA) (Camp Lejeune)<br>154,932<br>Drinking water contamination - Ecological assessment | Cumulative TCE (µg//L-months)<br>≤ 1<br>> 1–155<br>> 155–380<br>> 380–8,585 | | ICD NR<br>HR mortality<br>1.0 (27)<br>0.90 (0.42–1.92); 10<br>0.75 (0.33–1.70); 8<br>1.15 (0.56–2.34); 13 | Estimated mean levels (µg/L): TCE: 358.7; overall cumulative exposure (µg/L months) for TCE, mean = 6,369.3, median = 5,289.0, 20% were exposed to levels between 7,700 and 39,745<br>Covariates: Sex, race, and education; other variable considered in the model (did not change risk estimates by 10%) include marital status, birth cohort, date of death, duty occupation<br>Limitations; Young cohort; aggregate exposure assessment; potential confounding from other contaminants e.g., tetrachloroethylene<br>Null: No evidence of an association; limited ability to detect an effect |

HR = hazard ratio; ICD = International Classification of Diseases; JEM = job-exposure matrix; NHL = non-Hodgkin lymphoma; NR = not reported; OR = odds ratio; ppm = parts per million; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRR = standardized rate ratio; TCE = trichloroethylene.
[a]See Table 5.3 for NHL subtypes and related cancers.

**Table 5-2. Case-control studies of trichloroethylene exposure: findings for NHL[a]**

| Reference | Study Size (N) Exposure assessment | Exposure groups | RR or OR (95% CI) # exposed cases/controls | Interpretation |
|---|---|---|---|---|
| Christensen *et al.* 2013 | Montreal (Canada)<br>Population- and hospital-based<br>1975–1985<br>NHL: 215 cases, 2,341 cancer controls<br>Expert assessment of occupational data from interviews | Ever exposed<br>Substantial exposure | *ICD-9 200, 202*<br>1.2 (0.5–2.9); 7/65[b]<br>1.0 (0.3–3.5); 3/30[b] | Exposure prevalence to TCE was very rare; ≤ 2% of cancer controls or population controls had substantial exposure and 3% had any exposure<br>Covariates: age, census tract, median income, ethnicity, self vs. proxy respondent, smoking, alcohol assumption, coffee use<br>Strengths: Adequate quality of exposure assessment<br>Limitations: Low statistical power<br>Null: Small increase risk for ever –exposed but study had low statistical power |
| Cocco *et al.* 2013 | 4 pooled multi-center studies (Italy, France, Europe "EPILYMPH" multi-center study, U.S. region 4 SEER study)<br>Population-based<br>NHL: 3,788 cases, 4,279 controls<br>Questionnaires on occupational history, industrial hygiene reports, expert assessments | High probability exposure<br>All exposed<br>*Duration (yr)*<br>No exposure<br>1–14<br>15–29<br>30–39<br>40+<br>$P_{trend}$<br>*Intensity (ppm)*<br>≤ 5 | *NHL (all subtypes) InterLymph consortium classification*[c]<br>1.4 (0.9–2.1); 50/38<br>1.0; 3,453/3,903<br>0.7 (0.4–1.5); 15/23<br>1.9 (0.8–4.3); 17/9<br>2.8 (1.0–7.8); 15/5<br>3.3 (0.3–33); 3/1<br>0.009<br>1.1 (0.4–3.0); 8/8 | Exposure prevalence: 9% ever exposed; 1% high probability of exposure. Exposure levels not measured but high exposure categories are > 75 ppm<br>Covariates: age, sex, study location<br>Strengths: Good exposure and disease assessment; analysis of NHL subtypes<br>Limitations: Reduced statistical power in NHL subtype analysis, no adjustment for lifestyle factors or co-exposures<br>Evidence of an positive association with NHL and exposure-response with multiple metrics |

| Reference | Study Size (N) Exposure assessment | Exposure groups | RR or OR (95% CI) # exposed cases/controls | Interpretation |
|---|---|---|---|---|
| | | 5–75<br>> 75<br>$P_{trend}$ | 1.3 (0.8–2.2); 33/25<br>2.2 (0.7–6.7); 9/5<br>0.059 | |
| Purdue *et al.* 2011[d]<br>incorporated in pooled analysis (Cocco *et al.* 2013) | U.S. SEER registry<br>Population-based<br>NHL: 1,189 cases, 982 controls<br>Interviews on occupational histories and exposures; expert assessment by industrial hygienists based on questionnaire data and systematic industrial hygiene literature review | Exposure-response analyses<br>*Average exposure*<br>Per 90 ppm-hr/wk[e]<br>$P_{trend}$<br>> 360 ppm-hr/wk<br><br>*Average exp. intensity*<br>Per estimated 99 ppm<br>$P_{trend}$<br><br>*Exposure duration (yr)*<br>Per 10 yr<br>$P_{trend}$<br><br>*Cumulative exposure*<br>Per 65,520 ppm-hr<br>$P_{trend}$<br>> 234,000 ppm-hr | *ICD-O-2*<br><br>*OR (# cases NR)*<br>1.1 (1.02–1.21)<br>0.02<br>7.9 (1.8–34.3)<br><br>1.18 (0.80–1.76)<br>0.41<br><br>1.13 (0.85–1.51)<br>0.40<br><br>1.10 (0.99–1.22)<br>0.08<br>3.3 (1.1–10.01) | Exposure not measured but high exposure categories are > 99 ppm, 360 ppm-hr-wk and 234,000 ppm-hr<br>Covariates: Age, sex, race, education level, and study area<br>Strengths: Good exposure and disease assessment, detailed analyses using multiple exposure metrics including analyses per estimated quantitative exposure, by intra-category high exposure and NHL subtype<br>Limitations: Reduced statistical power in NHL subtype analysis, no adjustment for lifestyle factors or co-exposures<br>Evidence of an association and exposure-response relationships with multiple metrics |
| Deng *et al.* 2013<br>Wang *et al.* 2009 | Connecticut (USA)<br>All NHL: 601 cases, 717 controls<br>Questionnaire on occupational history. Linkage of occupation code to JEM | *Wang* et al. *2009*<br>Ever exposed<br>Exposure intensity<br>Low intensity<br>Medium/high intensity<br>$P_{trend}$<br><br>*Deng* et al. *2013*<br>*polymorphism*<br>*Ever exposed*<br>IL12A_07 genotype<br>TT<br>AA<br>*P* interaction | *ICD-O-2; OR*<br>1.2 (0.9–1.8); 77<br><br>1.1 (0.8–1.6); 64<br>2.2 (0.9–5.4); 13<br>0.06<br><br>*NHL (ICD-O-2)*<br><br>0.70 (0.34–1.42); 14<br>2.09 (1.28–3.42); 51<br>0.009 | No cases or controls with high probability of exposure and medium/high exposure. Exposure prevalence 8%<br>Covariates: Age, history of hematopoietic cancer, race, and alcohol consumption. Smoking, medial history of immune diseases, income, education level did not affect OR<br>Strengths: Consideration of potential confounding from lifestyle factors, analyses by genotype & NHL subtype<br>Limitations: Limited JEM (not calendar year specific and based on occupations not job tasks), no control for co-exposures |

| Reference | Study Size (N) Exposure assessment | Exposure groups | RR or OR (95% CI) # exposed cases/controls | Interpretation |
|---|---|---|---|---|
| | | | | Evidence of an association and exposure-response relationship with exposure intensity |
| Hardell *et al.* 1994 | Sweden<br>Population-based<br>NHL: 105 cases, 335 controls<br>Questionnaire on occupational history and leisure activities | Ever exposed | *Rappaport classification*<br>7.2 (1.3–4.2); 4 | Exposure prevalence: 1% in controls<br>Covariates: Age, vital status<br>Limitations: Limited exposure assessment, and potential for exposure misclassification is substantial<br>Limited evidence of an association |
| Persson and Fredrikson 1999 | Sweden<br>Population-based<br>NHL: 199 cases, 479 controls<br>Questionnaire on occupational history | Ever exposure | *ICD-8 used in 2nd study, NR 1st study*<br>1.2 (0.5–2.4); 16 | Exposure prevalence 1% in controls<br>Covariates: Age, sex<br>Limitations: Limited exposure assessment, potential for exposure misclassification is substantial.<br>Weak evidence of an association |

ICD = International Classification of Diseases; JEM = job-exposure matrix; NHL = non-Hodgkin lymphoma; NR = not reported; OR = odds ratio; ppm = parts per million; RR = relative risk; SEER = Surveillance, Epidemiology and End Results program
[a]See Table 5-3 for findings on NHL subtypes and related cancers.
[b]Cancer controls only reported.
[c]The InterLymph Consortium classification (see Morton *et al.* 2007) was harmonized with earlier WHO lymphoid neoplasms classification and the ICD-O-3.
[d]Study findings presented that provide additional informative analyses that are not available in the pooled analyses. Findings from other studies are not presented in the tables since they did not have additional information thought to be informative.
[e]Intracategory based on mean among controls.

**Table 5-3. Cohort, nested case-control and population-based case-control studies of trichloroethylene exposure and NHL subtypes**

| Reference | Exposure group | DLBCL | Follicular lymphoma | CLL | Multiple myeloma |
|---|---|---|---|---|---|
| **Cohort and nested case-control studies** | | | | | |
| Hansen *et al.* 2013 | Men<br>Women<br>Men & women | NR | NR | NR | *ICD-7; SIR*<br>0.47 (0.13–1.20); 4<br>1.04 (0.29–2.67); 4<br>0.65 (0.28–1.27); 8 |
| Raaschou-Nielsen *et al.* 2003 | *Entire cohort*<br>Men (588,047 pyar)<br>Women (118,270 pyar) | NR | NR | NR | *ICD-7; SIR*<br>1.1 (0.70–1.52); 28<br>0.90 (0.18–2.56); 3 |
| Vlaanderen *et al.* 2013 | *Cumulative exp. (unit-yr)*<br>0<br>0.04<br>0.13<br>0.74<br>*High exposure group*<br>Cumulative (0.83 unit-yr)<br>Intensity × prevalence (0.04 unit) | NR | NR | NR | *ICD-7; HR (incidence)*<br>1.00<br>0.93 (0.84–1.03); 468<br>0.92 (0.84–1.01); 574<br>0.96 (0.88–1.06); 541<br><br>1.01 (0.84–1.22); 132<br>1.03 (0.88–1.22); 134 |
| Boice *et al.* 2006 | | | | *ICD-9; SMR*<br>0.21 (0.01–1.1.8) 1 | *ICD-9; SMR*<br>0.50 (0.01–2.77) 1 |
| Lipworth *et al.* 2011 | Ever exposed<br>*TCE: years exposed*<br>0<br>< 1<br>1–4<br>5+<br>$P_{trend}$ | NR | NR | .93 (0.40–1.83); 8 | *ICD time of death: SMR*<br>1.21 (0.76–1.81); 23<br>*RR mortality*<br>1.00<br>0.70 (0.31–1.58); 8<br>1.45 (0.68–3.09); 10<br>0.67 (0.25–1.83); 5<br>> 0.20 |
| Radican *et al.* 2008 Mortality | *Ever exposed M & W*<br>*Cumulative exp. (unit-yrs)*<br>Men[a]<br>All<br>0–5 | NR | NR | NR | *HR mortality (ICDA-8, ICD-9 and 10)*<br>1.35 (0.62–2.93); 25<br><br><br>1.08 (0.43–2.71); 19<br>0.69 (0.21–2.27); 5 |

| Reference | Exposure group | DLBCL | Follicular lymphoma | CLL | Multiple myeloma |
|---|---|---|---|---|---|
| **Cohort and nested case-control studies** | | | | | |
| | 2–25<br>> 25 | | | | 1.58 (0.53–4.71); 7<br>1.19 (0.40–3.54); 7 |
| Blair *et al.* 1998<br>Incidence (RR)<br>Same population as Radican *et al.* | *Ever exposed M& W*<br>*Cumulative exposure Men*[b]<br>No exposure<br>< 5<br>5–25<br>> 25 | NR | NR | NR | ICD NR RR (incidence)<br>1.3 (0.5–3.4); 14<br><br>1.7 (0.5–5.5); 10<br>1.0 (0.2– 4.2); 4<br>0.8 (0.1–4.4); 2<br>1.2 (0.3–4.7); 4 |
| Yiin *et al.* 2009<br>Nested case-control study | Average cumulative TCE exposure score/100 | | | | *OR (ICD-8)*<br>1.02 (0.98-1.05) NR |
| Silver *et al.* 2014 | 5 modified exposure duration yr (exposure duration modified by exposure potential) | | | | *ICD time of death (HR mortality)*<br>1.18 (0.70–1.99) NR |
| Bove *et al.* 2014 | Cumulative (µg//L-mth)<br>≤ 1<br>> 1–155<br>> 155–380<br>> 380–8,585 | NR | NR | NR | HR (ICD NR)<br>1.0; 6<br>2.09 (0.66–6.62); 7<br>1.29 (0.34–4.88); 4<br>0 cases |
| **Case-control studies (OR)** | | | | | |
| Cocco *et al.* 2013<br>Pooled analysis | Intensity (ppm)<br>≤ 5<br>5–75<br>> 75<br>$P_{trend}$ | *InterLymph classification*[a]*; OR*<br>1.2 (0.3–4.4); 3/8<br>0.6 (0.2–1.6); 5/25<br>2.0 (0.5–8.7); 3/5<br>0.114 | *InterLymph classification*[a]*; OR*<br>1.1 (0.1–9.2); 1/8<br>1.7 (0.7–4.1); 7/25<br>1.5 (0.2–13); 1/5<br>0.10 | *InterLymph classification*[a]*; OR*<br>1.4 (0.3–7.0); 2/8<br>1.7 (0.7–4.0); 7/25<br>3.2 (0.6–18); 2/5<br>0.055 | NR |
| Purdue *et al.* 2011<br>Incorporated into the pooled analysis | *Average exposure*<br>Per 90 ppm-hr/week<br>$P_{trend}$<br>*Cumulative exposure*<br>Per 65,520 ppm-hrs<br>$P_{trend}$ | ICD-O-2; OR<br>1.11 (1.01–1.23)<br>0.03<br><br>1.07 (0.94–1.22)<br>0.29 | ICD-O-2; OR<br>1.15 (1.04–1.28)<br>0.005<br><br>1.17 (1.04–1.32)<br>0.01 | ICD-O-2; OR<br>1.09 (0.96–1.24)<br>0.16<br><br>1.11 (0.96–1.27)<br>0.16 | NR |

| Reference | Exposure group | DLBCL | Follicular lymphoma | CLL | Multiple myeloma |
|---|---|---|---|---|---|
| **Cohort and nested case-control studies** | | | | | |
| Cocco *et al.* 2010<br>Incorporated into pooled analysis | Ever exposed<br>*Cumulative exposure*<br>Low exposure<br>Medium exposure<br>High exposure<br>$P_{trend}$ | *2001 WHO REAL classification; OR*<br>0.7 (0.4–1.1); 17<br><br>0.7 (CI NR); 6<br>0.4 (CI NR); 4<br>0.9 (CI NR); 7<br>0.16 | *2001 WHO REAL classification; OR*<br>1.2 (0.6–2.3); 11<br><br>2.4 (CI NR); 7<br>0.3 (CI NR); 1<br>1.0 (CI NR); 3<br>0.16 | *2001 WHO REAL classification; OR*<br>0.9 (0.5–1.5); 18<br><br>1.0 (CI NR); 6<br>0.4 (CI NR); 3<br>1.2 (CI NR); 9<br>0.94 | *2001 WHO REAL classification; OR*<br>0.6 (0.3–1)<br><br>0.2 (CI NR); 2<br>0.7 (CI NR); 4<br>0.8 (CI NR); 40/22 |
| Deng *et al.* 2013/Wang *et al.* 2009 | *Ever exposed*<br>IL12A_07 genotype<br>TT<br>AA<br>*P* interaction | *2001 WHO REAL classification; OR*<br>0.59 (0.19–1.85); 4<br>2.66 (1.42–4.96); 21<br>0.0119 | *2001 WHO REAL classification; OR*<br>0.82 (0.25–2.72); 4<br>1.71 (0.78–3.77); 10<br>0.3498 | NR | NR |
| Gold *et al.* 2011<br>Seattle Region (SEER) | High confidence 10-yr lag<br>*Cumulative exposure*<br>No exposure<br>1–415<br>416–3,000<br>3,001–6,592<br>6,593–49,500<br>$P_{trend}$ | NR | NR | NR | *ICD-O-2/3; OR*<br><br>1.0; 139/409<br>1.1 (0.4–2.9); 6/18<br>1.6 (0.7–3.5); 11/20<br>1.4 (0.5–3.8); 6/16<br>2.3 (1.1–5.0); 18/18<br>0.02 |
| Costantini *et al.* 2008<br>Italy | Exposure intensity<br>Very low/low<br>Medium/high<br>≤ 15 years' exposure<br>> 15 years' exposure<br>$P_{trend}$ | | | *ICD-9; OR*<br>1.2 (0.5–2.7); 8/47<br>0.9 (0.3–2.6); 4/35<br>0.7 (0.1–3.4); 2/24<br>1.2 (0.2–6.2); 2/11 | *1CD-9; OR*<br>1.5 (0.7–3.5); 9/28<br>0.9 (0.3–2.4); 5/27<br>0.5 (0.1–2.3); 2/19<br>1.3 (0.3–5.9); 8/13<br>0.82 |
| Nordstrom *et al.* 1998 | Ever exposed | | | *HCL (ICD NR); OR*<br>1.5 (0.7–3.3); 9/26 | |

DlBCL = diffuse large B-cell lymphoma; CLL = chronic lymphocytic leukemia; HR = hazard ratio; ICD = International Classification of Diseases; JEM = job-exposure matrix; HCL = hairy cell leukemia; NHL = non-Hodgkin lymphoma; NR = not reported; OR = odds ratio; ppm = parts per million; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRR = standardized rate ratio; TCE = trichloroethylene; WHO REAL = World Health Organization Revised European American Classification of Lymphoid Neoplasms.

[a]The InterLymph Consortium classification (see Morton *et al.* 2007) was harmonized with the earlier WHO lymphoid neoplasms classification and the ICD-O-3. It combines chronic lymphocytic leukemia (CLL) with small lymphocytic lymphoma (SLL).

#### *5.1.3.1 Meta-analyses of trichloroethylene exposure and NHL and related subtypes*

Several recent meta-analyses of NHL and trichloroethylene exposure have been conducted (Wartenberg *et al.* 2000, Mandel *et al.* 2006, EPA 2011, Scott and Jinot 2011, Karami *et al.* 2013). Since a number of studies have been published since 2000, the present review will focus primarily on the most recent meta-analyses by the EPA (EPA 2011, Scott and Jinot 2011) and by Karami *et al.* (2013). Both meta-analyses were conducted prior to the publication of studies by Hansen *et al.* (2013), Vlaanderen *et al.* (2013), Christensen *et al.* (2013) and Bove *et al.* (2014) or the InterLymph study by Cocco *et al.* 2013), all of which are included in our review. The individual studies contributing to the two pooled studies (Hansen *et al.* 2013, Cocco *et al.* 2013) were included in the meta-analysis; however, the pooled study by Hansen also updated their constituent cohorts.

The EPA meta-analyses included systematic data extraction of nine cohort and eight case-control studies in which potential trichloroethylene exposure was documented and risk estimates for NHL and trichloroethylene exposure were calculated. Studies with evidence of a low potential for exposure to trichloroethylene were excluded. Fixed and random effects models, tests for heterogeneity and publication bias, and sensitivity analyses (to examine the impact of individual studies and selection of alternative relative risk selections on meta-relative risk estimates) were used to calculate summary meta-relative risks, using, where provided, adjusted or crude risk estimates from internal analyses rather than external (SMR or SIR) estimates. In addition, separate meta-analyses were conducted for the highest exposure groups (either by duration and/or intensity) within trichloroethylene-exposed populations (reported in 17 of the 19 constituent studies). Low to moderate heterogeneity among risk estimates was observed and there was some evidence of publication bias.

Karami *et al.* (2013) used similar exclusion criteria and methods of analysis to the EPA analysis and considered a closely overlapping body of 10 cohort and 9 case-control studies (see Table D-7). Low to moderate heterogeneity but little evidence of publication bias was observed. Slightly higher mRRs were observed among the four European cohorts (mRR = 1.66, 95% CI = 1.29 to 2.14) than among the 6 U.S. cohorts (mRR = 1.41, 95% CI = 1.11 to 1.78), and among studies reporting NHL incidence compared with combined incidence and mortality.

In the EPA analysis, mRRs for the highest exposure groups within studies (where reported) were used to calculate mRRs for the highest exposure (intensity and/or duration) group(s) within studies. In contrast, Karami *et al.* calculated mRRs by high or low intensity of exposure and separately by high and low duration of exposure, based on a subset of studies that reported these metrics, thus yielding somewhat different mRR estimates from those in the EPA analysis. The summary mRRs for NHL are given in Table 5-4 below.

**Table 5-4. Meta-analyses of trichloroethylene exposure and NHL and related subtypes[a]**

| Reference | Study design (number of studies) | mRR (95% CI) All | mRR (95% CI) Highest exposure | Comments |
|---|---|---|---|---|
| EPA 2011/Scott and Jinot 2011 | Combined cohort and case-control studies<br>17 for any exposure<br>13 for high exposure) | 1.23 (1.07–1.42)[b] | 1.43 (1.13–1.82) | Random effects model<br>Low sensitivity to removal of individual studies or selection of alternative RRs<br>Low to moderate heterogeneity; some evidence of publication bias |
| EPA 2011/Scott and Jinot 2011 | Cohorts (9) | 1.33 (1.13–1.58) | 1.60 (1.24–2.08) | No sig. diff. between cohort and case-control mRRs (any or highest exposure); lower heterogeneity for highest exposure groups |
| EPA 2011/Scott and Jinot 2011 | Case-control (8) | 1.11 (0.89–1.38) | 1.29 (0.76–2.20) | |
| Karami *et al.* 2013 | TCE-exposed cohort + case-control studies (19) | 1.32 (1.14–1.54) | NR | Random effects model<br>Little evidence of heterogeneity and publication bias |
| Karami *et al.* 2013 | TCE-exposed cohorts (10)<br><br>*Exp-response*:<br>Long duration<br>Short duration<br><br>High intensity [c]<br>Low intensity<br><br>Subset of U-TCA studies (3) | 1.52 (1.29–1.79)<br><br><br><br><br><br><br><br><br>2.15 (1.34–3.45) | <br><br><br>1.56 (1.02–2.40)<br>1.30 (0.92–1.84)<br><br>1.27 (0.83–1.96)<br>1.68 (1.14–2.46) | Some evidence of positive exposure response among a total of 4 studies using measures of duration<br>Negative exposure response observed among 5[b] studies using measures of intensity (excluding 3 Nordic studies of U-TCA) |
| Karami *et al.* 2013 | TCE-exposed case-control (9)<br><br>*Exp-response*:<br>Long duration<br>Short duration<br><br>High intensity<br>Low intensity | 1.14 (0.93–1.40) | <br><br><br>1.18 (0.60–2.34)<br>1.46 (0.78–2.73)<br><br>1.42 (0.86–2.33)<br>1.06 (0.79–1.42) | Some evidence of publication bias<br>No association between exposure duration among 2 studies or intensity among 3 studies |

mRR = meta-relative risk; NR = not reported; RR = relative risk; U-TCA = urine trichloroacetic acid.
[a:]See Table D-7 for a list of studies in each meta-analysis.
[b]Adjustment for publication bias yielded mRR = 1.15 (95% CI = 0.97–1.36).
[c]6 studies cited in text, 5 in table.

The overall results of both meta-analyses (EPA 2011/Scott and Jinot 2011, Karami *et al.* 2013), are broadly comparable. Both show statistically significant mRRs for cohort and case-control

studies combined and the body of cohort studies. The mRR for case-control studies was lower, but not significantly different, than the mRR for cohort studies (Scott and Jinot 2011). Importantly, the mRR was robust and not sensitive to the removal of individual studies or selection of alternative RRs. Overall, there was evidence from the EPA meta-analysis, among the body of cohort studies, and to a somewhat lesser extent among the case-control studies, that the risk of NHL is greater in the subgroups with the highest exposure compared with the overall exposure groups. In the analysis by Karami *et al.* (2013), associations between intensity or duration of exposure were less clear; the differences may be attributable to the smaller number of studies, the use of separate analyses of intensity and duration, less comparability between high and low exposure groups, or some differences in the included studies. The highest mRR was observed among the three Nordic studies using biomonitoring of urine TCA (Karami *et al.* 2013), which was not observed in the later pooled and updated study by Hansen *et al.* (2013). Neither meta-analysis included the InterLymph pooled analyses, although they included three of the component studies, two of which were null. Substitution of the component studies with the InterLymph study could possibly strengthen the association with trichloroethylene exposure in the meta-analysis of case-control studies (higher risk, less heterogeneity). The more recent meta-analysis (Karami *et al.* 2013) found a stronger association among studies that specifically assessed trichloroethylene than among studies of broadly assessed chlorinated solvents, in which effects from trichloroethylene would be diluted.

Meta-analyses for other NHL subtypes have been largely inconclusive and were based on a small number of studies. Karami *et al.* (2013) conducted an analysis of multiple myeloma and CLL among the studies reporting for these endpoints that were included in their NHL meta-analysis, and found no significant increases in risk. However, this meta-analysis did not include recent studies reporting on one or other of these endpoints (Costantini *et al.* 2008, Gold *et al.* 2011, Hansen *et al.* 2013, Cocco *et al.* 2013, Vlaanderen *et al.* 2013, Bove *et al.* 2014).

### 5.1.4 Evaluation of potential confounding by occupational co-exposures or other risk factors

Section 3 discussed the adequacy of the methods used in the cohort (Section 3.1) and case-control studies (Section 3.2) for evaluating potential confounding from occupational co-exposures and non-occupational factors. However, that assessment was not specific for NHL. This section builds on that assessment, integrating it with other relevant information and evaluating whether confounding can explain the increased risks of NHL and its related subtypes observed in a number of the studies.

#### *5.1.4.1 Occupational co-exposures*

The major occupational risk factors that have been associated with NHL (with limited evidence) include benzene, ethylene oxide, 2,3,7,8-TCDD, polychlorinated biphenyls, phenoxy herbicides, styrene, and ionizing radiation by IARC and the Report on Carcinogens (Cogliano *et al.* 2011, NTP 2011). Organic solvents may be potential risk factors and have been the focus of the recent EPILYMPH study (Cocco *et al.* 2010). The most common co-exposures in the cohort studies are the chlorinated and possible other organic solvents and cutting oils such as mineral and petroleum oils. Radiation is a possible co-exposure in the two studies of uranium workers (Bahr *et al.* 2011, Yiin *et al.* 2009). Phenoxy herbicides may be a co-exposure in two of the Swedish studies (Nordstrom *et al.* (1998), Hardell *et al.* 1994) but neither of these studies contributes significantly to the evaluation. Benzene was also a potential co-exposure in the InterLymph

study (Cocco *et al.* 2013). Tetrachloroethylene exposure was correlated with trichloroethylene exposure in the Nordic population-based cohort; exposure to tetrachloroethylene but not to trichloroethylene was associated with increased risks of NHL.

None of the cohort and most of the case-control studies that reported NHL findings attempted to examine or control for potential confounding by co-exposures. The InterLymph study conducted sensitivity analyses that excluded subjects with benzene exposure; risks were elevated for both high probability (OR = 1.4, 95% CI = 0.8 to 2.6) and high intensity of exposure (OR = 1.9, 95% CI = 1.2 to 3.0) in the total cohort and analyses restricted to subjects with high probability of exposure (OR not reported), but trends were no longer apparent..

Several lines of evidence argue against a major impact from confounding of potential co-exposures across studies. None of the documented co-exposures are identified risk factors for NHL and the types and co-exposures of other agents are likely to vary in the patterns and levels across the various industries and time periods, especially in the studies of mixed occupation groups. In addition, an exposure-response relationship for NHL and exposure intensity was observed in the InterLymph study (considered to be the most informative study) and there was no evidence that other potential co-exposures were highly correlated with trichloroethylene exposure in that study. However, potential confounding by other solvents or chlorinated solvents may be possible, especially in the aircraft-manufacturing studies.

#### *5.1.4.2 Lifestyle and other potential confounders*

Of the non-occupational risk factors for NHL, which include viral infections, immunosuppressive disorders, autoimmune diseases, and exposure to immunosuppressive drugs or chemotherapy drugs (Hardell and Axelson 1998, Cogliano *et al.* 2011), there is little *a priori* reason to suspect that most of these would vary by trichloroethylene-exposure status in the cohort or nested case-control studies. Smoking is not considered to be a risk factor for NHL but may be a risk factor for follicular lymphoma. Each case-control study matched or adjusted for age, sex, birth year, or race, using conditional or unconditional logistic regression, as appropriate. Some studies (Deng *et al.* 2013/Wang *et al.* 2009, Costantini *et al.* 2008, Christensen *et al.* 2013), and some of the constituent studies of the pooled analysis (Miligi *et al.* 2006, Cocco *et al.* 2010, Purdue *et al.* 2011) also considered or adjusted for smoking, other lifestyle factors, and surrogates of socioeconomic status. Thus, confounding by these factors across studies seems unlikely.

### 5.1.5 Integration across studies

Overall, there is some evidence of an association between exposure to trichloroethylene based on findings of a modest increase in risk of NHL in several studies of different study designs and in different populations, although the strength of the evidence varied (see Figure 5-1). The strongest evidence of an association between exposure to trichloroethylene and NHL comes from the InterLymph pooled analysis (*P* for Fisher combined probability = 0.004), which was considered to be the most informative study and is supported by findings of relatively small, mostly statistically non-significant increases (> 20%) in NHL risk among workers exposed to trichloroethylene in most studies of moderate (Hansen *et al.* 2013, Radican *et al.* 2008) or low to moderate quality (Lipworth *et al.* 2011, Morgan *et al.* 1998, Raaschou-Nielsen *et al.* 2003, Deng *et al.* 2013/Wang *et al.* 2009). Limitations in studies would primarily bias findings toward the

null. The high increased risk reported by Hardell *et al.* (1994) should be viewed with caution and is most likely biased towards a positive finding. There was little evidence (≤ 20%) (Bove *et al.* 2014, Persson and Fredrikson 1999) to no evidence (OR ≤ 1.0) (Silver *et al.* 2014, Vlaanderen *et al.* 2013, Bahr *et al.* 2011) for an association in most studies considered to be of lower quality, primarily because of low sensitivity to detect an effect. (Only 1 case of NHL was reported by Boice *et al.* 2006.)

Statistically significant increases in NHL risk were found in two recent meta-analyses (mRR = 1.23, 95% CI = 1.07 to 1.42, Scott and Jinot 2011; mRR = 1.23, 95% CI = 1.07 to 1.42, Karami *et al.* 2013 for combined cohort and case-control studies). In the meta-analysis by Scott and Jinot, the mRR was robust and not sensitive to removal of individual studies or use of alternative risk estimates. In the most recent meta-analysis, there was little evidence of heterogeneity or publication bias (for the analysis of the combined cohort and case-control studies); however, there was some evidence for both publication bias and low to moderate heterogeneity in the EPA meta-analysis.

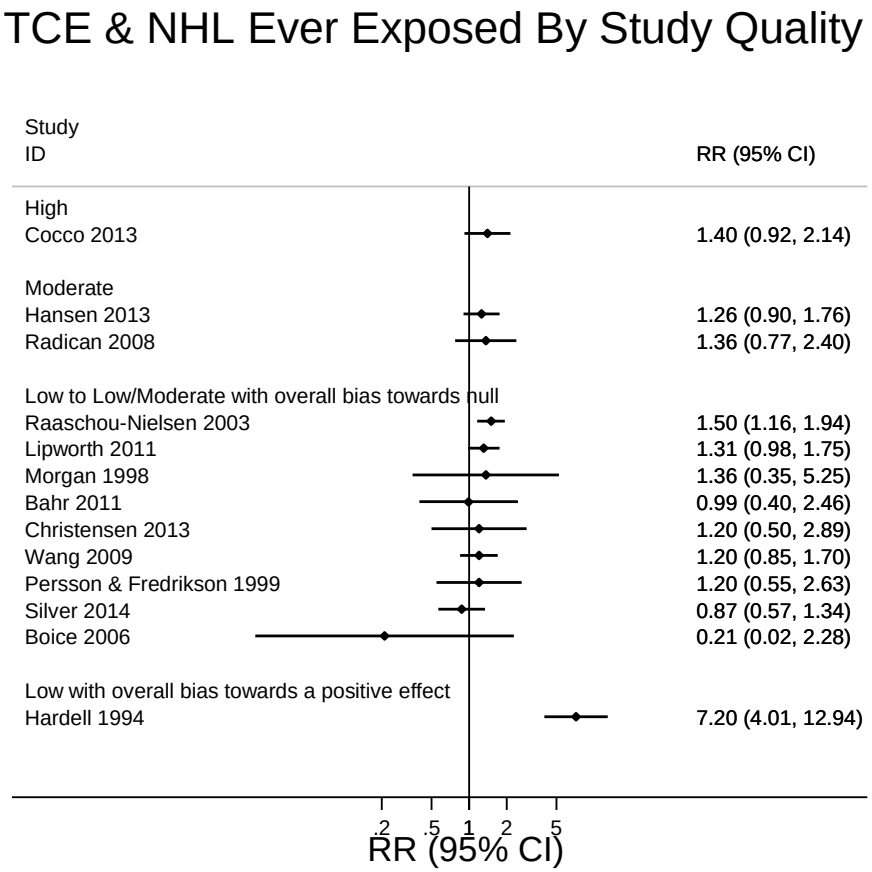
Some, but not all, studies found evidence for exposure-response relationships. The InterLymph study (Cocco *et al.* 2013) found that the risk of NHL increased with longer duration and higher intensity of exposure and its constituent study by Purdue *et al.* (2011) also found exposure-response relationships with other exposure metrics, including average weekly exposure and cumulative exposure. The study of Connecticut women (Deng *et al.* 2013/Wang *et al.* 2009) found higher risks among women with the medium-high exposure intensity compared with women with low exposure. However, evidence for an exposure-response relationship was lacking among cohort studies (Hansen *et al.* 2013, Raaschou-Nielsen *et al.* 2003, Lipworth *et al.* 2011, Radican *et al.* 2008) and in some cases risks were lower among the higher exposed compared with the lowest exposed. These studies had limited ability to evaluate exposure-response relationships because of low statistical power or concerns about exposure misclassification. The EPA meta-analyses found a somewhat higher risk in analyses of high exposure than ever exposure; however, the latest meta-analysis found some evidence for exposure response with duration but not intensity. This pattern could possibly change with the inclusion of the InterLymph study.

No biases (such as selection) were identified that would bias towards a positive association with the possible exception of the Hardell *et al.* study. Confounding by other co-exposures can be ruled out reasonably in most of the large case-control studies and the Nordic studies of workers of diverse industries because the co-exposures to other agents are likely to vary in pattern and levels across the various industries and different time periods. Confounding by other solvents or chlorinated solvents may be possible in the aircraft-manufacturing studies. No evidence for confounding by lifestyle factors was found.

No association between NHL and exposure was found in some cohort studies with more limited designs or limited statistical power (Bove *et al.* 2014, Bahr *et al.* 2011, Morgan *et al.* 1998) and the recent, large population-based Nordic cohort study (Vlaanderen *et al.* 2013) in which exposures were likely low and non-differential exposure misclassification was likely. The studies by Vlaanderen *et al.* and Bove *et al.* were not included in the most recent meta-analyses.

With respect to related subtypes of NHL, the strongest evidence of an association for follicular lymphoma and CLL is based on positive associations in the InterLymph study (Cocco *et al.* 2013) and its constituent study, the NCI-SEER study by Purdue *et al.* (2011). The most informative study on multiple myeloma (Gold *et al.* 2011) reported a statistically significant increase in incidence with increasing cumulative exposure. Weaker associations were found in some of the cohort studies. The meta-analysis on trichloroethylene exposure and NHL and related subtypes by Karami *et al.* (2013) also reported a meta-risk of 1.05 (95% CI = 0.88 to 1.27) for multiple myeloma and 0.98 (95% CI = 0.69 to 1.41) for combined chronic/small cell leukemia.

**Figure 5-2. Forest plot of risk estimates for ever exposure to trichloroethylene and NHL**




Relative risk and 95% CI for ever exposure to TCE and NHL according to study quality (see Section 3, Appendix D, and Figure 5-1). Studies with low/moderate and low quality were combined into one category. Low quality studies were grouped according to overall direction of bias although direction of bias was less clear for Bahr *et al.* 2011 because of limited reporting and Boice *et al.* (2006) because only one NHL case was observed. Studies by Bove *et al.* (2014), and Vlaanderen *et al.* (2013) are not graphed because they did not report relative risk for ever exposure. Findings for these studies are reported in Table 5-1.

## 5.2 Mechanistic data for NHL and related neoplasms

A slight increased risk of NHL and related neoplasms (e.g., follicular lymphoma, multiple myeloma, chronic lymphocytic leukemia) was identified in humans exposed to trichloroethylene (see Section 5.1). In addition, increased incidences of lymphoma (female mice) and leukemia (female rats) were reported in experimental animals exposed to trichloroethylene (NTP 2011). Most of the recognized risk factors for NHL involve immune modulation (Ponce *et al.* 2014, Baecklund *et al.* 2014, Dias and Isenberg 2011, Grulich *et al.* 2007). Although the mode of action of trichloroethylene-induced NHL and related neoplasms is unknown, the key events may be related to effects of trichloroethylene on the immune system (including both immune suppression and autoimmunity). The following sections include a brief review of the immune effects of trichloroethylene in humans and experimental animals (Section 5.2.1), risk factors for NHL (Section 5.2.2), possible modes of action for trichloroethylene-induced immune modulation and NHL (Section 5.2.3), and a summary (Section 5.2.4).

### 5.2.1 Immune effects of trichloroethylene

The effects of trichloroethylene on the immune system have been investigated in humans and experimental animals. Reported effects include autoimmunity and immunosuppression and are reviewed below.

#### *5.2.1.1 Autoimmune disease in humans*

Studies of trichloroethylene exposure and autoimmune diseases consisted of three case-control studies (Diot *et al.* 2002, Garabrant *et al.* 2003, Nietert *et al.* 1998) and one prospective cohort study (Marie *et al.* 2014) of systemic sclerosis (scleroderma) and one case-control study of undifferentiated connective tissue disease (Lacey *et al.* 1999). Results from these studies are summarized in Table 5-5). No epidemiological studies of trichloroethylene exposure and rheumatoid arthritis or other autoimmune diseases were identified.

There is reasonably strong evidence that trichloroethylene exposure is associated with scleroderma, especially for men (Table 5-5). In a pooled analysis of the three case-control studies of scleroderma, combined ORs of 2.5 (95% CI = 1.1 to 5.4) among men and 1.2 (95% CI = 0.6 to 2.6) among women were reported (Cooper *et al.* 2009). Data were insufficient to evaluate the findings for undifferentiated connective tissue disease.

**Table 5-5. Trichloroethylene exposure and autoimmune diseases in humans[a].**

| Reference | Study population # cases:controls or exposed subjects | Exposure assessment | Endpoints | Summary of findings |
|---|---|---|---|---|
| Nietert *et al.* 1998 | Population-based case-control study, South Carolina (USA) | Self-reported exposure via hobbies | Systemic sclerosis | OR<br>2.0 (0.7–5.3) M<br>1.2 (0.5–2.6) F |
| Diot *et al.* 2002 | Hospital-based case-control study, France<br>80 cases; 160 controls | Job history, self-reported exposure, expert review | Systemic sclerosis | OR<br>7.6 (1.5–37.4) |

| Reference | Study population # cases:controls or exposed subjects | Exposure assessment | Endpoints | Summary of findings |
|---|---|---|---|---|
| Garabrant *et al.* 2003 | Population-based case-control study, Michigan & Ohio (USA)<br>660 cases; 2,227 controls | Individual job history for 9 solvents, expert review | Systemic sclerosis | Women only:<br>OR<br>1.9 (0.6–6.6) |
| Cooper *et al.* 2009 | Pooled case-control analysis (Nietert *et al.* 1998, Diot *et al.* 2002, Garabrant *et al.* 2003) | | Systemic sclerosis | OR<br>2.5 (1.1–5.4) M<br>1.2 (0.6–2.6) F |
| Marie *et al.* 2014 | Population-based case-control study, France<br>100 cases; 300 controls | Individual job history, self-reported exposures, expert review | Systemic sclerosis | OR (high cumulative exposure)<br>3.63 (1.15–12.09)<br>Men higher risk than women (any exposure) |
| Lacey *et al.* 1999<br>205 cases: 2,079 controls (F) | Population-based case-control study, Michigan, Ohio (USA) | Individual job history for 9 solvents, expert review | Undifferentiated connective tissue disease | Women only<br>OR<br>1.7 (0.2–15.0) |

#### *5.2.1.2 Immunosuppression in humans*

Studies of trichloroethylene exposure and immune suppression (e.g., lymphocyte subset populations, antibodies, or biomarkers of immune function) consisted of the following two subgroups: (1) occupational studies of trichloroethylene-exposed workers in metalworking and electronic factories in Guangdong province, China (Bassig *et al.* 2013, Dai *et al.* 2004, Dai *et al.* 2009, Hosgood *et al.* 2012, Huang *et al.* 2006, Huang *et al.* 2012, Kamijima *et al.* 2008, Lan *et al.* 2010, Liu *et al.* 2009a, Zhang *et al.* 2013a) and of trichloroethylene-exposed workers in the Italian printing industry (Iavicoli *et al.* 2005); and (2) population-based cross-sectional studies of autoimmune antibodies in hospital patients in Tours, France (Beaudreuil *et al.* 2005) and a prospective study of immune markers among a birth cohort exposed pre- and postnatally to trichloroethylene in Leipzig, Germany (Lehmann *et al.* 2001, Lehmann *et al.* 2002). Further details of these studies are provided in Table 5-6).

**Table 5-6. Trichloroethylene exposure and lymphocytes, and related immune markers in humans[a]**

| Reference | Study population # cases:controls or exposed subjects | Exposure assessment | Endpoints | Summary of findings |
|---|---|---|---|---|
| ***Occupational studies*** | | | | |
| *Lymphocyte subsets* | | | | |

| Reference | Study population # cases:controls or exposed subjects | Exposure assessment | Endpoints | Summary of findings |
|---|---|---|---|---|
| Lan *et al.* 2010 | Metal/electronics factory workers<br>China<br>80 exposed, 96 unexposed workers | Personal air samples 3 weeks prior to blood collection<br><br>Urine TCA | CD-4, 8<br><br>sCD27, sCD30 markers for TNF receptor<br><br>NK, B cells | Significant dose-related decreases in CD-4, CD-8, NK, B cells, and sCD27, sCD30 levels among exposed group |
| Hosgood *et al.* 2012 | Metal/electronics factory workers<br>China<br>Cross-sectional study<br>80 exposed, 96 unexposed workers (see Lan *et al.* 2010 above) | As above | CD-3, CD-4 and CD-8 naïve and effector memory T cells<br><br>Regulatory T cells | Significant decreases in CD-4 and CD-8 naïve T cells, plus CD-4 effector memory cells among exposed group |
| *Cytokines, antibodies, immunoglobulins and related measures* | | | | |
| Dai *et al.* 2004 | Metal/electronics factory workers<br>China<br>Case-control (cross-sectional) study<br>111 TCE-exposed with SGD: 152 TCE exposed w/o SGE | Air TCE levels in workplaces from which exposed workers + SGD selected<br>(degreasing operations) | Severe generalized dermatitis (SGD)<br>Polymorphisms for IL-4 and TNF-α and β | Significant increase in TNF-α 380 wild allele in SGD vs. non-SGD subjects but decrease in heterozygous TNF-α 380 in SGE subjects vs. homozygous genotype |
| Bassig *et al.* 2013 | Metal/electronics factory workers<br>China<br>Cross-sectional<br>71 exposed, 78 unexposed workers | Personal air samples<br>Urine TCA | IL-6, 10<br>TNF-α | Significant dose-related decrease in IL-10 in exposed workers, adjusted for smoking, BMI, recent infection; no differences in IL-6, TNF-α |
| Zhang *et al.* 2013b | Metal/electronics factory workers<br>China<br>Cross-sectional<br>80 exposed, 45 unexposed workers | Personal air samples<br>Urine TCA | IgG, IgE, IgM | Significant decrease in IgG and IgM in exposed workers, no difference in IgE |
| Kamijima *et al.* 2007, Kamijima *et al.* 2008, Kamijima *et al.* 2013 | Metal/electronics factory workers<br>China<br>28 patients with TCE-induced HSD, 48 healthy TCE-exposed | Case-series<br>no exposure assessment | Hypersensitivity skin disorder (mostly exfoliative dermatitis) and accompanying hepatitis | Significant increases in Human herpesvirus 6 (HHV6), IL- 6, IL-10, IFN-γ, TNF-α in HSD |

| Reference | Study population # cases:controls or exposed subjects | Exposure assessment | Endpoints | Summary of findings |
|---|---|---|---|---|
| | workers | | IL-Iβ, 2,4,5, 6, 10<br>IFN-γ<br>TNF-α<br>(HHV6 reactivation | patients vs. healthy workers |
| Liu *et al.* 2009a | Patients<br>Guandong China<br>5 TCE-exposed patients with dermatitis<br>5 TCE-exposed patients post-dermatitis<br>4 healthy controls | NR; subjects selected based on HSD and workplace | Dermatitis, hepatitis<br>6 antigenic proteins[c] | Increases in autoantigens in current and post-dermatitis patients vs. healthy controls |
| Huang *et al.* 2006 | Metal/electronics factory workers<br>China<br>59 TCE-exposed workers with HSD<br>59 healthy exposed workers | Duration of TCE exposure and job task | Hypersensitivity skin disorder<br>Hepatic dysfunction, HHV6 reactivation<br>Infectious disease antibodies | Significant increase in HHV6 reactivation (no differences for other infectious disease titers) |
| Huang *et al.* 2012 | Metal/electronics factory workers<br>China<br>8 patients pre- and post-acute dermatitis | Duration of TCE exposure<br><br>Urine TCA | Calprotectin and retinol binding protein (biomarkers for TCE-induced hypersensitivity dermatitis | Upregulation of calprotectin (SA100A8/A9) and downregulation of retinol binding protein (RBP4) during acute phase |
| Iavicoli *et al.* 2005<br>35 exposed, 30 unexposed (internal analysis) | Printing workers<br>Italy<br>35 TCE-exposed workers<br>30 unexposed factory workers<br>40 office workers | Duration of TCE exposure<br>Job task<br>Urine TCA | IL-2, IL-4<br>IFN-γ | Significant increase in IL-2, IFN-γ; significant decrease in IL-4 among TCE-exposed workers compared with unexposed workers and office workers |
| ***Other studies*** | | | | |
| Beaudreuil *et al.* 2005 | Hospital patients<br>France<br>60 ANCA+ cases; 120 hospital controls | Work history questionnaire<br>Expert review | ANCA | No association with estimated TCE exposure |
| Lehmann *et al.* 2001 | Longitudinal birth cohort<br>Germany<br>200 3-year old children<br>(cytokines on subgroup | Passive air sampling VOCs in infant bedrooms | Milk, egg allergies CD-3,4,8<br>IL-4<br>IL and IFN-γ producing CD 3,4,8 | No association for TCE exposure and allergies, CD cells or cytokines |

| Reference | Study population # cases:controls or exposed subjects | Exposure assessment | Endpoints | Summary of findings |
|---|---|---|---|---|
| | of 28) | | cell | |
| Lehmann *et al.* 2002 | Longitudinal birth cohort<br>Germany<br>85 randomly selected infants from study population of approx. 976 parents | As above plus maternal exposure questionnaire | IL-2, 4<br>IFN-γ<br>TNF-α<br>Measured in cord blood | Significant reduction in IL-2 for higher TCE exposure category |

ANCA = antinuclear antibodies; CD = Cluster of differentiation (T-cell types); HHV6 = Human herpesvirus 6; IL = interleukin; IFN = interferon; TNF = tumor necrosis factor; IgG, E, M = immunoglobulin G, E, M; NK = natural killer cells; VOC = volatile organic compounds.
[a]Case reports, studies of mixed or chlorinated solvents, or ecological studies are excluded.
[b]Autoantibodies include antithyroglobulin, antimicrosomal antibodies.
[c]NM23 protein, purine nucleoside phosphorylase, enoyl coenzyme A hydratase peroxisoma 1, ribosomal protein P0, lactate dehydrogenase B and proteasome activator subunit 1 isoform 1.

The most informative studies were the occupational cross-sectional studies of metal and electronics workers in Guangdong province, China, and the Italian study of printing workers. These studies provided clear evidence that the subjects were exposed to moderate to high levels of trichloroethylene. Findings from the studies by Lan *et al.* (2010), Hosgood *et al.* (2012), Bassig *et al.* (2013), and Zhang *et al.* (2013a) suggest that trichloroethylene exerts immunosuppressive effects. Workers exposed to trichloroethylene were reported to have lower counts of B and T lymphocytes in peripheral blood. Some trichloroethylene-exposed workers had lower serum levels of IgG, IgM, sCD27, and sCD30, suggesting that trichloroethylene impairs B-cell stimulation. Bassig *et al.* (2013) also reported lower serum levels of IL-10 among exposed workers, which may indicate chemically induced alterations in Th1/Th2 balance. However, in an *in vitro* assay dichloroacetic acid markedly increased production of IL-10 in peripheral blood mononuclear cells from healthy volunteer (Eleftheriadis *et al.* 2013). Iavicoli *et al.* (2005) also reported lower serum levels of the Th2 cytokine, Il-4, and increased levels of the Th1 cytokines, IL-2 and interferon-gamma among trichloroethylene-exposed workers. Overall, these studies provide evidence of immune suppression associated with trichloroethylene exposure, and possibly with measures of precursors of autoimmunity (e.g., IFN- γ).

Cases of severe generalized dermatitis (i.e., hypersensitivity skin disorders) also were reported among the Chinese workers (Dai *et al.* 2004, Dai *et al.* 2009, Huang *et al.* 2006, Huang *et al.* 2012, Kamijima *et al.* 2008, Kamijima *et al.* 2013, Liu *et al.* 2009a) and in Japan, the United States, Canada, and Spain (Watanabe 2011). Disease onset usually occurs within 2 to 5 weeks of exposure, resembles severe drug-induced hypersensitivity syndrome, and is associated with elevated inflammatory responses, oxidative stress, and reactivation of latent human herpesvirus 6 (Kamijima *et al.* 2013, Huang *et al.* 2012, 2006). The cases of hypersensitivity skin disorders are frequently accompanied by immune-mediated (toxic) hepatitis and liver dysfunction (Kamijima *et al.* 2013, Watanabe 2011, Huang *et al.* 2006). Kim and Kim (2010) also reported cases of idiosyncratic toxic hepatitis in Korean workers occupationally exposed to trichloroethylene. An immunologic-type reaction was thought to be responsible because disease onset was sporadic, generally not dose related, and usually occurred after 30 days of exposure.

A study of antineutrophil cytoplasmic autoantibody-positive patients by Beaudreuil *et al.* (2005), a biomarker for small vessel vasculitis, did not observe an association with trichloroethylene compared with control patients, but there are no other studies of this endpoint and the relevance of this endpoint is unclear. The German birth cohort studies (Lehmann *et al.* 2001, 2002) reported no association for trichloroethylene exposure and allergies, CD cells or cytokines, except for a reduction in IL-2 among subjects with higher exposure. However, these studies are of limited utility, in part due to the limited exposure assessment of maternal and child exposure and low overall levels of trichloroethylene reported.

#### *5.2.1.3 Immunosuppression and autoimmunity in experimental animals*

Many studies were identified that examined the immunological effects of trichloroethylene in experimental animals. Many of the relevant studies were conducted in MRL+/+ mice, which spontaneously develop a systemic lupus erythematosus-like autoimmunity. The various study designs and immunomodulatory endpoints are presented in Appendix E (Tables E-1 and E-2). Results from these studies are summarized by endpoint in Tables E-3 (blood - adducts and leukocyte numbers), E-4 (blood – antibodies), E-5 (spleen), E-6 (liver and kidney), and E-7 (splenic *ex vivo* cytokines, lymph nodes, and anti-bacterial response).

Overall indications of immunosuppression from exposure to trichloroethylene or its metabolites were seen as changes in leukocyte numbers, proliferation, activation, and function (see Table E-4). However, there were some inconsistencies among different tissues and studies. Overall, immunosuppression was suggested in the peripheral blood by decreases in leukocytes, neutrophils, lymphocytes, $CD4^+$ T cells, $CD8^+$ T cells, and B cells (Chen *et al.* 2006, Hobara *et al.* 1984, Ravel *et al.* 2004). Immunosuppression was suggested in the liver as the cytolytic activity of NK cells was decreased (Wright *et al.* 1991). Looking at the terminal outcome of immunosuppression, there was a decrease in the ability of the mice to fight bacterial infections in the lung and an increase in death from these infections (Aranyi *et al.* 1986, Selgrade and Gilmour 2010). Mixed results were seen in the spleen and lymph nodes. In the spleen, most studies found no differences with exposure to trichloroethylene or its metabolites; however, in some studies there were decreases in the number of $CD4^+$ T cells (2/4 studies), $CD8^+$ T cells (1/7 studies), and B cells (2/7 studies) and increases in lymphocyte number (2/2 studies), lymphocyte proliferation (1/1 study), and $CD4^+$ T-cell proliferation (2/3 studies) (Blossom and Doss 2007, Blossom *et al.* 2007, Blossom and Gilbert 2006, Blossom *et al.* 2004, Cai *et al.* 2006, Gilbert *et al.* 2011, Griffin *et al.* 2000a, Griffin *et al.* 2000c, Kauffmann *et al.* 1982, Keil *et al.* 2009, Peden-Adams *et al.* 2006, Peden-Adams *et al.* 2008, Wang *et al.* 2008b). Initial B-cell activation against sheep red blood cells in the spleen was increased in one study and decreased in two studies (Kauffmann *et al.* 1982, Peden-Adams *et al.* 2006, Sanders *et al.* 1982). The numbers of $CD4^+$ T cells, $CD8^+$ T cells, and B cells in lymph nodes and activation of those B cells were unaffected (Blossom *et al.* 2006, Blossom *et al.* 2004, Gilbert *et al.* 2012, Gilbert *et al.* 2011). The mixed results in the spleen and lack of effect in the lymph nodes suggest that trichloroethylene does not affect the amount or activity of immune cells in those organs. The decreased number of immune cells in the peripheral blood and the decreased ability to fight bacterial infections suggests trichloroethylene may cause immunosuppression.

In the available studies, direct cellular effects on B cells were mixed or minimal. However, indirect effects of B-cell activity, indicated by increased bacterial infection, showed

immunosuppression. Neither B-cell activation (based on the expression of MHC II) nor proliferation were affected by exposure (Blossom and Doss 2007, Blossom *et al.* 2004, Griffin *et al.* 2000a, Kauffmann *et al.* 1982, Keil *et al.* 2009, Peden-Adams *et al.* 2006, Peden-Adams *et al.* 2008, Wang *et al.* 2008b); however, the most appropriate biomarkers for B-cell activation (e.g., CD23, CD27, CD30, CD44, and CXCL13) (De Roos *et al.* 2012, Hussain *et al.* 2013) were not examined in these studies. B-cell activity based on the initial IgM-mediated activation, decreased in two studies and increased in one study (Kauffmann *et al.* 1982, Peden-Adams *et al.* 2006, Sanders *et al.* 1982). The initial B-cell activation response would not likely play a significant role in the response to persistent antigens (Matthews *et al.* 2014). The reduced ability to fight bacterial challenges supports the idea of immunosuppression, especially against immunogens that would normally produce a B-cell response; however, other leukocytes are involved in an antibacterial response and their reduced activity might be the cause of immunosuppression. The reduced ability to fight bacterial infections would allow for the persistence of bacterial antigens to lead to continual B-cell activation; however, no evidence of B-cell activation markers or proliferation were reported. These results suggest that either the persistent bacteria did not affect B-cell activation for some reason; or that B-cell activation did occur, but could not be detected based on cell proliferation or MHC II expression. Other indications of B-cell activation are seen below in an autoimmune response.

General signs of autoimmune disease were suggested by changes in antibodies and immune cell activities and autoimmune hepatitis in experimental animals (particularly autoimmune-prone MRL+/+ mice) exposed to trichloroethylene or its metabolites (see Appendix F, Tables F-1 to F-4). Exposure-related effects included increased IgG and autoantibody formation (anti-nuclear, anti-DNA, anti-albumin, and anti-liver) (Wang *et al.* 2007b, Wang *et al.* 2007a, Wang *et al.* 2013, Khan *et al.* 1995, Keil *et al.* 2009, Griffin *et al.* 2000a, Griffin *et al.* 2000b, Wang *et al.* 2012b, Blossom *et al.* 2004, Wang *et al.* 2008b, Cai *et al.* 2006, Cai *et al.* 2007b, Gilbert *et al.* 2009). The presence of autoantibodies indicated that self-antigens were recognized by the immune system as "foreign" which can provide persistent antigen stimulation and B-cell activation. However, as mentioned above, markers for B-cell activation and B-cell proliferation were not consistently altered and other markers were not examined. In addition to autoantibodies, lymphocyte numbers (especially $CD4^+$ T cells) were increased in the spleen as well as lymphocyte proliferation (Cai *et al.* 2006, Griffin *et al.* 2000c, Sanders *et al.* 1982, Wang *et al.* 2008b). These general signs support the idea that autoimmunity is induced by trichloroethylene or its metabolites and that continual B-cell activation may be occurring.

Exposure to trichloroethylene or its metabolites caused the formation of protein adducts with metabolites (dichloroacetyl-protein) and, through increased oxidative stress, with products of lipid peroxidation (malondialdehyde-protein, hydroxynonenal-protein) in the serum and liver resulting in the formation of antibodies against these adducts (Cai *et al.* 2007b, Cai *et al.* 2006, Griffin *et al.* 2000a, Griffin *et al.* 2000c, Griffin *et al.* 2000b, Halmes *et al.* 1997, Khan *et al.* 1995, Khan *et al.* 2001, Wang *et al.* 2007a, Wang *et al.* 2008b, Wang *et al.* 2012b, Wang *et al.* 2013). Inhibition of CYP2E1 by co-exposure with diallyl sulfide prevented the formation of dichloroacetyl-protein adducts and its specific antibodies (Griffin *et al.* 2000c), while decreased oxidative stress from the enhancement of antioxidant activity of glutathione, by co-exposure to *N*-acetylcysteine, prevented the formation of malondialdehyde-protein and hydroxynonenal-protein adducts and their specific antibodies (Wang *et al.* 2013). Splenocytes from trichloroethylene-exposed mice produced Th1 cytokines (IFN-gamma, IL-2) when stimulated

with preformed lipid peroxidation product-albumin adducts (malondialdehyde-albumin, hydroxynonenal-albumin) (Wang *et al.* 2008b, Wang *et al.* 2012b, Cai *et al.* 2006). These studies show that trichloroethylene induced neoimmunogenic protein adducts in the serum and liver by both CYP2E1-mediated metabolic activation and increased oxidative stress. In addition to antibodies against the protein adducts found in the liver, antibodies against normal, non-adducted, liver proteins were formed (Gilbert *et al.* 2009). Similarly, exposure to preformed trichloroethylene-albumin adducts not only induced the formation of antibodies against the albumin adducts (formyl-albumin, trichloroethene oxide-albumin, and dichloroacetyl-albumin), but also to the non-adducted albumin (Cai *et al.* 2007b). These results indicate that trichloroethylene is inducing autoimmunity toward "self" proteins found in the blood and liver.

### 5.2.2 Risk factors for NHL

Most of the known risk factors for NHL are related to chronic antigenic stimulation due to immunosuppression and/or autoimmunity (Grulich *et al.* 2007, Hardell *et al.* 1998, Ponce *et al.* 2014, Dias and Isenberg 2011, Baecklund *et al.* 2014). In addition, both clinical and experimental data clearly show that chronic inflammation mediated by immunoglobulins and immune complexes contributes to cancer development (Balkwill *et al.* 2005, Coussens and Werb 2002, de Visser *et al.* 2006, Tan and Coussens 2007). Increased incidences of NHL have been reported among patients with congenital immune deficiency, autoimmune disease, or virus infection (e.g., HIV, human T-cell leukemia/lymphoma virus, Epstein-Barr virus); patients receiving immunosuppressive therapy following bone marrow or organ transplants; or as a late complication of certain chemotherapy and radiotherapy regimens for Hodgkin lymphoma (Aligo *et al.* 2014, Bernatsky *et al.* 2006, Besson *et al.* 2006, Hardell *et al.* 1998, Ponce *et al.* 2014). NHL (predominantly B cell) accounts for about half the cancers observed in patients with primary immunodeficiencies and increases to about 75% in patients diagnosed with severe combined immunodeficiency (Ponce *et al.* 2014). Lymphoma risk also appears to increase with autoimmune disease severity. In addition, exposure to various immunotoxic industrial chemicals and pesticides (e.g., phenoxyacetic acids, chlorophenols, dioxins, organic solvents, DDT, PCBs, toxaphene, and chlordane) are recognized risk factors for NHL (Cantor *et al.* 1992, Hardell *et al.* 1998).

Autoimmune disorders associated with an increased risk of NHL and related neoplasms include rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, sarcoidosis, and systemic sclerosis (scleroderma) (Ponce *et al.* 2014). Although NHL includes many subtypes (e.g., diffuse large B-cell lymphoma, T-cell NHL, follicular lymphoma, chronic lymphocytic leukemia, and others), diffuse large B-cell lymphoma is the most common among patients with autoimmune disorders. Autoimmune disorders are characterized by B-cell hyperactivity and chronic inflammation. B cells initiate autoimmunity through several mechanisms including enhanced production of autoantibodies and immune complexes, dendritic and T-cell activation, and cytokine production (Tan and Coussens 2007).

Mature B cells are particularly susceptible to oncogenic transformation because of DNA hypermutation and recombination during their differentiation (Ponce *et al.* 2014). Specifically, the risk of genetic damage is increased during B-cell maturation because the various events involved in this process (i.e., somatic recombination of immunoglobulin variable region genes, somatic hypermutation, and class-switch recombination) involve double-strand breaks and chromosomal translocations (Ponce *et al.* 2014, Baecklund *et al.* 2013). Lymphomas can develop

from errors arising during the hypermutable stages of B-cell development and can arise from either chronic antigenic stimulation (autoimmunity) or from impaired pathogen control (immunosuppression). Chromosomal translocations resulting from aberrant rearrangements of immunoglobulin and B- (or T-) cell receptor genes can lead to inappropriate expression of genes that regulate a variety of cellular functions such as gene transcription, cell cycle, apoptosis, and tumor progression. Inflammatory cells are known to be largely responsible for changes in the tumor microenvironment that support proliferation, survival, and migration of neoplastic cells (Balkwill *et al.* 2005, Coussens and Werb 2002, Whiteside 2006). An abundance of infiltrating innate immune cells (e.g., macrophages, mast cells, neutrophils) in and around malignant tissue correlates with increased angiogenesis and a poor prognosis (de Visser *et al.* 2006).

The markers that may be important indicators for NHL risk include autoantibodies, lymphocyte subsets and activated lymphocytes, immunoglobulins, serum cytokines, and natural killer (NK) cell cytotoxicity. Several studies have reported an association between immune biomarkers and risk of NHL. Case-control studies using pre-diagnostic blood or serum and cohort studies of several immune biomarkers have reported predictive value for some lymphocyte subsets or immune markers and NHL. Several biomarkers or cytokines (such as sCD27, sCD30, sCD44, CXCL13, CD30, TNF-R1, sTNF2, BCA-1, vascular endothelial growth factor receptor, intercellular adhesion molecule (ICAM), IL-2, IL-10) are associated with NHL (De Roos *et al.* 2012, Vermeulen *et al.* 2010, Purdue *et al.* 2011b, 2013b, Hosnijeh *et al.* 2010, Conroy *et al.* 2013).

Most malignancies, as well as pre-malignant tissues associated with chronic inflammatory diseases, have an altered immune cell status (Dalgleish and O'Byrne 2002, Tan and Coussens 2007). These alterations frequently include suppressed cell-mediated immunity and enhanced humoral immunity marked by a decrease in Th1 T helper cells and an increase in Th2 T helper cells (Tan and Coussens 2007). Th1 cells produce interleukin (IL)-2 and interferon (IFN)-γ and direct cell-mediated immunity while Th2 cells produce IL-4, IL-6, IL-10, and IL-13 and facilitate local humoral immune responses by activating B cells. Chronic antigenic stimulation, inflammation, and B-cell activation are likely key events that drive lymphoma risk (Ponce *et al.* 2014). B-cell activation inhibits Th1 anti-tumor immunity while initiating recruitment of innate immune cells (e.g., macrophages, neutrophils, and mast cells) leading to chronic tumor-promoting inflammatory responses and angiogenesis. A number of case-control studies have reported that polymorphisms in genes coding for immunoregulatory cytokines that mediate inflammation, apoptosis, and Th1/Th2 balance influence susceptibility to NHL (Bel Hadj Jrad *et al.* 2006, Deng *et al.* 2013, Hosnijeh *et al.* 2010, Lan *et al.* 2006, Purdue *et al.* 2007, Rothman *et al.* 2006, Wang *et al.* 2007c). The combined effects of suppressed cell-mediated immunity and enhanced humoral immunity include lower anti-tumor activity with a concomitant increase in angiogenesis, reduced apoptosis, and enhanced tumor promotion and progression (Tan and Coussens 2007, Dalgleish and O'Byrne 2002).

#### *5.2.2.1 Possible modes of action for trichloroethylene-induced immune modulation and NHL*

As discussed above, trichloroethylene induces immunosuppression and induces or accelerates autoimmune responses in humans and laboratory animals (Boverhof *et al.* 2013, Cooper *et al.* 2009, Rusyn *et al.* 2014, Weinhold 2009). Both immune suppression and autoimmunity can lead to chronic inflammation and antigenic stimulation. Only a few studies in humans examined the

immunosuppressive and autoimmune effects of trichloroethylene. Most studies in experimental animals used mouse strains that spontaneously develop conditions resembling systemic lupus erythematosus. Since immunosuppression and autoimmune diseases are known risk factors for NHL, altered immunity and chronic inflammation may be involved in trichloroethylene-induced NHL.

The relationship between immune status and cancer risk is complex. It is well accepted that chronic inflammation plays an essential role in tumorigenesis; however, the underlying molecular mechanisms linking inflammation and cancer are not completely understood (Wu *et al.* 2013). The normal physiological response to infection or tissue damage is acute inflammation. Cases of unresolved inflammation, as occurs with immune suppression or autoimmune disease, evoke chronic inflammation and antigenic stimulation. Chronic inflammation predisposes the host to cancer by inducing DNA damage and chromosomal instability, and promoting tumor development. Possible modes of action include the following: (1) immunosuppression of tumor surveillance activity, (2) effects from oncogenic viruses (and, for NHL, Epstein-Barr virus [EBV] reactivation in particular) due to impaired viral surveillance and clearance, and (3) chronic antigenic stimulation due to an unchecked inflammatory response to foreign triggers (infections, allograft) or autoimmunity (Ponce *et al.* 2014). Chronic antigenic stimulation leads to a state of sustained B-cell hyperstimulation and the potential for oncogenic transformation (see Section 5.2.2).

Findings from the Chinese study generally suggest that trichloroethylene exerts immunosuppressive effects; however, lower serum levels of IgG, IgM, sCD27, and sCD30 suggest that trichloroethylene impairs B-cell stimulation and is counter to the proposed mechanism of B-cell activation. Trichloroethylene-exposed workers generally had lower levels of B and T lymphocytes but not of granulocytes, platelets, or monocytes. These data suggest that trichloroethylene exerts a specific effect on lymphoid progenitor cell division or maturation. However, reduced $CD4^+$ T cells reflect immunosuppressive effects that could impair control over inflammation and increase B-cell activation. Autoimmune effects in humans, in particular, are consistent with the hypothesized mechanisms of action linking severe immune dysregulation and NHL. It is quite possible that the observed immunologic effects of trichloroethylene are reflective of other poorly understood mechanisms that increase the risk of malignant transformation of B cells.

The data show that trichloroethylene is immunomodulatory in rodents (see Section 5.2.1.3). Several studies in MRL+/+ mice suggested that oxidative and nitrosative stress from reactive oxygen and nitrogen species may contribute to the autoimmune response (Khan *et al.* 2001, Wang *et al.* 2007a, Wang *et al.* 2007b, Wang *et al.* 2008b, Wang *et al.* 2012b, Wang *et al.* 2013, Wang *et al.* 2009b). Reactive oxygen and nitrogen species have been implicated in the pathogenesis of several autoimmune diseases including systemic lupus erythematosus (Wang *et al.* 2007b). Other studies with MRL+/+ mice demonstrated that trichloroethylene metabolites also formed immunoreactive protein adducts resulting in antibody formation (Cai *et al.* 2007a, Cai *et al.* 2007b, Cai *et al.* 2006, Griffin *et al.* 2000a, Griffin *et al.* 2000c, Griffin *et al.* 2000b, Halmes *et al.* 1996, Halmes *et al.* 1997, Khan *et al.* 1995). Metabolic activation by CYP2E1 was at least partially responsible for the autoimmune response (Griffin *et al.* 2000c).

### 5.2.3 Summary

Severe immune dysregulation, whether from immunosuppression or autoimmune disease, is conclusively associated with an increased risk of NHL. Thus, it is biologically plausible that the mode of action of trichloroethylene-induced NHL could involve altered immunity. However, no human or animal studies directly investigated the possible relationship between trichloroethylene exposure, immunomodulation, and lymphoproliferative disorders and some of the data were not consistent with the proposed mechanisms. Use of other activation markers (e.g., CD23, CD27, CD30, CD44, and CXCL13) might have allowed for a more complete assessment of B-cell response. Although few applicable studies were conducted in humans, the available data provide evidence that trichloroethylene can alter the immune system based on some studies finding an association between markers of immune suppression and other studies showing an association with autoimmune disease (e.g., systemic sclerosis). Studies in MRL+ /+ mice show that trichloroethylene accelerates lupus conditions. Possible key events demonstrated in mice (mostly in strains predisposed to autoimmune disease) include lipid peroxidation, CYP2E1 metabolism to reactive metabolites, formation of immunoreactive protein adducts, formation of antibodies against the adducted proteins, autoimmune response via cross-reaction of antibodies to non-adducted (normal “self”) proteins, and chronic inflammation. Chronic inflammation is a known risk factor for tumor promotion and progression. However, the available data are insufficient to demonstrate that immunomodulation is operant as a mode of action for trichloroethylene-induced NHL.

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# 6 Liver Cancer

Previous sections of the cancer evaluation component contain relevant information – ADME (Section 1), genetic and related effects (Section 2), and overview and assessment of the quality of the human cancer studies – that are important for several of the three cancer endpoints of interest (Section 3). This section builds on that information and evaluates the human cancer studies (Section 6.1), mechanistic data, including immune effects of trichloroethylene (Section 6.2), specifically for liver cancer.

## 6.1 Human cancer studies

Liver cancer is considered to be rare with higher rates observed among males; the age-adjusted rates (per 100,000 males or females) in the United States from 2006 to 2010 (U.S. SEER Statistics) are 11.9 (male) and 4.0 (female) for incidence and 8.3 (male) and 3.4 (female) for mortality. The 5-year survival rate is 16.6%, suggesting that mortality and incidence data are likely to be broadly comparable, at least for recent years. Liver cancer is reported in some studies as cancer of the liver and intrahepatic bile ducts (ICD-9 155, ICD-10 22) and in others as combined cancers of the liver and intrahepatic and extrahepatic bile ducts and gallbladder (ICD-9 155+156, ICD-10 22-24); some papers report primary liver cancer (ICD-9 155.1) separately.

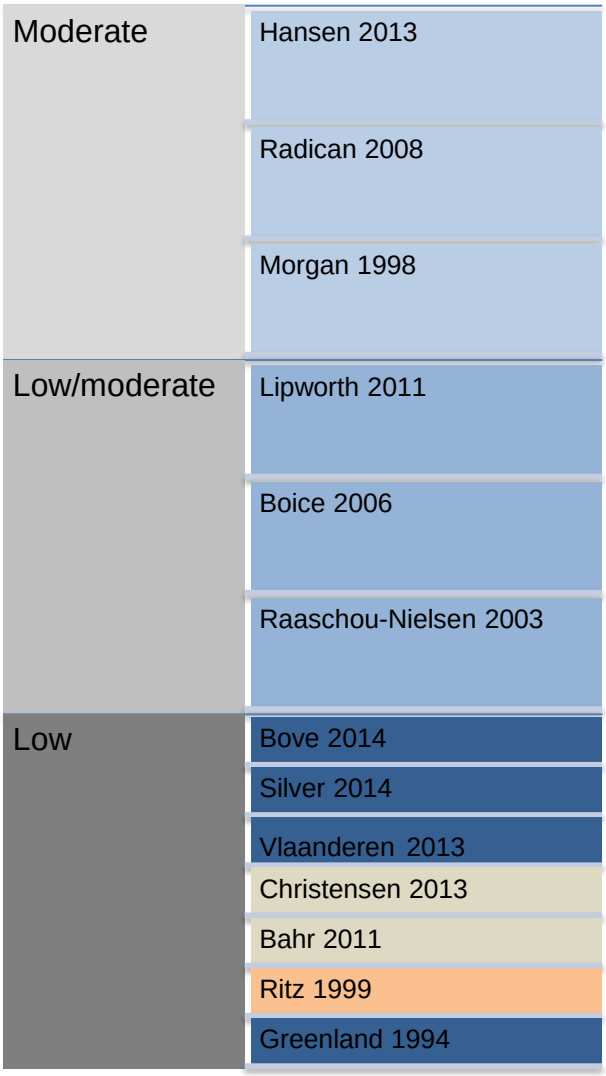
For each of the reviewed studies, summary data on study design, methods and findings, systematically extracted from relevant publications as described in the study protocol, are presented in Table D-1 in Appendix D. The evaluation of study quality, including study design, methods of exposure and cancer endpoint assessment, analysis and other relevant data, is reported in Tables D-4a,b in Appendix D. Section 3 provided an overview of the study population characteristics and methods and a discussion of study quality across studies. The overall evaluation of study quality, and the potential for and direction of bias, if present, is summarized in Figure 6-1, below.

### 6.1.1 Study findings

This section summarizes and interprets the findings for liver cancer from the individual epidemiological studies brought forward for evaluation, and integrates the evidence across studies, applies the RoC listing criteria to the body of evidence, and reaches a preliminary recommendation for the level of evidence for liver cancer using the same criteria as described for the evaluation of kidney cancer in Section 4 and NHL in Section 5.

The cancer evaluation reports on the latest update of a cohort study unless there are additional relevant data (e.g., analyses or exposure information) in previous publications. The available studies that reported on liver cancer and trichloroethylene exposure and were considered for inclusion in the cancer evaluation include 12 cohort or nested case-control studies and 1 population-based case-control study (Christensen *et al.* 2013). The cohort studies include three studies of occupationally exposed subjects from Nordic countries (Hansen *et al.* 2013, Raaschou-Nielsen *et al.* 2003, Vlaanderen *et al.* 2013), four studies of U.S. aerospace or aircraft manufacturing workers (Boice *et al.* 2006, Lipworth *et al.* 2011, Morgan *et al.* 1998, Radican *et al.* 2008), two studies of U.S uranium processing workers (Ritz 1999, Bahr *et al.* 2011), one nested case-control study and one cohort study of U.S. electronic workers (Greenland *et al.* 1994 and Silver *et al.* 2014, respectively), and a cohort of military personnel exposed to trichloroethylene in drinking water (Bove *et al.* 2014). Two meta-analyses were also identified that contributed to the evaluation.

**Figure 6-1. Summary of study quality: Liver cancer**




Key: Grey = study quality: darkest = lowest study quality
Blue = overall direction of bias towards null based on study sensitivity: darkest blue = least sensitive
Peach = overall direction of bias towards a positive effect
Tan = multiple methodological concerns or 1 exposed case (for Christensen *et al.* 2013).

Although the available database consists of several well-conducted studies, liver cancer is rare, and few workers were exposed to high levels of trichloroethylene with reasonable confidence of exposure. Thus, the major overall limitation across studies is low statistical power to evaluate a modest risk of liver cancer from exposure to trichloroethylene and exposure-response relationships. In addition, some of the studies report findings for both liver and biliary cancer combined and others for primary liver cancer only, making

cross comparisons more difficult. Similar to kidney cancer, meta-analyses may be informative, although heterogeneity of findings, if considerable, can reduce their utility and should be noted. The findings of the individual studies are discussed below and presented in Table 6-1.

#### *6.1.1.1 Nordic studies*

These three studies include subjects with occupational exposure to trichloroethylene from diverse industries and workers identified from a broad occupational or a broad population-based database. Two studies reported an association with potential trichloroethylene exposure and liver cancer, with the strongest evidence from the pooled analyses of biomonitored workers (Hansen *et al.* 2013), in which a statistically significant increase in risk was observed among men and women combined (SIR = 1.77, 95% CI = 1.24 to 2.45, 36 cases). Risks increased with increasing latency (as assessed by lag time), which partly reflect the longer average latencies of liver cancer (Manton *et al.* 2009), and provides support for an association between trichloroethylene exposure and liver cancer in this population. However, in internal analyses, which examined exposure-response relationships, risks were less than one and the highest risk (with the largest number of cases) was in the lowest exposure group, the referent group in this analysis, which complicates the interpretation of the study. Few U-TCA samples were available for each subject, and thus U-TCA, which is a measure of short-term exposure, may not have accurately captured exposure intensity from the past or in the future.

Increases in liver cancer risk were observed among women (total trichloroethylene-exposed cohort) in the Danish study of Raaschou-Nielsen *et al.* (2003) (SIR = 2.8, 95% CI = 1.13 to 5.80, 7 cases for ever exposed) and a SIR of 4.1 (95% CI = 1.1 to 10.5, 4 cases) was observed among workers with 1 to 4 years employment duration. A higher risk occurred among women with later years of first employment, when exposures were reportedly lower than the earlier years; however, the number of cases is small. In contrast, among men (with more overall cases than women), the highest risk was found among men employed before 1970 (SIR = 1.5, 95% CI = 0.9 to 2.4, 17 cases). It is important to note that the authors only conducted analyses for liver in the total cohort and not among the subcohort of workers considered to have higher exposure (as they did for kidney cancer). Some misclassification of exposure is likely as only a portion of the cohort was exposed to trichloroethylene. There was little evidence of an association with liver cancer in the large population-based study (Vlaanderen *et al.* 2013), although, as noted previously, exposure misclassification is likely to be substantial and estimated exposures were low.

#### *6.1.1.2 Aerospace and aircraft workers*

The evidence for an increase in liver cancer risk among the group of U.S. studies of aerospace and aircraft workers (Morgan *et al.* 1998, Boice *et al.* 2006, Radican *et al.* 2008/Blair *et al.* 1998, Lipworth *et al.* 2011) is limited. In most of the studies, there were few exposed cases, especially in subgroup analyses, if reported, and the studies had limited ability to evaluate exposure-response relationships. Three mortality studies (Radican *et al.* 2008, Boice *et al.* 2006, Morgan *et al.* 1998) observed non-statistically significant increases in liver cancer, based on small numbers of exposed cases. In the Radican *et al.* (2008) cohort, which evaluated primary liver separately from liver and biliary combined, non-statistically significant increases were observed for both cancer categories in analyses of cumulative exposure for all workers and workers with the highest exposure. There is some evidence of a weak exposure response for cumulative exposure

and primary liver cancer among male workers, but confidence intervals are wide. The mortality study by Lipworth *et al.* (2011) observed a decrease in liver cancer by employment duration, a poor surrogate for cumulative exposure. It is not clear how many workers were exposed to trichloroethylene in the different categories of exposure duration, since exposure duration was short, so that exposure misclassification is likely. In addition, there is evidence of a healthy worker effect in this study, all of which limit the study's ability to inform the cancer hazard evaluation.

#### *6.1.1.3 Other studies*

The remaining studies are of more limited utility for informing the cancer hazard evaluation. Ritz (1999) found an increased risk of liver cancer among uranium processing workers; risks increased with increasing lag time, exposure duration, and exposure level in analyses controlling for radiation exposure, which suggests a positive relationship between trichloroethylene exposure and cancer risk; however, the numbers are based on small numbers of workers, most with low exposure to trichloroethylene. In addition, there is the potential for selection bias and residual confounding, possibly by radiation exposure. The electronics worker cohort (Silver *et al.* 2014) reported no increase in risk but had several limitations, including limitations in the exposure assessment, and was a relatively young cohort. The drinking water study (Bove *et al.* 2014) observed a small but non-statistically significant increase in risk among subjects with the highest exposure; this study was also of a young cohort and lacked information on individual consumption of water. Overall, these limitations would tend to bias findings towards the null. The cohort study of uranium workers by Bahr *et al.* (2011) and the nested case-control study (Greenland *et al.* 1994), both of which have a number of methodological limitations, report decreases in risk, and neither study reported numbers of deaths. The electronics worker cohort (Silver *et al.* 2014) reported no increase in risk but had several limitations, including limitations in the exposure assessment, and was a relatively young cohort. The drinking water study (Bove *et al.* 2014) observed a small but non-statistically significant increase in risk; this study was also of a young cohort, and did not directly estimate individual exposure to trichloroethylene. Finally, while the Montreal study (Christensen *et al.* 2013) had adequate exposure assessment and analytical methods, only one case of liver cancer was observed in the substantially exposed group, so this study is uninformative for this endpoint.

**Table 6-1. Findings for trichloroethylene and cancers of the liver, biliary tract or gallbladder**

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # exposed cases/deaths | Internal analysis RR (95% CI)[a] # exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| **Nordic studies** | | | | | |
| Hansen *et al.* 2013<br>(potential overlap with Raaschou-Nielsen *et al.* 2003) | Pooled and updated Nordic cohorts<br>Axelson *et al.* 1994, Anttila *et al.* 1995 Hansen *et al.* 2001<br>5,553<br>(3,776 M, 1,777 F)<br>Biomonitoring (U-TCA) | All exposed subjects<br>0-yr lag<br>10-yr lag<br>20-yr lag<br><br>U-TCA (mg/L)<br>< 5<br>5–25<br>25–50<br>>50<br>$P_{trend}$ | *SIR (ICD-7 155)*<br>1.77 (1.24–2.45); 36<br>1.83 (1.24–2.45); 32<br>2.09 (1.34–3.11); 24 | *HR incidence (no lag)*<br>16<br>0.66 (0.31–1.42); 12<br>0.45 (0.13–1.54); 5<br>0.63 (0.22–1.68); 3<br>0.20 | Low exposure levels (only 20% exposed to ≥ 20 ppm) and short duration of exposure<br>Covariates: Age, sex, calendar period; indirect consideration of smoking and alcohol consumption<br>Strengths: Biomonitoring data; large numbers of workers ever exposed<br>Limitations: Only 2 or 3 U-TCA measurements per individual; do not measure lifetime exposure<br>Evidence of an association |
| Raaschou-Nielsen *et al.* 2003<br>(Potential overlap with Hansen *et al.* 2013) | Danish blue-collar workers<br>40,049 M+F<br>(approx. 70% M)<br>Working at TCE company; size of company surrogate for TCE exposure prevalence | *Men (588,047 pyar)*<br>Primary liver (ICD-7 155)<br>Other liver (ICD-7 156)<br><br>*Women (118,270 pyar)*<br>Primary liver (155)<br>Other liver (156)<br><br>*Primary liver*<br>*Men and women*<br>*Yr. of 1st employment*<br>Women<br>Before 1970<br>1970–1979<br>1980 and later | *SIR (Total cohort)*<br>1.1 (0.74–1.64); 27<br>1.2 (0.73–1.77); 22<br><br>2.8 (1.13–5.80); 7<br>1.1 (0.22–3.23); 3<br><br>1.28 (0.89–1.8)[ab]<br><br>2.5 (0.5–7.3); 3<br>2.1 (0.2–7.7); 2<br>5.9 (0.7–21.2); 2 | NR | ~ 41% of workers with TCE exposure; higher levels of TCE prior to 1970 (40–60 ppm); low levels of exposure after that time<br>Covariates: age, sex, calendar year<br>Strengths: Large numbers of exposed cases<br>Limitations: Young cohort, possible selection bias of difference in SES, external analysis only<br>Potential for confounding by |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # exposed cases/deaths | Internal analysis RR (95% CI)[a] # exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| | | Men<br>Before 1970<br>1970–1979<br>1980 and later<br><br>*Duration employment (yrs)*<br>*Men*<br>< 1<br>1 to 4<br>≥ 5<br>Women<br>< 1<br>1 to 4<br>≥ 5 | <br>1.5 (0.9–2.4); 17<br>0.8 (0.3–1.6); 7<br>0.9 (0.2–2.6); 3<br><br><br>1.3 (0.6–2.5); 9<br>1.0 (0.52.9); 9<br>1.1 (0.5–2.1); 9<br><br>2.8 (0.3–10.); 2<br>4.1 (1.1–10.5); 4<br>1.3 (0.0–7.1); 1<br>No exposure-response pattern for lagged exposure, | | smoking among women<br>Weak evidence of an association |
| Vlaanderen *et al.* 2013 | 5 Nordic countries<br>Record linkage of cancer registry with census questionnaire<br>Semi-quantitative JEM<br>M: 14702 cases cases, 73510 controls<br>F: 9194 cases, 45970 controls | *Cumulative exp.(unit-yrs)*<br>0<br>0.04<br>0.13<br>0.72<br>*High exposure group*<br>Cumulative<br>Men<br>Women (W)<br>Intensity × prevalence<br>Men<br>Women | | *HR* (ICD-7 155)<br>*Incidence*<br>1.00<br>1.03 (0.91–1.16); 340<br>0.99 (0.90–1.09); 508<br>1.00 (0.90–1.11); 422<br><br><br>1.01 (0.78–1.31); 69<br>1.02 (0.72–1.46); 37<br><br>1.07 (0.86–1.33); 99<br>1.26 (0.88–1.80); 38 | Low prevalence of exposure (TCE) and exposure levels likely to be low<br>TCE correlated with tetrachloroethylene<br>Strengths; long follow-up, large numbers of cases<br>Limitations: Misclassification of exposure likely; JEM had poor sensitivity and did not account for heterogeneity within jobs and over time<br>Little evidence of elevated risk |
| **Aerospace and aircraft manufacturing workers** | | | | | |
| Boice *et al.* | Los Angeles (USA) | | *SMR (ICD-9* | | Exposure occurred during test |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # exposed cases/deaths | Internal analysis RR (95% CI)[a] # exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| 2006 (overlap with Zhao *et al.* 2005) | Rocket engine testing workers<br>1,111 Men<br>Qualitative JEM; Individual work histories | Ever exposed | *155+156)*<br>1.28 (0.35–3.27); 4 | | engine flush, which is likely to be high<br>Covariates: Date of birth, year of hire, pay type (surrogate for SES) and exposure to hydrazine<br>Strengths: Adequate follow up<br>Limitations: Qualitative exposure assessment; few exposed deaths<br>Elevated SMR based on few exposed deaths |
| Lipworth *et al.* 2011 (update of Boice *et al.* 1999) | Burbank (USA) aircraft manufacturing workers<br>5,443 (approx. 80% M)<br>Qualitative JEM Individual work histories | TCE<br>Ever exposed<br>TCE: years exposed<br>0<br>< 1<br>1–4<br>5+<br>$P_{trend}$ | *SMR*<br>*(ICD-9 155+156)*<br>0.89 (0.57–1.33); 24 | *RR mortality*<br>1.00; 32<br>0.67 (0.32–1.42); 10<br>0.69 (0.28–1.71); 6<br>0.83 (0.36–1.91); 8<br>0.20 | Exposure levels NR, short exposure duration<br>Covariates: age, date of birth, date of hire, termination date, sex, and race<br>Strengths: Long follow-up<br>Limitations: Evidence of HWE, few exposed deaths in subgroup analysis; likely exposure misclassification; no evaluation of exposure intensity, 70% had exposure to mixed solvents<br>Null: No evidence of an association but limited ability to evaluate |
| Radican *et al.* 2008 (mortality to 2000) | Utah (USA) aircraft maintenance workers<br>N = 7,204 (5,153 M, | Radican *et al.*:<br>*Ever-exposed* | NR | *HR mortality*<br>*(ICD-9 155+156)*<br>1.12 (0.57–2.19); 31<br>*Primary liver (155.1)* | Estimated exposure: Most workers exposed to low levels (~10 ppm), modest number of workers exposed to higher levels (~100 |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # exposed cases/deaths | Internal analysis RR (95% CI)[a] # exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| Blair *et al.* 1998 (incidence 1973–1990) | 1,051 F)<br><br>Semi-quantitative JEM, individual work histories | *Ever exposed*<br><br>*Cum. exp. (unit-yrs) Men*[a]<br>All<br>0–5<br>5–25<br>> 25<br><br>All<br>0–5<br>5–25<br>> 25<br><br>Blair *et al.* 1998<br>*Cumulative Exp Men*<br>No TCE exposure<br>< 5 units-yr<br>5–25 units-yr<br>≥ 35 units-yr | | 1.25 (0.31–4.97); 8<br><br>*ICD-9 155+156)*<br>1.36 (0.59–3.11); 28<br>1.17 (0.45–3.09); 10<br>1.16 (0.39–3.46); 6<br>1.72 (0.68–4.38); 12<br>*Primary liver*<br>2.72 (0.34–21.88); 8<br>3.28 (0.37–29.45); 4<br>0<br>4.05 (0.45–36.41); 4<br><br>*RR incidence (ICD-9 155+156)*<br>0.2 (0.1–2.4); 1<br>0.6 (0.1–3.1); 3<br>0.6 (0.1–3.8); 2<br>1.1 (0.2–4.8); 4 | ppm).<br><br>Covariates: age, calendar year and sex<br><br>Strengths: Adequate semi-quantitative JEM, long follow-up, adequate statistical power for ever exposure<br><br>Limitations: Potential for exposure misclassification because of missing information for some workers; limited numbers or higher exposed workers<br><br>Limited evidence of an association |
| Morgan *et al.* 1998 | Arizona (USA) aircraft manufacturing workers<br>N = 4,733 (2,555 M, 2,178 F)<br><br>Semi-quantitative JEM; individual work history | Ever exposed<br>Cumulative exp. score<br>Low (2,357)<br>High (2,376)<br>Peak (med/high) vs. low/no | *SMR (liver & biliary)*<br>0.98 (0.36–2.13); 6<br><br>1.32 (0.27–3.85); 3<br>0.78 (0.16–2.28); 3 | *RR mortality*<br>1.48 (0.76–2.89); 6[b]<br><br>2.12 (0.59–7.66); 3<br>1.19 (0.34–4.16); 3<br>0.98 (0.29–3.35); 3 | High-exposure jobs were considered to be ≥ 50 ppm<br><br>Covariates: age at hire, gender (decade of hire considered but no effect)<br><br>Strengths: Long follow-up and semi-quantitative exposure<br><br>Limitations: Evidence of a HWE; potential exposure misclassification among low/medium exposure groups; mortality analysis and few exposed cases |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # exposed cases/deaths | Internal analysis RR (95% CI)[a] # exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| | | | | | Null: No evidence of an association, but few exposed subjects |
| **Other studies of occupational exposure (cohort and case-control** | | | | | |
| Silver *et al.* 2014 | New York State (USA) micro-electronics manufacturing workers cohort mortality<br><br>3,113 TCE exposed<br><br>Semi-qualitative JEM | 5 modified exposure years (exposure duration modified by exposure potential); 10-yr lag | | HR (at 5 years) ("liver, biliary and gallbladder")<br>0.99 (0.50–1.95); NR | Exposure levels NR; only 13.9% of cohort exposed.<br>Covariates: Paycode and sex, age, Variables considered in analyses but did not change risk estimate were birth cohort, time since last exposure (healthy worker survival), hire era, and employment duration prior to 1966<br>Limitations: Evidence of HWE, Exposure classification based on potential exposure and duration; only one cumulative exposure variable reported in analysis. Limited information on comparison and # of exposed cases NR. Young cohort with only 17% deaths<br>Null: No evidence of an association and limited ability to detect an effect. |
| Christensen *et al.* 2013 (case-control) | Montreal (Canada)<br>Population- and hospital-exposure | Ever exposure<br>Substantial exposure | | *OR (incidence) (liver, presume 155)*<br>1.1 (0.1–8.5); 1<br>2.1 (0.2–18); 1 | Number of cases inadequate for evaluation |
| Bahr *et al.* 2011 | Kentucky (USA) uranium processing workers (gaseous diffusion plant) | Exp level (rank-ordered)<br><br>1<br>2 | | *SRR (mortality) ("liver & biliary")*<br>1.00<br>0.34 (0.05–2.07); NR | No information on exposure level or number of workers in each exposure category |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # exposed cases/deaths | Internal analysis RR (95% CI)[a] # exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| | 5,535 Men | 3<br>All | | 0.39 (0.08–1.94); NR<br>0.43 (0.10–1.84); NR | Limitations: Unclear descriptions of methods and findings; limited statistical power; evidence of HWE and survival effect<br>Null: No evidence of an association but limited ability to evaluate |
| Ritz 1999 | Ohio (USA) uranium processing workers<br>2,971 (M) | Low exp. no lag<br>> 2 years<br>> 5 years<br>Moderate exp. no lag<br>> 2 years<br>> 5 years<br>Low exp. 15-yr lag<br>> 2 years<br>> 5 years<br>Moderate exp. 15-yr lag<br>> 2 years<br>> 5 years | NR | *RR mortality (ICD-9 155+156)*<br>0.93 (0.19–4.53); 3<br>1.90 (0.35–10.3); 3<br>4.97 (0.48–51.1); 1<br>8.82 (0.79–98.6); 1<br>1.16 (0.24–5.60); 3<br>2.80 (0.48–17.3); 3<br>5.53 (0.54–56.9); 1<br>12.1 (1.03–144.0); 1 | 96% workers with low exposure<br>Covariates: Time since 1st hire, pay type, internal radiation, & same chemical different level<br>Strengths: Follow-up adequate<br>Limitations: Low exposure, limited power; selection bias possible<br>Possible residual confounding by radiation<br>Limited evidence of an increase in risk based on elevated risks and pattern of increasing risk with increasing latency and exposure duration and level, but limited by small number of deaths |
| Greenland *et al.* 1994<br>(nested case-control study) | Massachusetts (USA) electrical manufacturers<br>N = 12 cases (exposed controls NR) | Ever exposure | | *OR (mortality) (ICD-8 155+156)*<br>0.54 (0.11–2.63); NR | Limited statistical power; only 10% of jobs had exposure to TCE, most of which were from indirect exposure<br>Covariates: Age, date of death, covariates that changed risk estimate by 20% |

| Reference | Study Size (N) Exposure assessment | Exposure groups | External analysis SMR, SIR (95% CI) # exposed cases/deaths | Internal analysis RR (95% CI)[a] # exposed cases/deaths or cases/controls | Interpretation |
|---|---|---|---|---|---|
| | | | | | Limitations: Small numbers of cases and controls and short follow-up, possible selection bias, low quality exposure assessment<br>Insufficient data for evaluation and numerous study limitations |
| **Environmental exposure** | | | | | |
| Bove *et al.* 2014 | North Carolina (USA) (Camp Lejeune)<br>Drinking water contamination<br>Ecological exposure assessment<br>154,932 men and women | TCE in drinking water (µg/L-month)<br>≤ 1<br>> 1–155<br>> 155–380<br>> 380–8,585 | | *HR (mortality) ("liver and biliary")*<br>1.0 (19)<br>1.02 (0.48–2.15); 12<br>1.04 (0.47–2.27); 11<br>0.86 (0.37–1.97); 9 | Estimated mean levels (µg/L/month): TCE = 358.7 from water supply; cumulative exposure = 6,369 median, 5,289 mean; 20% were exposed to levels between 7,700 and 39,745.<br>Covariates: sex, race, and education; other variables considered in the model (did not change risk estimates by 10%) include marital status, birth cohort, date of death, duty occupation.<br>Strengths: Large cohort and adequate modeling of exposure<br>Limitations: Young cohort; no information on individual water consumption<br>Null: No evidence of an association; limited ability to detect an effect |

Studies reported one or more of primary liver, liver plus intrahepatic biliary ducts, or liver, intrahepatic and extrahepatic biliary ducts and gallbladder combined (as noted). Not all studies reported ICD diagnostic codes used.

CI = confidence interval; HR = hazard ratio; OR = odds ratio, RR = relative risk; SIR = standardized incidence ratio, SMR = standardized mortality ratio, SRR = standardized rate ratio.

[a]Study also report risk by exposure patterns (continuous and peak). Among men, HR > 1 for both primary liver and liver + biliary cancer in all exposure categories with no clear exposure- response relationships. Few cases of liver + biliary cancer were reported for women: HR < 1.0 for all cumulative exposure and exposure pattern categories except for peak, infrequent, HR = 4.30 (0.87–21.33); 2.

[a] HR, OR, RR, or SRR.

[b] Reported by Scott and Jinot (2011): combined risk for men and women in Raaschou-Nielsen *et al.* (2003), and RR adjusted for age and sex for Morgan *et al.* (1998).

### 6.1.2 Meta-analyses

Two meta-analyses have been conducted on the cohort studies of liver cancer, by the EPA (EPA 2011a, Scott and Jinot 2011) and by Alexander *et al.* (2007a). The inclusion and exclusion criteria, systematic data extraction, and methods of analysis used in the EPA meta-analysis were identical to those used for kidney cancer and NHL meta-analyses and have been described in Sections 4 and 5, respectively. (See Appendix D, Table D-7 for a list of the studies included in these meta-analyses.) Studies included in this review that are not part of the meta-analyses include the pooled analyses by Hansen *et al.* 2013 (which includes the populations reported on by Axelson *et al.* (1994), Anttila *et al.* (1995), and Hansen *et al.* (2001), the population-based cancer registry study of Nordic countries by Vlaanderen *et al.* (2013), two studies of uranium processing workers (Ritz 1999, Bahr *et al.* 2011), the microelectronics workers study by Silver *et al.* (2014) and the drinking water study by Bove *et al.* (2014).

**Table 6-2. Meta-analyses of liver cancer (including gall bladder and biliary passages) and trichloroethylene exposure**

| Reference | Study design (number of studies) | mRR (95% CI) All | mRR (95% CI) Highest exposure | Comments |
|---|---|---|---|---|
| EPA 2011a/Scott and Jinot *et al.* 2011 | Cohort studies (8) and nested case-control study (1) | 1.29 (1.07–1.56) | 1.28 (0.93–1.77) | Random and fixed effects models; little evidence of heterogeneity or publication bias |
| Alexander *et al.* 2007a | Cohort studies (8) | 1.30 (1.09–1.55) | NR | Random effects model; some evidence of heterogeneity |

mRR = meta-relative risk; NR = not reported; RR = relative risk.

The two meta-analyses are broadly comparable and suggest an overall statistically significant increase in the mRR for combined liver and biliary cancers. Alexander *et al.* (2007a) also calculated mRRs for studies that reported primary liver cancer and biliary tract cancers separately, and reported closely comparable risk estimates. In the EPA meta-analysis, the mRR was elevated but less precise and no longer statistically significant (OR = 1.22, 95% CI = 0.93 to 1.61) with the removal of Raaschou-Nielsen *et al.* (2003), which was the largest study in that analysis. Differences in exposure metrics used in the component studies place limitations on analyses by exposure intensity or duration. In the EPA analysis, the lower mRR observed among the highest exposed groups primarily reflects the inverse exposure-duration response relationship for exposure duration reported in the largest study by Raaschou-Nielsen *et al.* (2003) (Scott and Jinot 2011); as also noted in the discussion of individual studies, relative risks for other cohort studies, where calculated, were generally similar among higher exposure groups, where reported.

#### *6.1.2.1 Occupational co-exposures*

With respect to occupational carcinogens, IARC and/or the Report on Carcinogens (Cogliano *et al.* 2011, NTP 2011, Lauby-Secretan *et al.* 2013) have identified some types of radiation (plutonium, thorium and its decay products), vinyl chloride and polychlorinated biphenyls as

known human liver carcinogens, and concluded that there was limited evidence of human carcinogenicity for inorganic arsenic, and X- and gamma-radiation. Trichloroethylene-exposed workers in some studies may have been exposed to a range of other chemical or physical agents, primarily (1) chlorinated solvents (primarily tetrachloroethylene and 1,1,1-trichloroethane) in the Nordic studies, the studies of aircraft manufacturing and aerospace workers, and the drinking water study, (2) cutting fluids such as mineral and petroleum oils, organic solvents, hydrazine, benzene, chromates, and PAHs in the aerospace and aircraft industries, and (3) radiation (Ritz 1999), or cutting oils and metals in the studies of uranium processing workers (Bahr *et al.* 2011), and (4) vinyl chloride in the drinking water study (Bove *et al.* 2014). The co-exposure with the strongest potential for confounding is ionizing radiation in the study of uranium workers by Ritz (1999). A positive association was observed for liver cancer in this study after adjusting for exposure to radiation, which helps to reduce concern that confounding occurred, although residual confounding cannot be ruled out. In addition, there is limited evidence of exposure-response patterns with trichloroethylene intensity and duration in this study; however, few workers were exposed to moderate levels of trichloroethylene. Vinyl chloride is not a concern because no association with trichloroethylene was found in the drinking water study.

The other principal co-exposures identified in these studies have not been classified as known or suspected liver carcinogens in humans; however, there is some or sufficient evidence in animal studies for the liver carcinogenicity of several chlorinated and non-chlorinated solvents, including tetrachloroethylene, 1,1,2,2- and 1,1,1,2-tetrachloroethane, carbon tetrachloride, methylene chloride, and hydrazine. The chlorinated solvents tetrachloroethylene and 1,1,1-trichloroethane are probably common co-exposures in the aircraft manufacturing studies and possibly in the Nordic studies. In addition, the strength of the association with trichloroethylene was limited in these studies. Thus, confounding, especially in the aircraft manufacturing studies, cannot be reasonably ruled out.

#### *6.1.2.2 Lifestyle and other potential confounders*

Non-occupational risk factors include alcohol consumption, aflatoxins, estrogen-progestogen contraceptives, tobacco smoking, betel quid use without tobacco, viral infections (hepatitis B and C and human immunodeficiency virus type 1), parasites (liver flukes and *Schistosoma*), long-term use of anabolic steroids, and ionizing radiation (Cogliano *et al.* 2011, NTP 2011). Some of these factors, such as smoking, alcohol consumption, and possibly biological infections, may be related to socioeconomic status and could possibly vary by trichloroethylene exposure status.

The majority of cohort and nested case-control studies conducted age-, sex-, race- and calendar-year or period-standardized comparisons in external analyses (SMR or SIR) where appropriate and age-, sex-, race- and in some cases calendar period-adjusted comparisons in internal analyses. In addition, all of the studies, except for the Danish blue-collar worker study, conducted internal analyses, which would mitigate potential confounding from lifestyle factors. Although none of the cohort studies adjusted for smoking, tobacco smoking is a weaker risk factor for liver cancer than other cancers (meta-risk estimate ~1.5, Lee *et al.* 2009) and as noted in Section 4 for kidney cancer, there was little evidence for an association of trichloroethylene and lung cancer, which suggests that confounding from smoking is not a concern.

While none of the studies directly addressed alcohol consumption, incidence rates of cancers of the oral cavity, pharynx, or esophagus or cirrhosis (where reported) and cirrhosis may provide

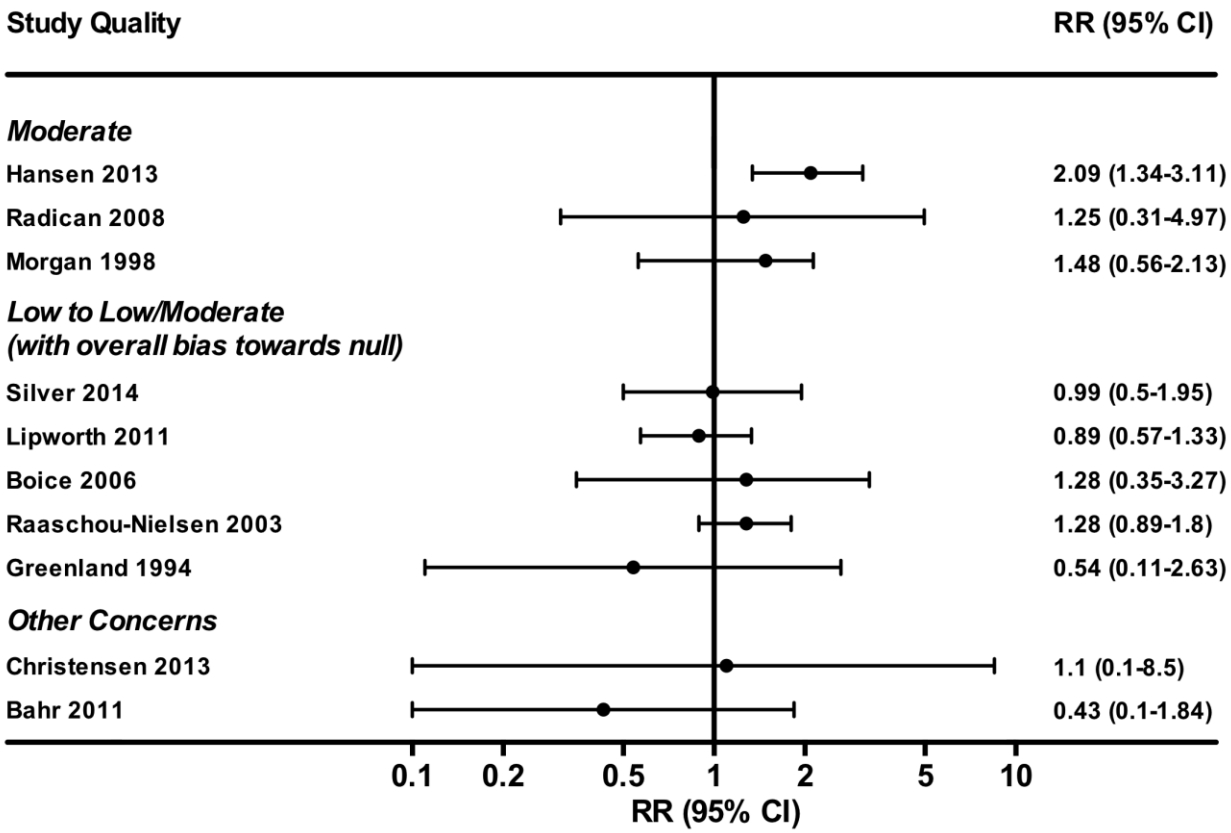
indirect evidence of alcohol consumption relative to the reference population. While these rates are unremarkable in most of the studies, approximately 2-fold, statistically non-significant increases in incidence rates were observed for oropharyngeal and esophageal cancers among women in the Danish blue-collar workers cohort (Raaschou-Nielsen *et al.* (2003). Smoking- and alcohol-related diseases were not statistically significantly increased in the pooled analysis reported by Hansen *et al.* (2013). Overall, there is no strong indirect evidence for potential confounding by alcohol use in most of the cohorts, with the possible exception of the Danish cohort of trichloroethylene-exposed women workers (Raaschou-Nielsen *et al.* 2003).

### 6.1.3 Integration

Several individual cohort studies with moderate or low to moderate study quality found modest increases in risk of liver cancer (Hansen *et al.* 2013, Raaschou-Nielsen *et al.* 2003, Radican *et al.* 2008, Boice *et al.* 2006, Morgan *et al.* 1998) with the strongest evidence from the external analysis in the updated and pooled analysis of biomonitored workers in Nordic countries (Hansen *et al.* 2013). (See Figure 6-2 for a plot of risk estimates for groups ever exposed to trichloroethylene grouped according to study quality.) However, no exposure-response relationship was observed in the internal analysis in this study and there was little evidence of an exposure-response relationship in any study with the possible exception of the Utah aircraft-manufacturing workers in analyses specific for primary liver cancer (Radican *et al.* 2008).

No or little evidence of an association of trichloroethylene exposure (for either ever exposed groups or among the highest exposed) and liver cancer risk was found in other studies, most of which were considered to be of low to low/moderate quality because of inadequate sensitivity to detect rare cancers such as liver cancer, concerns about non-differential exposure misclassification (Silver *et al.* 2014, Bove *et al.* 2014, Vlaanderen *et al.* 2013, Lipworth *et al.* 2011, Greenland *et al.* 1994) and/or other methodological concerns (Bahr *et al.* 2011). The only case-control study (Christensen *et al.* 2013) had too few exposed cases (one) to be informative. Ritz *et al.* (1999) reported a positive association among uranium processing workers; however, this should be viewed with some caution because of potential residual confounding from exposure to radiation and small numbers of exposed cases. Two meta-analyses based on either nine or eight studies suggest a modest but statistically significant increase in liver cancer risk (Scott and Jinot 2011 and Alexander *et al.* 2007a), although they did not include some recent studies. Confounding by one or more of the common co-exposures, or chance, cannot be completely ruled out in some studies.

**Figure 6-2. Forest plot: Liver cancer by study quality**




Relative risk and 95% CI for ever exposure to TCE and liver according to study quality (see Section 3, Appendix D and Figure 6-1). Studies with low/moderate and low were combined into one category. Low quality studies were grouped according to overall direction of bias. Direction of bias was less clear for Bahr *et al.* 2011 because of limited reporting and Christensen *et al.* 2013 because only one liver case was observed. Studies by Bove *et al.* (2014), Vlaanderen *et al.* (2013), and Ritz *et al.* (1999) are not graphed because they did not report relative risk for ever exposure. Findings for these studies are reported in Table 6-1. For studies reporting multiple risk estimates, preference was given to studies with longer lag (Hansen *et al.* 2013) and internal analysis. Risk estimates for Raaschou-Nielsen *et al.* (2003) (combined men and women) and internal analysis for Morgan *et al.* (1998) are reported by Scott and Jinot (2011).

## 6.2 Mechanistic data for liver carcinogenicity

Trichloroethylene metabolites produced by P450 oxidation, primarily CYP2E1, (see Section 1.3) are most likely responsible for liver toxicity and cancer (EPA 2011a). Support for this hypothesis includes the following: trichloroethylene and its oxidative metabolites have similar hepatotoxic and hepatocarcinogenic effects, pretreatment with CYP inducers enhances hepatotoxicity, and treatment with CYP inhibitors decreases hepatotoxicity. In addition, liver tumor analyses based on immunostaining for c-Jun show that neither trichloroacetic acid nor dichloroacetic acid alone can account for the full characteristics of trichloroethylene-induced liver tumors (Bull *et al.* 2002).

This section reviews the hypothesized modes of action for liver carcinogenicity and is divided into two subsections: those with some experimental support and those that are inadequately defined or have limited experimental support. As with the previous mechanistic sections for kidney cancer and non-Hodgkin lymphoma, the discussion relies on recent comprehensive reviews by EPA (2011a,b) and IARC (2014). The findings from these reviews are supplemented with primary literature that was not included in the reviews or as needed for clarity.

### 6.2.1 Hypothesized modes of action with some experimental support

Modes of action proposed for trichloroethylene-induced liver cancer that are perhaps the most biologically plausible include the following: genotoxicity from oxidative metabolites, PPARα activation, oxidative stress, and hypomethylation and gene expression changes (IARC 2014, EPA 2011a,b). Another possible mode of action is autoimmune hepatitis (Czaja 2013, Wang *et al.* 2013).

There are several similarities between the hypothesized modes of action in trichloroethylene-induced liver tumors in mice and some of the known characteristics of human hepatocellular carcinoma (EPA 2011a). However, the mode of action for trichloroethylene-induced liver tumors is complex and likely involves key events from several pathways. Overall, a role for many of the key events could not be ruled out; however, the data were inadequate to support a definite conclusion that any of the proposed modes of action are operant. The key events associated with the proposed modes of action with the most experimental support are listed in Table 6-3 and are discussed below.

**Table 6-3. Possible modes of action and key events for trichlorethylene-induced liver cancer**

| Mode of action | Key events |
|---|---|
| Genotoxicity | 1. One or more oxidative metabolites are produced *in situ* or delivered systemically to the liver.<br>2. Genotoxicity induced by oxidative metabolites advances acquisition of the multiple critical traits contributing to carcinogenesis. |
| PPARα activation | 1. Oxidative metabolites activate PPARα in the liver.<br>2. PPARα activation leads to alterations in cell proliferation and apoptosis.<br>3. Alterations in cell proliferation and apoptosis cause clonal expansion of initiated cells.<br>4. Clonal expansion of initiated cells leads to tumor formation. |
| Oxidative stress | 1. Trichloroethylene or its metabolites induce oxidative stress.<br>2. Oxidative stress leads to chronic inflammation, mutations, and damage to |

| Mode of action | Key events |
|---|---|
| | proteins, lipids, and DNA.<br>3. Mutations and damage to macromolecules activates cell-signaling pathways, induces genomic instability and cell transformation, and leads to cancer. |
| Epigenetic changes | 1. Epigenetic changes, particularly DNA methylation, are induced by one or more metabolites.<br>2. These changes advance acquisition of multiple critical traits contributing to carcinogenesis. |
| Autoimmune hepatitis | 1. Reactive metabolites form protein adducts and/or induce oxidative stress leading to lipid peroxidation and oxidative modifications to proteins in the liver (neoantigens).<br>2. Activation and hepatic infiltration of $CD4^+$ T cells and secretion of inflammatory cytokines.<br>3. Inhibition of apoptosis in self-reactive $CD4^+$ T cells.<br>4. Formation of anti-malondialdehyde- and anti-hydroxynonenal-protein adduct antibodies in association with increases in anti-nuclear antibodies.<br>5. Hepatocyte damage/autoimmune hepatitis.<br>6. Autoimmune hepatitis/cirrhosis contributes to hepatocarcinogenesis. |

Sources: Czaja 2013, EPA 2011a, Gilbert *et al.* 2006, Griffin *et al.* 2000b, Wang *et al.* 2013.

#### *6.2.1.1 Genotoxicity*

Since genotoxicity is a well-established cause of carcinogenicity, one hypothesis is that trichloroethylene causes liver cancer by a genotoxic/mutagenic mode of action, presumably through formation of reactive oxidative metabolites that cause direct alterations in hepatocyte DNA (e.g., mutations, DNA damage, and/or clastogenic effects) (EPA 2011a). The genotoxic effects of trichloroethylene and its metabolites were presented in Section 2. Chloral hydrate appears to have the greatest genotoxic potential among the oxidative metabolites. Genotoxic effects associated with chloral hydrate included mutagenicity in the Ames test; micronucleus formation, chromosome aberrations, aneuploidy, and cell transformation in mammalian cell cultures; and *in vivo* studies reported DNA single-strand breaks and micronucleus induction in mice. Some have argued that chloral hydrate is unlikely to be the cause of trichloroethylene carcinogenicity because it is a short-lived intermediate metabolite that is rapidly converted to trichloroacetic acid and trichloroethanol in the liver. Furthermore, doses used in the *in vitro* genotoxic studies were generally much higher than the reported peak concentrations achieved in the liver of rodents administered hepatocarcinogenic doses of trichloroethylene. However, it is uncertain if a direct comparison between concentrations in cultured media used in genotoxicity assays *in vitro* and concentrations in whole-liver homogenates achieved *in vivo* is appropriate. Furthermore, some *in vivo* genotoxicity assays with chloral hydrate reported positive results at doses similar to those that induced a carcinogenic response in chronic bioassays.

Several studies investigated the frequency and spectra of H-*ras* mutations in liver tumors induced by trichloroethylene, trichloroacetic acid, or dichloroacetic acid (Bull 2000, Bull *et al.* 2002). Overall, the H-*ras* mutation frequency and spectrum of trichloroethylene-induced tumors were similar to those observed in spontaneous tumors and dichloroacetic acid-induced tumors. In contrast, liver tumors induced by trichloroacetic acid had a significantly higher frequency of H-*ras* codon 61 mutations compared with trichloroethylene-induced tumors. The data also indicated that H-*ras* mutations were a late event. The frequency of H-*ras* mutations increased with time and was higher in hepatocellular carcinomas compared with adenomas. The effects of

dichloroacetic acid and trichloroacetic acid were not typical of genotoxic agents and suggested that these compounds promoted clonal expansion of initiated cells while DNA damage accumulated with tumor growth.

It is clear that human and rodent livers are exposed to the oxidative metabolites of trichloroethylene. Chloral hydrate is the most genotoxic oxidative metabolite but is rapidly converted to trichloroacetic acid and trichloroethanol. The data are insufficient to assess the genotoxic contributions from the nongenotoxic contributions of chloral hydrate or other oxidative metabolites. Although the data are inadequate to conclude that a genotoxic mode of action is responsible for trichloroethylene-induced liver tumors, a genotoxic mode of action mediated by the oxidative metabolites is biologically plausible and cannot be ruled out.

#### *6.2.1.2 PPARα activation*

Trichloroethylene, trichloroacetic acid, and dichloroacetic acid induce peroxisome proliferation in mice but are relatively weak PPARα agonists requiring mM concentrations (Corton 2008, Keshava and Caldwell 2006). The peroxisome-related effects of trichloroethylene are most likely mediated through trichloroacetic acid because it is a primary oxidative metabolite of trichloroethylene and is a stronger PPARα agonist than dichloroacetic acid. The data linking trichloroethylene-induced liver tumors to a PPARα-dependent mechanism include the following: (1) there is a relatively good correlation between trichloroethylene- and trichloroacetic acid-induced liver tumors and induction of markers of PPARα activation in the mouse but not in the rat, (2) transactivation assays show that trichloroacetic acid activates mouse and human PPARα, (3) markers of PPARα activation are elevated at trichloroethylene or trichloroacetic acid doses below or coincident with doses that induce mouse liver tumors in a manner similar to other peroxisome proliferators, (4) trichloroethylene increases hepatocyte proliferation and peroxisome proliferator-associated genes in wild-type but not PPARα-null mice (93% of the altered genes in wild-type mice were PPARα dependent), and (5) trichloroacetic acid-induced mouse liver tumors have properties similar to those induced by classic peroxisome proliferators in rat liver (Corton 2008, Laughter *et al.* 2004).

However, it is unlikely that trichloroethylene induces liver tumors solely through metabolism to trichloroacetic acid and PPARα activation. The dose-response for liver weight increases were different for the two compounds, and liver weight increases did not correlate with peroxisomal enzyme activity or changes in peroxisomal number or volume (EPA 2011a). Bull *et al.* (2002) also reported differences in tumor phenotypes (based on c-Jun expression) between trichloroethylene and trichloroacetic-acid-induced liver tumors. The H-*ras* mutation frequency in trichloroethylene-induced liver tumors was more similar to spontaneous or dichloroacetic acid-induced tumors than to trichloroacetic acid-induced tumors (discussed above in the Genotoxicity subsection) (Bull *et al.* 2002, 2000). The H-*ras* mutation frequency pattern in trichloroacetic acid-induced liver tumors also was opposite that observed with other peroxisome proliferators. Furthermore, recent studies have demonstrated that PPARα activation is not the sole mode-of-action of hepatocarcinogenesis for known PPARα agonists (EPA 2011a, Guyton *et al.* 2009).

Although trichloroethylene clearly activates PPARα and other key events in the hypothesized mode of action, most of the proposed key events are nonspecific and may be caused by multiple mechanisms. A causal linkage between trichloroethylene exposure and alterations in gene

expression and DNA synthesis with PPARα has not been established. Together, these data strongly suggest that multiple mechanisms and cell types are likely involved in the hepatocarcinogenicity of PPARα agonists. It is biologically plausible that PPARα agonism mediated by trichloroacetic acid is operant; however, it is unlikely that it is the sole or predominant mode of action for trichloroethylene-induced hepatocarcinogenicity in mice.

#### *6.2.1.3 Oxidative stress*

Oxidative stress is an important factor in a number of human diseases, including cancer, and occurs when the concentration of reactive oxygen species (ROS) generated exceeds the antioxidant capacity of the cell (Klaunig *et al.* 1998). It can be induced by exposure to drugs or other chemicals, but also is part of normal cellular respiration and cell signaling. The consequences of oxidative stress may include damage to critical cellular macromolecules including DNA, lipids, and proteins. One of the most common forms of damage is the generation of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a highly mutagenic adduct capable of causing cellular DNA damage. Other common biomarkers of oxidative stress include thiobarbituric acid-reactive substances (TBARS, an index of lipid peroxidation) and superoxide anion production.

Several studies reported evidence of oxidative stress in the liver of mice or rats following acute, subacute, or subchronic exposure to trichloroethylene, trichloroacetic acid, or dichloroacetic acid (Austin *et al.* 1996, Channel *et al.* 1998, Larson and Bull 1992, Parrish *et al.* 1996, Tabrez and Ahmad 2009, Toraason *et al.* 1999). EPA (2011a,b) identified several issues in most of these studies (i.e., lack of appropriate controls, incomplete reporting, marked toxicity, and possible confounding by vehicle or route of administration effects) that limited interpretation of the data. However, a series of more recent studies show that dichloroacetic acid and trichloroacetic acid induce oxidative stress and macrophage activation in B6C3F$_1$ mice (Hassoun and Cearfoss 2011, Hassoun *et al.* 2013, Hassoun *et al.* 2010b, Hassoun and Dey 2008, Hassoun and Ray 2003, Hassoun *et al.* 2010a). These studies were not reviewed by EPA (2011a,b) and are briefly reviewed below.

*In vitro* studies using murine macrophage J774A.1 cells exposed to dichloroacetic acid or trichloroacetic acid showed dose- and time-dependent increases in superoxide anion production, cellular death, and lactate dehydrogenase (LDH) release (a marker of cell death) (Hassoun and Ray 2003). In contrast to *in vivo* studies (discussed below), there were no significant differences in the effects of these two compounds.

A series of *in vivo* studies were conducted to investigate oxidative stress in male B6C3F$_1$ mice exposed to dichloroacetic acid and trichloroacetic acid (Cearfoss and Hassoun 2012, Hassoun and Cearfoss 2011, Hassoun *et al.* 2013, Hassoun *et al.* 2010b, Hassoun and Dey 2008, Hassoun *et al.* 2010a). Data from these studies are summarized in Appendix F and include the following: superoxide anion production in liver and peritoneal lavage cells (Table F-1), lipid peroxidation and DNA single-strand breaks in liver cells (Table F-2), phagocyte activation and superoxide dismutase (SOD) in peritoneal lavage cells (Table F-3), and antioxidant enzymes in liver cells (Table F-4).

Overall, these data show that both dichloroacetic acid and trichloroacetic acid induced dose- and time-dependent increases in superoxide anion production, lipid peroxidation, and DNA single-strand breaks. The data also indicated that antioxidant enzymes (e.g., SOD, catalase, and

glutathione peroxidase) were involved in cellular resistance to oxidative stress. In most cases, dichloroacetic acid had a greater effect than trichloroacetic acid. These data suggest that superoxide anion production contributes to lipid peroxidation and DNA damage in the liver. There also was a strong correlation between superoxide anion production in peritoneal lavage cells (considered as a surrogate for Kupffer cells) and hepatic tissues that suggested phagocytic activation may contribute to oxidative stress in the liver.

Hepatocyte oxidative stress also was identified as a key event associated with other modes of action. These include PPARα activation (Klaunig *et al.* 2003), GST-zeta inhibition (Blackburn *et al.* 2006), and autoimmunity (see Section 2.2) (Wang *et al.* 2007a, Wang *et al.* 2007b, Wang *et al.* 2012b, Wang *et al.* 2013, Wang *et al.* 2009b, Wang *et al.* 2012c). Parrish *et al.* (1996) showed that markers of peroxisome proliferation and 8-OHdG levels were not significantly different from controls in mice exposed to dichloroacetic acid and concluded that oxidative damage did not play an important role in the chronic hepatotoxicity of peroxisome proliferators. Blackburn *et al.* (2006) reported that GST-zeta deficiency results in a constant level of oxidative stress due to the accumulation of maleylacetone and maleylacetoacetate. As discussed below, dichloroacetic acid is an inhibitor of GST-zeta, thus, dichloroacetic acid could cause oxidative stress by diminishing GST-zeta levels. Finally, Wang *et al.* (2013) reported that *N*-acetylcysteine supplementation protected against trichloroethylene-induced autoimmunity by attenuating oxidative stress.

There is evidence that oxidative metabolites of trichloroethylene can cause oxidative stress in the liver and it is biologically plausible that oxidative stress can contribute to hepatotoxicity and hepatocarcinogenicity. However, the key events for this mode of action have not been fully specified and the data are insufficient to determine the necessity or sufficiency of oxidative stress in trichloroethylene-induced hepatocarcinogenicity.

#### *6.2.1.4 Epigenetic changes (altered gene expression/hypomethylation)*

Altered gene expression, whether through global DNA hypomethylation or other mechanisms, can contribute to carcinogenesis by affecting genes identified with cell growth and differentiation, tissue remodeling, signal transduction, metabolism, apoptosis, cancer progression, and other processes (Caldwell and Keshava 2006, EPA 2011a). Genetic expression studies and studies of changes in methylation status induced by trichloroethylene and its metabolites are reviewed below.

A limited number of *in vitro* and *in vivo* studies in experimental animals have investigated gene expression changes in liver induced by trichloroethylene or its oxidative metabolites (Caldwell and Keshava 2006, EPA 2011a,b). These studies reported that trichloroethylene alters expression of various stress-response, xenobiotic metabolizing, and homeostatic genes. Mice exposed to dichloroacetic acid also showed altered expression patterns in genes associated with cell growth, tissue remodeling, apoptosis, cancer progression, and xenobiotic metabolism in normal liver tissue and liver tumors.

Sano *et al.* (2009) investigated differences in gene expression profiles of liver in mice and rats exposed to acute and subacute oral doses of trichloroethylene. These differences included suppression of TGF-β signaling, activation of MAPK signaling, and alteration of the ubiquitin-proteasome system in mice but not rats and may play a role in the species-specific biochemical

effects of trichloroethylene-induced liver carcinogenesis. Bradford *et al.* (2011) analyzed whole liver gene expression profiles in male mice from 15 inbred strains exposed to a single oral dose of trichloroethylene. PPARα-mediated molecular networks, primarily consisting of upregulation of lipid and drug metabolism genes, were the most pronounced effects that were dependent on genetic background. Gene expression changes that were significantly affected by treatment but not genotype included cell death, liver necrosis, and inflammatory-mediated response networks; however, there was little observable liver toxicity in this study. Transcription factor analysis of these genes revealed several inflammation-related regulatory proteins that are associated with activation of macrophages and lymphocytes and suggested that trichloroethylene may affect Kupffer cells. Recent *in vitro* studies using human hepatic L-02 cells reported that exposure to trichloroethylene-induced alterations in the expression, distribution, and interactions of SET-associated proteins (Hong *et al.* 2012, Hong *et al.* 2013). SET (also known as protein phosphatase 2A inhibitor, 12PP2A, or template-activating factor-1, TAF-1) is a nuclear protein with roles in histone modification, gene transcription, DNA replication, nucleosome assembly, phosphatase activity, and kinase activity. Trichloroethylene also induced over-expression of several SET-binding proteins, including eukaryotic translation elongation factor 1 alpha 1 and 1 alpha 2 (eEF1A1 and eEF1A2), in a dose-dependent manner. Over-expression of eEF1A1 and eEF1A2 are associated with a variety of human tumors. Endogenous SET is known to decrease in the nucleus and increase in the cytoplasm upon cell death induced by toxic stress. eEF1A is primarily localized in the cytoplasm, but redistribution to the nucleus has been associated with cell proliferation and tumor development. Cytoplasmic translocation of SET and nuclear translocation of eEF1A also were observed in L-02 cells exposed to trichloroethylene. These results suggest that the translocation and over-expression of SET and eEF1A1/eEF1A2 are involved in trichloroethylene-induced liver cancer.

EPA (2011a,b) also reviewed several studies that investigated the effects of trichloroethylene, trichloroacetic acid, and dichloroacetic acid on DNA methylation status in mice. Aberrant DNA methylation is a common hallmark of all types of cancer; however, it has not yet been determined whether altered DNA methylation is a consequence or cause of cancer. Rats and mice fed diets that induce hypomethylation (deficient in choline and methionine) develop liver tumors. A high dose of methionine (8 g/kg) was reported to decrease the number of dichloroacetic acid-induced liver foci and adenomas; however, mice fed a lower level of methionine (4 g/kg) had a higher incidence of foci. Although the authors believed their data indicated that methionine supplementation slowed the progression of tumors, the study did not demonstrate that enhanced tumor progression is a key event for the mode of action for dichloroacetic acid-induced liver carcinogenicity. Other studies reported that female $B6C3F_1$ mice administered subacute oral doses of trichloroethylene (1,000 mg/kg), trichloroacetic acid (500 mg/kg), or dichloroacetic acid (500 mg/kg) had increased cell proliferation and hypomethylation of the promoter regions of *c-Jun* and *c-Myc* in the liver. Methionine treatment was reported to eliminate this effect in one study but low doses of methionine had no effect. Hypomethylation also was reported in total liver and liver tumor DNA in mice initiated with *N*-methyl-*N*-nitrosourea and exposed to trichloroacetic acid or dichloroacetic acid for 46 weeks.

A few studies have reported altered gene expression and/or hypomethylation of liver DNA in mice exposed to high doses of trichloroethylene, trichloroacetic acid, and dichloroacetic acid; thus, it is biologically plausible that these events could contribute to trichloroethylene-induced liver carcinogenesis. Although there is evidence that hypomethylation is sufficient for

carcinogenesis, it is uncertain if it is necessary for trichloroethylene-induced liver carcinogenesis. The doses of trichloroacetic acid and dichloroacetic acid tested for hypomethylation were higher than those used to induce liver tumors in mice. It is not known if hypomethylation also occurs at doses relevant to trichloroethylene carcinogenicity.

#### *6.2.1.5 Autoimmune hepatitis*

Autoimmune hepatitis is a risk factor for liver cancer in humans (Arslan *et al.* 2011, Czaja 2013, Nishiyama *et al.* 2004, Watanabe *et al.* 2009). Trichloroethylene exposure had been linked to non-viral (toxic) hepatitis (usually in association with idiosyncratic generalized hypersensitivity skin diseases), liver dysfunction, and liver cancer in humans (Hansen *et al.* 2013, Kamijima *et al.* 2007, Kamijima *et al.* 2008, Kim and Kim 2010) and autoimmune hepatitis in MRL+/+ mice (Gilbert *et al.* 2009, Gilbert *et al.* 2006, Griffin *et al.* 2000b). Autoimmune hepatitis in mice exposed to trichloroethylene was indicated by immune responses to protein adducts and liver inflammation (see Section 5.2.1.3). Inflammation of the liver in mice was induced by exposure to trichloroethylene and preformed metabolite protein adducts (Cai *et al.* 2008, Cai *et al.* 2007b, Gilbert *et al.* 2009, Kaneko *et al.* 2000, Kondraganti *et al.* 2012, Ramdhan *et al.* 2010, Tang *et al.* 2008). Autoantibodies were formed against "self" antigens of normal tissue, neoimmunogens of trichloroethylene-induced protein adducts, and the concomitant non-adducted proteins. Liver cirrhosis was not reported; however, cirrhosis, like cancer, takes time to develop (Meza-Junco *et al.* 2007). The longest study that looked at liver inflammation was 48 weeks, which might not have been long enough to allow for cirrhosis to develop. Nevertheless, these studies suggest that trichloroethylene exposure can initiate an autoimmune response, possibly resulting in B-cell activation and autoimmune hepatitis.

The underlying mechanisms of trichloroethylene-induced autoimmunity are not completely understood; however, the studies in MRL+/+ mice suggest that oxidative stress, formation of protein adducts, stimulation of $CD4^+$ T cells and release of inflammatory cytokines, and autoantibody formation may be involved (Gilbert *et al.* 2012, Gilbert *et al.* 2009, Gilbert *et al.* 2006, Griffin *et al.* 2000a, Griffin *et al.* 2000b, Khan *et al.* 1995, Khan *et al.* 2001, Wang *et al.* 2007a, Wang *et al.* 2007b, Wang *et al.* 2013). None of the MRL+/+ mice developed hepatocellular carcinoma; however, as noted above, the maximum study duration was 48 weeks with most studies lasting only 4 to 32 weeks. There also was no evidence of hepatitis or liver cirrhosis in exposed $B6C3F_1$ mice in the NTP (1990) study. The cases of non-viral hepatitis in humans were not evaluated for an immune component and the cases of liver cancer in humans did not report on hepatitis. Although the epidemiological and experimental data are not inconsistent with trichloroethylene promoting liver cancer via autoimmune hepatitis, the data are insufficient to determine if this proposed mode of action is operative.

### 6.2.2 Hypothesized modes of action with limited experimental support

Several other modes of action have been proposed for trichloroethylene-induced liver cancer that are incompletely defined or have limited experimental support. These include increased liver weight or liver/body weight ratios, negative selection, glycogen accumulation, inactivation of GST-zeta, and cytotoxicity and regenerative hyperplasia (IARC 2014, EPA 2011a,b). These modes of action are briefly discussed below.

*Increased liver weight:* Although increased liver weight or increased liver/body weight ratios are associated with an increased liver cancer risk, these effects are nonspecific and may be caused by a number of factors (EPA 2011a). Liver weight increases have been reported in rodents exposed to trichloroethylene, trichloroacetic acid, or dichloroacetic acid. However, no studies have evaluated the necessity of liver weight changes in trichloroethylene-induced liver carcinogenesis. Further, a mode of action hypothesis based on liver weight changes has not been adequately characterized and cannot be fully evaluated.

*Negative selection:* Negative selection refers to circumstances that convey a growth advantage to initiated cells relative to normal hepatocytes. This hypothesis suggests that the oxidative metabolites of trichloroethylene may contribute to liver tumor formation by several processes including the following: (1) downregulation of mitogenic stimulation in normal hepatocytes while initiated cells are refractory to this downregulation, (2) direct growth enhancement of certain populations of initiated cells, or (3) altered apoptosis (EPA 2011a, Bull 2000). Bull (2000) suggested that data showing that trichloroethylene and its oxidative metabolites induced a transient increase in DNA synthesis in the liver of mice were consistent with a "negative selection" mode of action. However, the transient increases in cellular proliferation were confined to small populations of hepatocytes and liver weight changes were associated with hypertrophy from increased glycogen storage and polyploidy rather than hyperplasia. Thus, mitogenic stimulation does not appear to play a significant role in trichloroethylene-induced liver cancer, and a mechanism for downregulation of mitogenic stimulation in normal hepatocytes has not been identified. Selective clonal expansion of initiated cells is a general feature of carcinogenesis and is not specific to trichloroethylene or its oxidative metabolites. Finally, trichloroethylene either does not affect apoptosis or causes only a slight increase at high doses. Although dichloroacetic acid has been reported to decrease apoptosis in mice, the data are inadequate to determine its relevance to liver cancer considering that mice have a very low background rate of apoptosis (EPA 2011a, Carter *et al.* 1995). Therefore, the data are currently inadequate to properly define a mode of action based on negative selection. In addition, some of the data are inconsistent with this hypothesis.

*Polyploidization*: Tetraploidy has been associated with chromosome instability (CIN) that might persist or give way to a stably propagating aneuploid karyotype (Ganem *et al.* 2007). Both CIN and stable aneuploidy are common features of neoplasms, and tetraploidy is known to promote chromosomal aberrations and tumorigenesis *in vivo*. There is considerable experimental evidence that supports the theory that tetraploid cells are an important intermediate in the route to aneuploidy and cancer (Storchova and Kuffer 2008). Several chemicals, including trichloroethylene and dichloroacetic acid, that induce liver cancer in experimental animals also shift the hepatocyte ploidy distribution toward a greater percentage of diploid or polyploid cells (EPA 2011a). Although polyploidization may be an important key event in tumor induction, the mechanisms are not well understood. Although it is biologically plausible that polyploidy can contribute to hepatocarcinogenicity, it is not known if polyploidization is necessary for trichloroethylene-induced liver tumors. Therefore, the data are inadequate to support polyploidization as operant in trichloroethylene-induced mouse liver tumors.

*Glycogen storage*: Several studies reviewed by EPA (2011a) reported that mice and rats exposed to dichloroacetic acid developed hepatomegaly that was partially attributable to accumulation of glycogen. Glycogen accumulation was observed as early as 1 week in normal liver while liver

tumors were consistently glycogen-poor. However, rodent studies with trichloroethylene or trichloroacetic acid have reported either no change or a slight decrease in liver glycogen content, or have not addressed this endpoint. Several studies have shown that glycogen accumulation can be pathogenic and that glycogen storage disease or poorly controlled diabetes is associated with an increased risk of liver cancer in humans (EPA 2011a, Lingohr *et al.* 2002). Although it is biologically plausible that hepatocyte glycogen content may be affected by the apparent opposing actions of the trichloroethylene metabolites, dichloroacetic acid and trichloroacetic acid, the effects on glycogen content due to trichloroethylene exposure have not been adequately studied. Therefore, the data are inadequate to determine if this hypothesized mode of action contributes to trichloroethylene-induced hepatocarcinogenesis.

*Inactivation of GST-zeta:* Dichloroacetic acid inhibits its own metabolism through inactivation of GST-zeta (Board and Anders 2005, 2011). Successive doses of dichloroacetic acid have been reported to increase its plasma half-life in humans and mice and reduce its biotransformation in rat liver (Board and Anders 2005, Schultz *et al.* 2002). Several polymorphic variants of GST-zeta also have been identified that differ in their susceptibility to inactivation (Board and Anders 2011, Fang *et al.* 2006, Li *et al.* 2012b). GST-zeta also is known as maleylacetoacetate isomerase (MMAI) and is part of the tyrosine catabolism pathway and metabolizes maleylacetoacetate and maleylacetone to fumarylacetoacetate and fumarylacetone, respectively (Board and Anders 2011, Stacpoole *et al.* 2008). Inhibition of GST-zeta by exposure to dichloroacetic acid results in the accumulation of maleylacetoacetate, maleylacetone, and succinylacetone and lower concentrations of fumarylacetoacetate (Blackburn *et al.* 2006, EPA 2011a). Hereditary tyrosinemia type 1 is a metabolic disease caused by a deficiency of an enzyme involved in the last step of tyrosine catabolism. Individuals with this disease develop hepatocellular carcinoma at a young age (Stacpoole 2011, Tanguay *et al.* 1996). The increased cancer risk may be caused by the accumulation of one or more reactive tyrosine metabolites; however, it is not known which of these metabolites poses the greatest risk. Schultz *et al.* (2002) concluded that reduced MMAI activity is unlikely to be the sole carcinogenic mode of action for dichloroacetic acid and may be important only during the early stages of exposure. This conclusion is further supported by observations that GST-zeta knockout mice do not spontaneously develop hepatocellular carcinoma. Thus, the available data are insufficient to fully define the key events associated with this mode of action or to determine their necessity or sufficiency for carcinogenicity.

*Cytotoxicity and regenerative hyperplasia*: Cytotoxicity and regenerative hyperplasia have been recognized as key events in the mode of action of some chlorinated solvents (e.g., carbon tetrachloride, chloroform); however, trichloroethylene, trichloroacetic acid, and dichloroacetic acid induce liver carcinogenicity at doses that do not produce cytotoxicity (Bull *et al.* 2004, EPA 2011a, NCI 1976, NTP 1990). Further, there is no evidence that the transient increases in DNA synthesis in mouse liver are related to reparative hyperplasia. Thus, it is unlikely that cytotoxicity and reparative hyperplasia play a significant role in trichloroethylene-induced liver carcinogenicity.

### 6.2.3 Summary

Although species differences in sensitivity to the proposed modes of action are likely, no data suggest that trichloroethylene causes liver tumors in mice by mechanisms that are irrelevant to humans. Most of the hypothesized modes of action for liver tumors have some experimental support and are biologically plausible in humans and rodents. However, the data currently are

inadequate to support the conclusion that any of the particular mode-of-action hypotheses are operant because a collection of key events sufficient to induce liver tumors has not been identified or demonstrated. It is likely that the oxidative metabolites (e.g., trichloroacetic acid, dichloroacetic acid, chloral hydrate) are involved in liver carcinogenicity because they induce hepatotoxic and hepatocarcinogenic effects that are similar to trichloroethylene. Liver tumor phenotype (e.g., immunostaining for c-Jun) and genotype (e.g., H-*ras* mutation frequency and spectrum) analyses support a role for both dichloroacetic acid and trichloroacetic acid and show that neither metabolite alone can account for the full characteristics of trichloroethylene-induced liver tumors. The data suggest that the mode of action is complex and likely involves key events from several pathways.

# 7 Preliminary listing recommendation

Trichloroethylene is currently listed in the RoC as *reasonably anticipated to be a human carcinogen.* Since it was first listed in the RoC, additional cancer studies have been published. The monograph focuses on the potential carcinogenicity of trichloroethylene for kidney cancer, non-Hodgkin lymphoma (NHL), and liver cancer. This section brings forward and integrates the evaluations of the human and mechanistic data for each of these cancers (Sections 4, 5, 6), other relevant data (Sections 1 and 2), and the level of evidence in experimental animals (current listing in the RoC), and reaches a preliminary listing recommendation for trichloroethylene in the RoC. The conclusions are based on applying the RoC listing criteria to the evidence across studies.

**Preliminary listing recommendation**

Trichloroethylene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans. This conclusion is based on evidence from human epidemiological studies together with toxicokinetic, toxicological, and mechanistic studies showing that trichloroethylene causes kidney cancer in humans. There is limited evidence for the carcinogenicity of trichloroethylene from studies of non-Hodgkin lymphoma (NHL) in humans.

Supporting evidence is provided by studies in experimental animals demonstrating that trichloroethylene causes cancer at several tissue sites, including some of the same sites as seen in humans – kidney tumors in male rats, liver tumors in mice of both sexes, and lymphoma in female mice – as well as tumors at other sites, including testicular tumors and leukemia in male rats, and lung tumors in mice of both sexes (NTP 2011).

A summary of the toxicokinetic, epidemiological, toxicological, and mechanistic evidence for the three cancer sites is discussed below.

## 7.1 Kidney cancer

Human epidemiological studies, together with toxicokinetic, toxicological and mechanistic studies in humans, provide sufficient evidence of a causal relationship between exposure to trichloroethylene and kidney cancer.

Epidemiological studies have demonstrated a credible association between exposure to trichloroethylene and kidney cancer based on consistent evidence of increased risks across studies with different study designs, in different geographical areas, and in different occupational settings; evidence of increasing cancer risk with increasing level or duration of exposure; and evidence of a combined statistically significantly increased risks for kidney cancer across studies from two meta-analyses.

Overall, increased risks of kidney cancer were found among individuals with the highest exposure in the most informative studies (e.g., studies with higher levels of exposure to trichloroethylene, better assessments of exposure and disease, see Figures 4-2 and 4-3). Although several studies did not find an association between kidney cancer and trichloroethylene exposure, their sensitivity to detect an association might have been low because of low exposure levels, small numbers of subjects with higher levels of exposure, or non-differential exposure

misclassification. The meta-analyses also provide strong evidence for an association with kidney cancer. One meta-analysis conducted a sensitivity analysis and found that the meta-relative risk was robust and not sensitive to removal of individual studies or use of alternative risk estimates. Finally, biases or confounding from known or suspected co-exposures, smoking or other lifestyle factors, are unlikely to explain the positive findings across studies (see Section 4.4 for a detailed discussion of the evidence).

Toxicokinetic and mechanistic data in both humans and animals provide credible evidence for the biological plausibility of mechanisms of trichloroethylene's carcinogenicity in humans. The key events most likely contributing to tumorigenicity include (1) GSH-conjugation-derived metabolites produced *in situ* or delivered systemically to the kidneys and (2) mutagenic and genotoxic effects induced by these metabolites in the kidneys. Humans and experimental animals have similar metabolism and similar mixtures of trichloroethylene and metabolites in their tissues. *In vitro* studies in kidney and liver cells from humans and animals demonstrate the formation of several GST-derived metabolites, some of which (NAcDCVC and DCVG) have been detected in the urine or blood of both trichloroethylene-exposed humans and experimental animals.

The available mechanistic data support a mutagenic mode of action mediated by GSH-conjugated metabolites. These metabolites have been shown to be mutagenic *in vitro* assay and genotoxic in both *in vitro* and *in vivo* assays, most notably showing damage *in vitro* in both human and animal kidney cells, cellular transformation in rat kidney cells and DNA damage and micronuclei in kidney cells from rats exposed *in vivo*. Finally, the finding of a higher risk for trichloroethylene exposure and renal-cell cancer among exposed individuals with a functionally active glutathione-S-transferase theta 1 (GSTT1) genotype compared with GST-null genotypes provides support for the importance of the GSH-conjugation pathway in humans (Moore *et al.* 2010). A potential mechanism that may contribute to trichloroethylene carcinogenicity is cytotoxicity and associated regenerative proliferation. Studies in humans also provide evidence that trichloroethylene causes nephrotoxicity (Vermeulen *et al.* 2013, Bolt *et al.* 2004, Brüning *et al.* 1999a,b), supporting this mechanism in humans. Thus, the mode of action for kidney carcinogenicity may involve a combination of mutagenicity and cytotoxicity.

## 7.2 NHL and related cancers

Epidemiological studies provided limited evidence for an association between exposure to trichloroethylene and NHL, based on positive associations in several studies and evidence of a combined increased risk for NHL across studies. The evidence across studies was less consistent than for kidney cancer, and alternative explanations such as chance or confounding could not reasonably be ruled out.

The strongest evidence of an association between exposure to trichloroethylene and NHL comes from the InterLymph pooled analysis (*P* for Fisher combined probability = 0.004) (Cocco *et al.* 2013) and is supported by modest increases in risk several cohort and case-control studies. The risk of NHL increased with level or duration of exposure in this study, one of its component studies (Purdue *et al.* 2011), and another case-control study (Wang *et al.* 2009); evidence for an exposure-response relationship was lacking in several cohort studies. No evidence for confounding by lifestyle factors was found; however, potential confounding by other solvents or chlorinated solvents may be possible in the aircraft-manufacturing studies.

The mechanisms of potential lymphomagenesis of trichloroethylene are largely unknown. There is evidence that trichloroethylene causes immunomodulation in both people and animals, with some support for both immunosuppression and autoimmunity. Immunomodulation and immunosuppression are strongly linked to NHL, thus, it is biologically plausible that it may play a role in the mode of action of trichloroethylene-induced NHL. The proposed model is that lymphomas can develop from errors arising during the hypermutable stages of B-cell activation and can arise from either chronic antigenic stimulation (autoimmunity) or from impaired pathogen control (immunosuppression). Some of the available studies in humans and animals that measured immune biomarkers (such as those for B-cell activation) were not consistent with this model. The mechanisms of immunomodulation and lymphomagenesis are not completely understood, and neither the proposed model nor the potential association between trichloroethylene-induced immune effects and lymphoma development have been directly tested in either humans or animals.

## 7.3 **Liver cancer**

The data available from studies in humans are inadequate to evaluate the relationship between liver cancer and exposure to trichloroethylene. A few studies, including two meta-analyses, found modest increases in the risk of liver cancer; however, findings were inconsistent across studies and there was little evidence of exposure-response relationships in the individual studies or the meta-analyses. Evidence from recent studies, published since the latest meta-analysis (EPA 2011), appears to be weaker. Most of the (recent and older) studies had limited ability to detect an association for rare cancers such as liver cancer. In addition, confounding by one or more of the common co-exposures or lifestyle factors, or chance, could not be completely ruled out.

The mode of action of trichloroethylene-induced liver cancer is unknown but likely is complex and involves key events from several pathways. These may include genotoxicity, oxidative damage, peroxisome proliferation, epigenetic events, and autoimmunity (hepatitis), resulting primarily from oxidative stress. Oxidative metabolites are considered to be more important in liver carcinogenicity because trichloroethylene, trichloroacetic acid, dichloroacetic acid, and chloral hydrate have similar hepatotoxic and hepatocarcinogenic effects. These metabolites are found in humans and chloral/chloral hydrate is genotoxic in several *in vitro* and *in vivo* test systems. Although species differences in sensitivity to the proposed modes of action are likely, no data suggest that trichloroethylene causes liver tumors in mice solely by mechanisms that are not relevant to humans.

### 7.3.1 Other cancer sites

This evaluation focused on NHL and related B-cell lymphoma, and cancers of the kidney and liver; however authoritative evaluations are available for other cancer sites. IARC (2014) concluded that although there were increases in cancer at several other sites, the data was insufficient to make an evaluation. Of some interest is cervical cancer for which statistically significant increases in risk were found among women in the pooled biomonitoring study (Hansen *et al.* 2013) and the study of blue-collar workers (Raaschou-Nielson *et al.* 2003), and non-statistically increases in risks were found among the Utah aircraft-manufacturing study (Radican *et al.* 2008) and a case-control study in the Arve Valley area of France, where the screw-cutting industry was prevalent (Carbotel *et al*. 2013). However, there was no association with cumulative exposure or duration of exposure in the latter study. The database for this

endpoint was limited by few studies reporting on this tissue site potential confounding form smoking or human papilloma virus infection may be concern.

## 7.4 Toxicological considerations across endpoints

The available evidence indicates that trichloroethylene causes genotoxicity, toxicity, and cancer via metabolic activation to reactive metabolites. Two distinct metabolic pathways of trichloroethylene have been identified that are common to all mammalian species studied: CYP oxidation and GSH conjugation. As mentioned above, the mechanism of kidney cancer is most likely mediated through the GSH conjugation pathway, whereas liver toxicity/cancer is thought to be mediated via the CYP oxidation pathway. The oxidative pathway, primarily through CYP2E1, predominates in all species studied. Genetic polymorphisms or exposure to CYP inducers or inhibitors can alter the balance between oxidation and GSH conjugation of trichloroethylene. Impacts may be more substantial at higher substrate concentrations, which is consistent with the findings of increased risk of kidney cancer primarily among workers with high exposure to trichloroethylene. Co-exposures or genetic susceptibility factors, both of which could affect the flux of the two metabolic pathways, across the different study populations, may explain some of the heterogeneity across studies and cancer endpoints. Potential sensitive subpopulations include individuals with GST or CYP2E1 active genotypes and with alcohol dehydrogenase polymorphism (IARC 2014). The frequency of GSTT1 or GSTM1 polymorphisms varies according to ethnic groups (Sharma *et al.* 2014) with 40% to 85% of the population having GSTM1 or GSTT1 active genotypes, and thus possibly having a higher risk for developing cancer from trichloroethylene exposure. (A higher percentage and larger range of GST genotypes are found in African populations.) In addition, sex differences in cancer risk in humans are unclear. Only a few human cancer studies reported risk estimates separately for men and women for specific cancer sites, and several studies had fewer women then men (see Sections 4, 5, 6), which limited the ability to evaluate consistent patterns of differences in cancer risk by sex.

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# Abbreviations

| | |
|---|---|
| $^{1}$H NMR: | proton nuclear magnetic resonance |
| ACGIH: | American Conference of Governmental Industrial Hygienists |
| ADD: | average daily dose |
| ADME: | absorption, distribution, metabolism, and excretion |
| AEGL: | Acute Exposure Guideline Level |
| AhR: | aryl hydrocarbon receptor |
| ALL: | acute lymphocytic leukemia |
| ALT: | serum alanine aminotransferase, alanine aminotransferase |
| ANOVA: | analysis of variance |
| ARNT: | aryl hydrocarbon nuclear translocator |
| AST: | serum aspartate aminotransferase, aspartate aminotransferase |
| atm: | atmosphere |
| ATSDR: | Agency for Toxic Substances and Disease Registry |
| BDL: | below detection limit |
| CA: | chromosomal aberration |
| CASRN: | Chemical Abstracts Service registry number |
| CDC: | Centers for Disease Control and Prevention |
| CDR: | Chemical Data Reporting Rule |
| CERHR: | Center for the Evaluation of Risks to Human Reproduction |
| CIN: | chromosomal instability |
| $cm^2$: | square centimeter |
| Cx: | connexin |
| Cx32: | gap junction beta 1-protein; connexin32 |
| DLMI: | dominant lethal mutation index |
| DLMR: | dominant lethal mutation rate |
| DNA: | deoxyribonucleic acid |
| dw: | drinking water |
| EASE: | Estimation and Assessment of Substance Exposure |
| EHOMO: | energy of the highest occupied molecular orbital |
| EPA: | Environmental Protection Agency |
| EQ: | exposure quartiles model |
| Erk MAPK: | extracellular signal-regulated kinase mitogen activated pathway |
| EUSES: | European Union System for the Evaluation of Substances |
| Exp.: | exposed |
| F: | female |
| FDA: | Food and Drug Administration |
| FLARE: | fragment length analysis with repair enzyme |
| FR: | *Federal Register* |
| ft: | feet |
| FTE: | full-time equivalent |
| FU: | follow-up |
| G: | guanine |
| GAC: | Genetic Alterations in Cancer |
| GC/MS: | gas chromatography/mass spectroscopy |

| | |
|---|---|
| GI: | gastrointestinal |
| GIS: | Geographic Information System |
| GM: | geometric mean |
| GSH: | glutathione |
| GSSH: | oxidized glutathione |
| GST: | glutathione-*S*-transferase |
| Hb: | hemoglobin |
| HBV: | Hepatitis B virus |
| HCB: | hexachlorobenzene |
| HCL: | hairy-cell leukemia |
| HCV: | Hepatitis C virus |
| HETA: | Health Hazard Evaluation and Technical Assistance |
| HHE: | Health Hazard Evaluation |
| HHS: | Department of Health and Human Services |
| HIC: | highest ineffective concentration |
| HID: | highest ineffective dose |
| HIV: | Human immunodeficiency virus |
| HPLC: | high-performance liquid chromatography |
| hr: | hour |
| HWE: | healthy worker (hire or survival) effect |
| I: | inconclusive |
| i.p.: | intraperitoneal |
| i.v.: | intravenous |
| IARC: | International Agency for Research on Cancer |
| ICD-9: | International Classification of Diseases, Ninth Revision |
| ICD-O-2: | International Classification of Diseases for Oncology (revision 2) |
| IDLH: | immediately dangerous to life and health |
| in: | inch |
| IUR: | Inventory Update Rule |
| JEM: | job-exposure matrix |
| kg: | kilogram |
| L: | liter |
| LEC: | lowest effective concentration |
| LED: | lowest effective dose |
| LHC: | lymphohematopoietic cancer |
| LOD: | limit of detection |
| Log $K_{ow}$: | logarithm of octanol/water partition coefficient |
| LOH: | loss of heterozygosity |
| M: | male |
| $m^3$: | cubic meter |
| MCL: | maximum contaminant level |
| MG: | methylguanine |
| mg: | milligram |
| mL: | milliliter |
| MM: | multiple myeloma |
| MN: | micronuclei |

| | |
|---|---|
| mol: | mole |
| MS: | mass spectrometry |
| N: | number |
| NA | not available; not applicable |
| NCE: | normochromatic erythrocyte |
| NCTR: | National Center for Toxicological Research |
| ND: | not detected; not determined; not done |
| ng: | nanogram |
| NHANES: | National Health and Nutrition Examination Survey |
| NHL: | non-Hodgkin lymphoma |
| NIEHS: | National Institute of Environmental Health Sciences |
| NIH: | National Institutes of Health |
| NIOSH: | National Institute for Occupational Safety and Health |
| NLM: | National Library of Medicine |
| NOES: | National Occupational Exposure Survey |
| NOS: | not otherwise specified |
| NPL: | National Priorities List |
| NR: | not reported; none reported |
| ns: | not specified |
| NS: | not significant |
| nt: | nucleotides |
| NT: | not tested |
| NTP: | National Toxicology Program |
| OHAT: | Office of Health Assessment and Translation |
| OR: | odds ratio |
| OSHA: | Occupational Safety and Health Administration |
| OTM: | olive tail moment |
| p.o.: | per os (oral administration) |
| PBZ: | personal breathing zone |
| PCE: | polychromatic erythrocyte |
| PCNA: | proliferating cell nuclear antigen |
| PEL: | permissible exposure limit |
| $PGE_2$: | prostaglandin $E_2$ |
| ppm: | parts per million |
| ppt: | parts per trillion |
| QSAR: | quantitative structure-activity relationship |
| R: | estimated daily production of adducts |
| r: | correlation coefficient |
| RAHC: | Reasonably anticipated to be a human carcinogen |
| RBC: | red blood cell |
| REL: | recommended exposure limit |
| RLV: | Rauscher-leukemia virus |
| RoC: | Report on Carcinogens |
| ROS: | reactive oxygen species |
| RQ: | reportable quantity |

| | |
|---|---|
| RR: | relative risk |
| RTG: | relative total growth |
| s.c.: | subcutaneous |
| SAFE: | significance analysis of function and expression |
| SCE: | sister-chromatid exchange |
| SD: | standard deviation |
| SIC: | Standard Industrial Classification |
| SIR: | standardized incidence ratio |
| SMR: | standardized mortality ratio |
| SOCMI: | synthetic organic chemical manufacturing industry |
| SRR: | standardized rate ratio, standardized relative risk |
| SSB: | single strand break |
| STS: | soft tissue sarcoma |
| TDS: | Total Diet Study |
| TL: | tail length |
| TLC: | thin-layer chromatography |
| TLV-TWA: | threshold limit value time-weighted average |
| TM: | tail moment |
| $t_{max}$: | time to maximum concentration in plasma |
| TMD: | tail moment dispersion coefficient |
| TRI: | Toxics Release Inventory |
| TSCA: | Toxic Substances Control Act |
| TSFE: | time since first employment |
| UDS: | unscheduled DNA synthesis |
| UK: | United Kingdom |
| $V_{max}$: | maximum reaction velocity |
| VOC: | volatile organic compound |
| WBC: | white blood cell |
| WHO: | World Health Organization |
| wt%: | weight percent |
| yr: | year or years |
| µg: | microgram |

# Glossary

**Alpha$_{2u}$-globulin:** $\alpha_{2u}$-Globulin is a low molecular weight protein that is synthesized in the liver of male rats and is regulated by complex hormonal interactions. Androgens stimulate synthesis, whereas estrogens repress synthesis.

**Ames assay:** The Ames *Salmonella*/microsome mutagenicity assay is a short-term bacterial reverse mutation assay specifically designed to detect a wide range of chemical substances that can produce genetic damage that leads to gene mutations.

**Aneuploidy:** An abnormality involving a chromosome number that is not an exact multiple of the haploid number (one chromosome set is incomplete).

**Apoptosis:** Cell deletion by fragmentation into membrane-bound particles, which are phagocytosed by other cells.

**Arabinose resistance:** The L-arabinose resistance test with *Salmonella typhimurium* (Ara test) is a forward mutation assay that selects a single phenotypic change (from L-arabinose sensitivity to L-arabinose resistance) in a unique tester strain (an araD mutant).

**Aroclor 1254-induced liver:** Liver tissue treated with the polychlorinated biphenyl mixture Aroclor 1254 used as a source of S9 fraction for mutagenic and genotoxic effects testing.

**Ascertainment bias:** Systematic failure to represent equally all classes of cases or persons supposed to be represented in a sample.

**Attrition bias:** Systematic differences between **comparison groups** in withdrawals or exclusions of **participants** from the results of a study.

**Biexponential process:** A process of drug (or xenobiotic) clearance with two phases with different rates. The first phase often involves rapid distribution of a drug to peripheral tissues, while the second phase represents clearance mechanisms that eliminate the drug from the body. (See "Two-compartment pharmacokinetic model.")

**Biodegradation:** Biotransformation; the conversion within an organism of molecules from one form to another. A change often associated with change in pharmacologic activity.

**Boiling point:** The boiling point of the anhydrous substance at atmospheric pressure (101.3 kPa) unless a different pressure is stated. If the substance decomposes below or at the boiling point, this is noted (dec). The temperature is rounded off to the nearest °C.

**CD8+ T-cell blast:** An immature, undifferentiated lymphocyte that expresses the CD8 transmembrane glycoprotein.

**Chemical Data Reporting Rule:** Chemical Data Reporting (CDR) is the new name for Inventory Update Reporting (IUR). The purpose of Chemical Data Reporting is to collect quality screening-level, exposure-related information on chemical substances and to make that information available for use by the U.S. Environmental Protection Agency (EPA) and, to the

extent possible, to the public. The IUR/CDR data are used to support risk screening, assessment, priority setting and management activities and constitute the most comprehensive source of basic screening-level, exposure-related information on chemicals available to EPA. The required frequency of reporting currently is once every four years.

**Cochran-Armitage trend test:** A statistical test used in categorical data analysis when the aim is to assess for the presence of an association between a variable with two categories and a variable with *k* categories. It modifies the chi-square test to incorporate a suspected ordering in the effects of the *k* categories of the second variable.

**Comet assay: Single cell gel electrophoresis for assessment of DNA damage in presumptive target tissues.**

**Connexin proteins:** A group of transmembrane proteins that form the intermembrane channels of gap junctions. They are used by inorganic ions and most small organic molecules to pass through cell interiors.

**Conversion factor:** A numerical factor used to multiply or divide a quantity when converting from one system of units to another.

**Critical temperature: T**he temperature at and above which a gas cannot be liquefied, no matter how much pressure is applied.

**Dehydrodehalogenation:** An elimination reaction in which a halogen is removed from one carbon and a hydrogen is removed from an adjacent carbon.

**Differential selection:** Selective pressure for self renewal. Gene mutations that confer a growth or survival advantage on the cells that express them will be selectively enriched in the genome of tumors.

**Disposition:** The description of absorption, distribution, metabolism, and excretion of a chemical in the body.

**Dominant lethal mutation assay:** The dominant lethal assay identifies germ cell mutagens by measuring the ability of a chemical to penetrate gonadal tissue and produce embryonic death due to chromosomal breakage in parent germ cells.

**Double acid conjugate:** A compound formed by the joining of two acids.

**Ecological study:** A study in which the units of analysis are populations or groups of people rather than individuals.

**ELISA assay:** Enzyme-linked immunosorbent assay; a sensitive immunoassay that uses an enzyme linked to an antibody or antigen as a marker for the detection of a specific protein, especially an antigen or antibody.

**Epigenetic mechanisms:** Changes in gene function that do not involve a change in DNA sequence but are nevertheless mitotically and/or meiotically heritable. Examples include DNA

methylation, alternative splicing of gene transcripts, and assembly of immunoglobulin genes in cells of the immune system.

**F0 generation:** F0 generation is the initial parent generation in a multi-generation reproduction study.

**F1 and F2 offspring:** F1 offspring is the first filial generation, which comprises offspring resulting from a cross between strains of distinct genotypes. The F1 generation is the generation resulting immediately from a cross of the first set of parents (parental generation, i.e., F0 generation). F2 offspring is the second filial generation, which comprises offspring resulting from a cross of the members of F1 generation. The F2 generation is the result of a cross between two F1 individuals (from F1 generation).

**FDA Good Laboratory Practice Regulations:** A quality system codified by the U.S. Food and Drug Administration that prescribes operating procedures for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration.

**Fisher's exact test:** The test for association in a two-by-two table that is based on the exact hypergeometric distribution of the frequencies within the table.

**Follow-up:** Observation over a period of time of a person, group, or initially defined population whose appropriate characteristics have been assessed to observe changes in health status or health-related variables.

**Freund's adjuvant:** A water-in-oil emulsion injected with immunogen (Freund's incomplete adjuvant) or with immunogen and killed mycobacteria (Freund's complete adjuvant) to enhance the immune response to the immunogen.

**Genomic instability:** An increased propensity for genomic alterations that often occurs in cancer cells. During the process of cell division (mitosis) the inaccurate duplication of the genome in parent cells or the improper distribution of genomic material between daughter cells can result from genomic instability.

**Glioma:** A cancer of the brain that begins in glial cells (cells that surround and support nerve cells).

**Hairy-cell leukemia:** A rare type of leukemia in which abnormal B-lymphocytes (a type of white blood cell) are present in the bone marrow, spleen, and peripheral blood. When viewed under a microscope, these cells appear to be covered with tiny hair-like projections.

**Healthy worker hire effect:** Initial selection of healthy individuals at time of hire so that their disease risks differ from the disease risks in the source (general) population.

**Healthy worker survival effect:** A continuing selection process such that those who remain employed tend to be healthier than those who leave employment.

**Hemangiosarcoma:** A type of cancer that begins in the cells that line blood vessels.

**Henry's Law constant:** The ratio of the aqueous-phase concentration of a chemical to its equilibrium partial pressure in the gas phase. The larger the Henry's law constant the less soluble it is (i.e., greater tendency for vapor phase). The relationship is defined for a constant temperature, e.g., 25°C.

**Hepatoma:** A liver tumor.

**Host-mediated assay:** This assay evaluates the genotoxicity of a substance to microbial cells introduced (e.g., by intravenous injection) into a host animal. The host animal receives the test compound orally, and therefore acts as a source of chemical metabolism, distribution and excretion of the test compound.

**Immersion cleaning:** A process in which a tank containing cleaning solvent at a temperature below its boiling point is used for metal parts cleaning. To use the vapor degreaser, the operator places the parts to be cleaned in a metal wire basket, removes the cover, and lowers the basket of parts by hand into the cleaning solvent. After a brief period of time, the operator raises the basket and allows the parts to drip-dry inside the degreaser.

**Keratosis:** A localized horny overgrowth of the skin, such as a wart or callus.

**Loss of heterozygosity:** If there is one normal and one abnormal allele at a particular locus, as might be seen in an inherited autosomal dominant cancer susceptibility disorder, loss of the normal allele produces a locus with no normal function. When the loss of heterozygosity involves the normal allele, it creates a cell that is more likely to show malignant growth if the altered gene is a tumor suppressor gene.

**Lymphokine-activated killer cell:** Killer cell lymphocytes activated in the presence of interleukin-2 (IL-2). Lymphokine-activated killer cells (LAKs) are cytotoxic effector cells with an exceptionally wide target cell spectrum including normal and malignant cells of different origins. LAKs exhibit a profound heterogeneity with regard to phenotype surface marker expression; it remains to be determined if they represent a unique cell lineage.

**Melting point:** The melting point of the substance at atmospheric pressure (101.3 kPa). When there is a significant difference between the melting point and the freezing point, a range is given. In case of hydrated substances (i.e., those with crystal water), the apparent melting point is given. If the substance decomposes at or below its melting point, this is noted (dec). The temperature is rounded off to the nearest °C.

**Metabolic activation:** The chemical alteration of an exogenous substance by or in a biological system. The alteration may inactivate the compound or it may result in the production of an active metabolite of an inactive parent compound.

**Metaplasia:** A change of cells to a form that does not normally occur in the tissue in which it is found.

**Methemoglobin:** A form of hemoglobin found in the blood in small amounts. Unlike normal hemoglobin, methemoglobin cannot carry oxygen. Injury or certain drugs, chemicals, or foods

may cause a higher-than-normal amount of methemoglobin to be made. This causes a condition called methemoglobinemia.

**Micronuclei:** Small nuclei separate from, and additional to, the main nucleus of a cell, produced during the telophase of mitosis or meiosis by lagging chromosomes or chromosome fragments derived from spontaneous or experimentally induced chromosomal structural changes.

**Miscible:** A physical characteristic of a liquid that forms one liquid phase with another liquid (e.g., water) when they are mixed in any proportion.

**Molecular chaperone:** Any of a diverse group of proteins that oversee the correct intracellular folding and assembly of polypeptides without being components of the final structure.

**Molecular weight:** The molecular weight of a substance is the weight in atomic mass units of all the atoms in a given formula. The value is rounded to the nearest tenth.

**Multiple myeloma:** A type of cancer that begins in plasma cells (white blood cells that produce antibodies). Also called Kahler disease, myelomatosis, and plasma cell myeloma.

**Mutations:** A change in the structure of a gene, resulting from the alteration of single base units in DNA, or the deletion, insertion, or rearrangement of larger sections of genes or chromosomes. The genetic variant can be transmitted to subsequent generations.

**National Health and Nutrition Examination Survey:** A program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations.

**Natural killer cells:** A type of white blood cell that contains granules with enzymes that can kill tumor cells or microbial cells. Also called large granular lymphocytes.

**Non-differential misclassification:** The probability of erroneous classification of an individual, a value, or an attribute into a category other than that to which it should be assigned is the same in all study groups.

**Non-Hodgkin lymphoma:** A heterogeneous group of malignant lymphomas; the only common feature being an absence of the giant Reed-Sternberg cells characteristic of Hodgkin disease.

**Normochromatic erythrocyte:** A mature erythrocyte that lacks ribosomes and can be distinguished from immature, polychromatic erythrocytes by stains selective for RNA.

**Octanol/water partition coefficient (log *K*ow):** A measure of the equilibrium concentration of a compound between octanol and water.

**One-compartment model:** A pharmacokinetic modeling approach that models the entire body as a single compartment into which a drug is added by a rapid single dose, or bolus. It is assumed that the drug concentration is uniform in the body compartment at all times and is eliminated by a first order process that is described by a first order rate constant.

**Ozone-depleting substance:** A family of man-made compounds that includes, but are not limited to, chlorofluorocarbons (CFCs), bromofluorocarbons (halons), methyl chloroform, carbon tetrachloride, methyl bromide, and hydrochlorofluorocarbons (HCFCs). These compounds have been shown to deplete stratospheric ozone.

**Papilloma:** A small solid benign tumor with a clear-cut border that projects above the surrounding tissue.

**Personal breathing zone:** A sampling area as close as practical to an employee's nose and mouth, (i.e., in a hemisphere forward of the shoulders within a radius of approximately nine inches) so that it does not interfere with work performance or safety of the employee.

**Personal protective equipment:** Specialized clothing or equipment, worn by an employee to minimize exposure to a variety of hazards. Examples of PPE include such items as gloves, foot and eye protection, protective hearing devices (earplugs, muffs) hard hats, respirators and full body suits.

**Phase I metabolism:** Metabolism of drugs or other xenobiotic molecules, usually by oxidation or hydrolysis and involving a cytochrome P450 monooxygenase.

**Phase II metabolism:** A conjugation reaction that forms a covalent linkage between a functional group on a xenobiotic molecule and glucuronic acid, sulfate, glutathione, amino acid, or acetate.

**Plaque assay:** An assay for antibody production by single lymphocytes using cells isolated from the spleen or lymph nodes of animals injected with sheep red blood cells as an antigen. Incubation of the antibody-forming cells together with sheep red cells in an agar layer with exposure to guinea pig serum as complement results in formation of microscopic plaques (i.e., circular areas of hemolytic clearance around a lymphoid cell) due to release of hemolysin.

**Plate incorporation:** A commonly used procedure for performing a bacterial reverse mutation test. Suspensions of bacterial cells are exposed to the test substance in the presence and in the absence of an exogenous metabolic activation system. In the plate-incorporation method, these suspensions are mixed with an overlay agar and plated immediately onto minimal medium. After two or three days of incubation, revertant colonies are counted and compared with the number of spontaneous revertant colonies on solvent control plates.

**Point emission:** A release that can be identified with a single discharge source or attributed to a specific physical location.

**Polychromatic erythrocyte:** A newly formed erythrocyte (reticulocyte) containing RNA.

**Prophage lambda (λ):** A virus in *Escherichia coli* (*E. coli*) bacteria that has integrated itself into the host *E. coli* DNA.

**Proto-oncogene:** A gene involved in normal cell growth. Mutations (changes) in a proto-oncogene may cause it to become an oncogene, which can cause the growth of cancer cells.

***$P_{trend}$*:** Level of statistical significance of a change over time in a group selected to represent a larger population.

**Pyknotic shrinkage:** A thickening, especially the degeneration of a cell in which the nucleus shrinks in size and the chromatin condenses to a solid, structureless mass or masses.

**Pyrolysis:** The chemical and physical decomposition of organic material that occurs at high temperatures in the absence of oxygen.

**QUOSA:** A collection of scientific literature management software and services for researchers and information professionals in the life sciences and related scientific and medical areas designed to retrieve, organize, and analyze full-text articles and documents.

**Selection bias:** An error in choosing the individuals or groups to take part in a study. Ideally, the subjects in a study should be very similar to one another and to the larger population from which they are drawn (for example, all individuals with the same disease or condition). If there are important differences, the results of the study may not be valid.

**Sister-chromatid exchange:** The exchange during mitosis of homologous genetic material between sister chromatids; increased as a result of inordinate chromosomal fragility due to genetic or environmental factors.

**SKF-525A:** An inhibitor of drug metabolism and cytochrome P-450 activity.

**Soft tissue sarcoma:** A cancer that begins in the muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body.

**Solubility:** The ability of a substance to dissolve in another substance and form a solution. The Report on Carcinogens uses the following definitions (and concentration ranges) for degrees of solubility: (1) *miscible* (see definition), (2) *freely soluble*- capable of being dissolved in a specified solvent to a high degree (> 1,000 g/L), (3) *soluble*- capable of being dissolved in a specified solvent (10–1,000 g/L), (4) *slightly soluble*- capable of being dissolved in a specified solvent to a limited degree (1-10 g/L), and (5) practically insoluble- incapable of dissolving to any significant extent in a specified solvent (< 1 g/L).

**Specific gravity:** The ratio of the density of a material to the density of a standard material, such as water at a specific temperature; when two temperatures are specified, the first is the temperature of the material and the second is the temperature of water.

**Spot test:** Qualitative assay in which a small amount of test chemical is added directly to a selective agar medium plate seeded with the test organism, e.g., *Salmonella*. As the chemical diffuses into the agar, a concentration gradient is formed. A mutagenic chemical will give rise to a ring of revertant colonies surrounding the area where the chemical was applied; if the chemical is toxic, a zone of growth inhibition will also be observed.

**Steric bulk:** An indicator of the stability of the spatial arrangement of atoms in a molecule.

**T-helper cell:** A type of immune cell that stimulates killer T cells, macrophages, and B cells to make immune responses. A helper T cell is a type of white blood cell and a type of lymphocyte. Also called CD4-positive T lymphocyte.

**Tg.AC:** A transgenic mouse model with the ability to mount a tumorigenic response within 6 months in skin paint assays when dosed topically with nonmutagenic carcinogens.

**Time-weighted average:** The average exposure concentration of a chemical measured over a period of time (not an instantaneous concentration).

**Toxicokinetics:** The mathematical description (toxicokinetic models) of the time course of disposition of a chemical in the body.

**Transitions:** DNA nucleotide substitution mutation in which a purine base is substituted for another purine base (adenine → guanine or guanine → adenine) or a pyrimidine base for another pyrimidine base (cytosine → thymine or thymine → cytosine).

**Transversions:** DNA nucleotide substitution mutation in which a purine base (adenine or guanine) is substituted for a pyrimidine base (cytosine or thymine) or vice versa.

**Two-compartment pharmacokinetic model:** A two-compartment pharmacokinetic model resolves the body into a central compartment and a peripheral compartment. The central compartment generally comprises tissues that are highly perfused such as heart, lungs, kidneys, liver and brain. The peripheral compartment comprises less well-perfused tissues such as muscle, fat and skin. A two-compartment model assumes that, following drug administration into the central compartment, the drug distributes between that compartment and the peripheral compartment. However, the drug does not achieve instantaneous distribution (i.e., equilibrium), between the two compartments. After a time interval (t), distribution equilibrium is achieved between the central and peripheral compartments, and elimination of the drug is assumed to occur from the central compartment.

**Type-I error:** The error of rejecting a true null hypothesis, i.e., declaring that a difference exists when it does not.

**Type-II error:** The error of failing to reject a false null hypothesis, i.e., declaring that a difference does not exist when in fact it does.

**Vapor degreasing:** A type of cleaning procedure using a refrigerated cooling coil around the top of the interior of a vapor chamber to condense solvent vapor into liquid droplets on the surface of parts to remove surface impurities. Excess solvent drips back into the solvent sump and is recycled as the parts ascend from the vapor to condensing zones.

**Vapor density, relative:** A value that indicates how many times a gas (or vapor) is heavier than air at the same temperature. If the substance is a liquid or solid, the value applies only to the vapor formed from the boiling liquid.

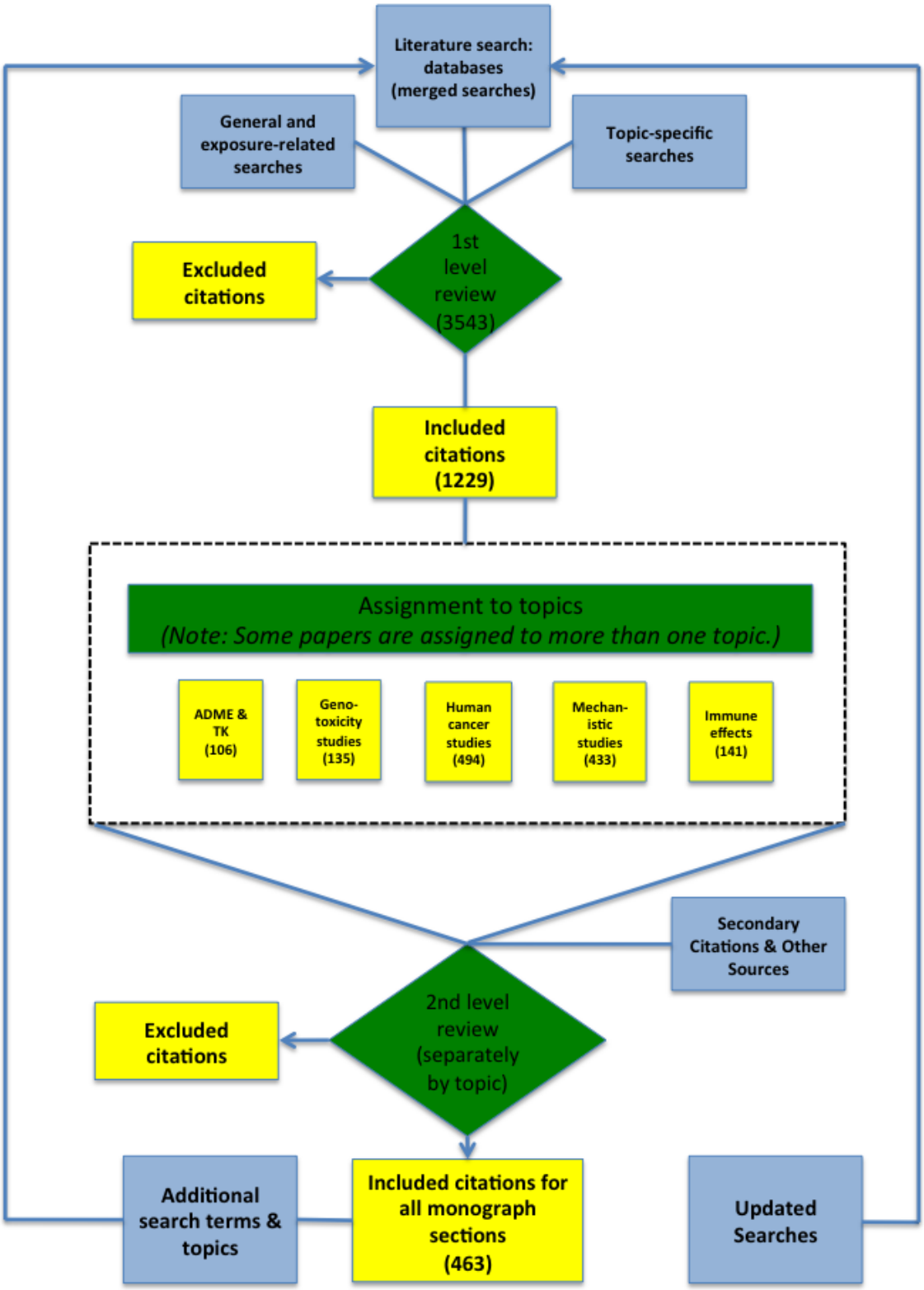
**Vapor pressure:** The pressure of the vapor over a liquid (and some solids) at equilibrium, usually expressed as mm Hg at a specific temperature (°C).

# Appendix A: Literature Search Strategy

The data sources, search terms, and search strategies that were used to identify literature for the draft monograph on trichloroethylene are described in the "Trichloroethylene Protocol" (http://ntp.niehs.nih.gov/ntp/roc/thirteenth/protocols/tce_protocol12-31-13_508.pdf).

Click here to return to text citing Appendix A in the Introduction.

**Figure A-1. Literature search strategy and review**



# Appendix B: ADME Tables

Click here to return to text citing Appendix B in Section 4

**Table B-1a. *In vitro* kinetics of oxidative metabolism of trichloroethylene**

| System | N | $K_m$ (μM) | $V_{max}$ (nmol TCE /min/mg protein) | 1,000 × $V_{max}/K_m$ | Reference |
|---|---|---|---|---|---|
| *Human* | | | | | |
| Hepatocytes | 6 | 210 ± 159[a] | 1.5 ± 1.2[b] | [13.7 ± 12.8] | Lipscomb *et al.* 1998a |
| Liver microsomes | 10<br>9<br>4<br>23 | 16.7 ± 2.45[c]<br>30.9 ± 3.3[d]<br>51.1 ± 3.77[e]<br>28.3 ± 12.9[f] | 1.25 ± 0.81[c]<br>1.44 ± 0.46[d]<br>2.77 ± 0.58[e]<br>1.59 ± 0.84[f] | [74.1 ± 44.1]<br>[47.0 ± 16.0]<br>[54.9 ± 14.1]<br>[60.2 ± 32.9] | Lipscomb *et al.* 1997 |
| Liver microsomes | 7 | 24.6 | 1.44 | 58.5 | Lipscomb *et al.* 1998b |
| Liver microsomes (high affinity) | 3<br>3 | 12 ± 3<br>26 ± 17 | 0.52 ± 0.17 (males)<br>0.33 ± 0.15 (females) | 48.0 ± 23.1<br>15.3 ± 10.1 | Elfarra *et al.* 1998 |
| Liver microsomes (low affinity) | 3<br>3 | 93 ± 26<br>160 ± 162 | 0.93 ± 0.17 (males)<br>0.72 ± 0.60 (females) | 10.7 ± 3.9<br>6.8 ± 5.6 | Elfarra *et al.* 1998 |
| *Rat* | | | | | |
| Liver microsomes | 5 | 55.5[g] | 4.83 | 87.0 | Lipscomb *et al.* 1998b |
| Liver microsomes (high affinity) | 5<br>3 | 72 ± 82<br>42 ± 21 | 0.96 ± 0.65 (males)<br>2.91 ± 0.71 (females) | 23.8 ± 20.6<br>80.0 ± 33.9 | Elfarra *et al.* 1998 |
| Liver microsomes (low affinity) | 5<br>3 | 482 ± 104<br>111 ± 27 | 2.48 ± 0.97 (males)<br>4.31 ± 0.31 (females) | 5.3 ± 2.2<br>40.1 ± 7.1 | Elfarra *et al.* 1998 |
| Kidney microsomes | 3 | 940[h] | 0.154 | [0.164] | Cummings *et al.* 2001 |
| *Mouse* | | | | | |
| Liver microsomes | 5 | 35.4[g] | 5.43 | 153.4 | Lipscomb *et al.* 1998b |
| Liver microsomes | 5<br>3 | 378 ± 414<br>161 ± 29 | 8.6 ± 4.5 (males)<br>26.1 ± 7.29 (females) | 42.0 ± 28.5<br>162.8 ± 36.7 | Elfarra *et al.* 1998 |

Values in brackets were calculated by NTP.
[a] Converted from ppm trichloroethylene in headspace.
[b] Converted from nmol/h/$10^6$ hepatocytes.
[c] Low $K_m$ (12 – 20) group.
[d] Mid $K_m$ (26 – 37) group.
[e] High $K_m$ (> 46) group.
[f] Combined across all $K_m$ groups.
[g] $K_m$ value for 0 – 5,000 μM TCE concentration.
[h] Mean of values calculated by Lineweaver-Burk and Eadie-Hofstee analysis.
Click here to return to text citing Table B-1a in Section 1

**Table B-1b. *In vitro* kinetics of chloral hydrate and dichloroacetic acid biotransformation**

| Metabolic step | System | $K_m$ (μM) | $V_{max}$ (nmol/min/mg protein) | 1,000 × $V_{max}/K_m$ |
|---|---|---|---|---|
| CH to TCOH | Human | 1,340 | 34.7 | 25.9 |
| | Rat | 520 | 24.3 | 46.7 |
| | Mouse | 190 | 11.3 | 59.5 |
| | high affinity | 120 | 6.3 | 52.5 |
| | low affinity | 510 | 6.1 | 12.0 |
| CH to TCA | Human | 23,900 | 65.2 | 2.7 |
| | Rat | 16,400 | 4.0 | 0.24 |
| | Mouse | 3,500 | 10.6 | 3.0 |
| DCA to glyoxylate | Human | 71 | 0.37 | 5.2 |
| | Rat | 280 | 11.6 | 41.4 |
| | Mouse | 350 | 13.1 | 37.4 |

Sources: Adapted from EPA 2011a, Lash *et al.* 2000a.
DCA = dichloroacetic acid, CH = chloral hydrate, TCA = trichloroacetic acid, TCOH = trichloroethanol.
Click here to return to text citing Table B-1b in Section 1

**Table B-2. Rates of DCVG formation from trichloroethylene conjugation[a]**

| System | Male | Female | Reference |
|---|---|---|---|
| *Human* | | | |
| Hepatocytes (0.9 mM, pooled) | 11 ± 3[b] | | Lash *et al.* 1999a |
| Liver cytosol (1 mM, individual samples) | 156 ± 16 | 174 ± 13 | Lash *et al.* 1999a |
| Liver cytosol (1 mM, pooled) | 420[b] | | Lash *et al.* 1999a |
| Liver cytosol (2 mM, pooled) | 346[b] | | Lash *et al.* 1999a |
| Liver cytosol (1.9 mM) | 0.011[c] | | Green *et al.* 1997 |
| Liver microsomes (1 mM, individual samples) | 108 ± 24 | 83 ± 11 | Lash *et al.* 1999a |
| Liver microsomes (1 mM, pooled) | 146[b] | | Lash *et al.* 1999a |
| Kidney cytosol (2 mM, pooled) | 42[b] | | Lash *et al.* 1999a |
| Kidney microsomes (1 mM, pooled) | 320[b] | | Lash *et al.* 1999a |
| *Rat* | | | |
| Hepatocytes (2 mM) | 9.7 ± 0.29* | 2.67 ± 0.69 | Lash *et al.* 1998 |
| Liver cytosol (2 mM) | 7.3 ± 2.8 | 4.86 ± 0.14 | Lash *et al.* 1998 |
| Liver cytosol (1.9 mM) | 0.097[c] | | Green *et al.* 1997 |
| Liver cytosol (4 mM) | nd | | Dekant *et al.* 1990 |
| Liver microsomes (2 mM) | 10.3 ± 2.8 | 7.24 ± 0.24 | Lash *et al.* 1998 |
| Liver microsomes (4 mM) | 0.12 | | Dekant *et al.* 1990 |
| Kidney cortical cells (2 mM) | 0.48 ± 0.02 | 0.65 ± 0.15 | Lash *et al.* 1998 |
| Kidney cytosol (2 mM) | 0.45 ± 0.22 | 0.32 ± 0.02 | Lash *et al.* 1998 |
| Kidney microsomes (2 mM) | nd | 0.61 ± 0.06 | Lash *et al.* 1998 |
| *Mouse* | | | |
| Liver cytosol (2 mM) | 24.5 ± 2.4 | 21.7 ± 0.9 | Lash *et al.* 1998 |
| Liver cytosol (1.9 mM) | 0.15[c] | | Green *et al.* 1997 |
| Liver microsomes (2 mM) | 40.0 ± 3.1* | 25.6 ± 0.8 | Lash *et al.* 1998 |
| Kidney cytosol (2 mM) | 5.6 ± 0.24* | 3.7 ± 0.48 | Lash *et al.* 1998 |
| Kidney microsomes (2 mM) | 5.47 ± 1.41* | 16.7 ± 4.7 | Lash *et al.* 1998 |

Source: Adapted from EPA 2011a.
nd = not detected.
* $P < 0.05$ (compared to corresponding tissue sample in females).
[a] Units are nmol/hr/mg protein or $10^6$ cells.
[b] Pooled samples include preparations derived from both sexes.

[c] Converted from pmol/min/mg protein.
Click here to return to text citing Table B-2 in Section 1

### Table B-3. Kinetics of *in vitro* glutathione conjugation of trichloroethylene

| System | $K_m$ (μM TCE) | $V_{max}$ (nmol DCVG /min/mg protein or $10^6$ cells) | 1,000 × $V_{max}/K_m$ |
|---|---|---|---|
| *Human* | | | |
| Hepatocytes | 37 ~ 106 | 0.16 ~ 0.26 | 2.4 ~ 4.5 |
| Liver cytosol: high affinity | 22.7 | 4.27 | 190 |
| Liver cytosol: low affinity | 333 | 8.77 | 26.3 |
| Liver microsomes: high affinity | 29.4 | 1.42 | 48.3 |
| Liver microsomes: low affinity | 250 | 3.1 | 12.4 |
| Kidney proximal tubular cells: high affinity | 580 | 0.11 | 0.19 |
| Kidney proximal tubular cells: low affinity | 29,400 | 1.35 | 0.046 |
| Kidney cytosol | 26.3 | 0.81 | 31 |
| Kidney microsomes | 167 | 6.29 | 38 |
| *Rat* | | | |
| Kidney proximal tubular cells: high affinity | 460 | 0.47 | 1.0 |
| Kidney proximal tubular cells: low affinity | 2,910 | 0.65 | 0.22 |

Sources: Cummings and Lash 2000, Cummings *et al.* 2000, EPA 2011a, Lash *et al.* 1999a.
Click here to return to text citing Table B-3 in Section 1

### Table B-4. β-Lyase activity from human, rat, and mouse kidney cytosol

| System | Substrate | $K_m$ (mM TCE) | $V_{max}$ (nmol TCE/min/mg protein) | Reference |
|---|---|---|---|---|
| *Human* | | | | |
| Male | TCVC | 2.53 ± 0.09 | 0.49 ± 0.07 | Green *et al.* 1990 |
| Female | TCVC | 2.67 ± 2.11 | 0.64 ± 0.54 | Green *et al.* 1990 |
| *F344 Rat* | | | | |
| Male | BTC | 1.66 ± 0.19 | 74.8 ± 6.5 | Lash *et al.* 1986 |
| Male | CTFC | 1.78 ± 0.17 | 11.6 ± 1.6 | Lash *et al.* 1986 |
| Male | DCVC | 1.36 ± 0.05 | 38.3 ± 1.4 | Lash *et al.* 1986 |
| Male | DCVC | 0.26 | 2.2 | Stevens *et al.* 1989 |
| Male | TCVC | 0.68 ± 0.06 | 4.00 ± 0.11 | Green *et al.* 1990 |
| Female | TCVC | 1.26 ± 0.21 | 3.64 ± 0.41 | Green *et al.* 1990 |
| *B6C3F$_1$ Mouse* | | | | |
| Male | TCVC | 5.69 ± 2.22 | 1.15 ± 0.31 | Green *et al.* 1990 |
| Female | TCVC | 4.43 ± 1.42 | 1.66 ± 0.27 | Green *et al.* 1990 |

Sources: Adapted from Lash *et al.* 2000a.
BTC = *S*-(2-benzothiazolyl)-L-cysteine, CTFC = *S*-(2-chloro-1,1,2-trifluoroethyl)-L-cysteine, DCVC = *S*-dichlorovinyl-L-cysteine, TCVC = *S*-(1,2,2-trichlorovinyl)-L-cysteine.
Click here to return to text citing Table B-4 in Section 1

**Table B-5. Comparison of hepatic *in vitro* oxidation and glutathione conjugation of trichloroethylene in human hepatocytes and liver subcellualr fractions[a]**

| System | Pathway | $K_m$ (μM in blood) | $V_{max}$ (nmol TCE/min/g tissue | $V_{max}/K_m$ (mL/min/g tissue) |
|---|---|---|---|---|
| Hepatocytes | Oxidation<br>Conjugation | 22.1–198<br>16–47 | 10–68.4<br>16–25 | 0.087–1.12<br>0.55–1.0 |
| Microsomes (option 1)[b] | Oxidation<br>Conjugation | 2.66–11.1<br>5.9 | 6.1–111<br>45 | 1.71–28.2<br>7.6 |
| Microsomes (option 2)[b] | Oxidation<br>Conjugation | 71–297<br>157 | 6.1–111<br>45 | 0.064–1.06<br>0.29 |
| Cytosol (option 1)[c] | Oxidation<br>Conjugation | na<br>4.5 | na<br>380 | na<br>84 |
| Cytosol (option 2)[c] | Oxidation<br>Conjugation | na<br>22.7 | na<br>380 | na<br>16.7 |

Sources: Adapted from EPA 2011a.
na = not applicable.
[a] When biphasic metabolism was reported, only the high affinity pathway is shown.
[b] $K_m$ values for microsomal protein calculated using different conversion assumptions: option 1 assumes $K_m$ in medium is equal to $K_m$ in tissue and converts to $K_m$ in blood by using a liver:blood partition coefficient of 5; option 2 converts $K_m$ in medium to $K_m$ in air using the measured microsomal protein:air partition coefficient of 1.78, then converts to $K_m$ in blood using blood:air partition coefficient of 9.5.
[c] $K_m$ values for cytosolic protein calculated using different conversion assumptions: option 1 assumes $K_m$ in medium is equal to $K_m$ in tissue and converts $K_m$ in blood by using a liver:blood partition coefficient of 5; option 2 assumes $K_m$ in medium is equal to $K_m$ in blood, thus no conversion was necessary.
Click here to return to text citing Table B-5 in Section 1

# Appendix C: Genetic Toxicology

The tables on the following pages contain data discussed in the section "Genetic and Related Effects" for trichloroethylene (Section 2).

Data are reported for *in vitro* studies of trichloroethylene, including mutagenicity in bacteria (Table C-1) and genotoxicity studies in non-mammalian eukaryotes (Table C-2) and mammalian cells (Table C-3). Studies on DNA and protein binding related to trichloroethylene exposure are included in Table C-4. *In vivo* studies of cytogenetic effects after trichloroethylene exposure in rodents are presented in Table C-5; studies of cytogenetic effects in peripheral blood lymphocytes from trichloroethylene-exposed workers are provided in Table C-6. The chemical purity of the test samples of trichloroethylene used in the studies is included here if available, or it is noted if the sample is of unknown purity/contained stabilizers or pure/not containing stabilizers.

Click here to return to text citing Appendix C in Section 2.

**Table C-1. *In vitro* studies of trichloroethylene mutagenicity in bacteria**

| Test system/endpoint | LEC/HIC | Without activation | With activation | Comments | References |
|---|---|---|---|---|---|
| *S. typhimurium* TA100 | 10 µL (epoxide-free) | – | – | Plate incorporation assay; contained stabilizers | Henschler *et al.* 1977 |
| *S. typhimurium* TA100 | 1.5% | – | (+) TA100 | Tested in dessicators; rat and mouse S9: increased but not doubled; effect greater with mouse S9; no stabilizers | Simmon *et al.* 1977 |
| *S. typhimurium* TA98, TA100 | 0.5%–10% | – | – | Study conducted in sealed dessicator vials; contained stabilizers | Waskell 1978 |
| *S. typhimurium* TA100, TA1535 | 1%–3% (unstabilized) | – | (+) TA100 | Tested in dessicator; rat S9; no stabilizers<br>Negative in preincubation assay both strains; authors report weak positive (30% increase) for vapor test in TA100 +S9 | Baden *et al.* 1979 |
| *S. typhimurium* TA100 | 5% (v/v) | – | (+) | Negative in plate incorporation; twofold increase in mutants in preincubation assay; no stabilizers detected; purity 99.5% | Bartsch *et al.* 1979 |
| *S. typhimurium* TA1535 | | (+) | | No stabilizers; purity 99.5%; plate incorporation | Kringstad *et al.* 1981 |
| *S. typhimurium* TA100 | 0.33%–1.33% (epoxide-free) | – | + | No stabilizers | Crebelli *et al.* 1982 |
| *S. typhimurium* TA1535, TA100 | 1%–5% | H: – both strains<br>L: (+) both strains | H: – both strains<br>L: (+) both strains | Tested higher (H) and lower (L) purity; TA100 ±S9 positive only at top dose and 3% survival; no stabilizers | Shimada *et al.* 1985 |
| *S. typhimurium* TA98, TA100, TA1535, TA1537, TA97 | 10–1,000 µL/plate | – | – | Preincubation protocol; analyzed purity 99+.<br>no stabilizers | Mortelmans *et al.* 1986 |
| *S. typhimurium* TA1535, TA100, TA1537, TA98 | | TA1535, TA100 +<br>TA1537, TA98 – | TA1535, TA100 +<br>TA1537, TA98 – | Vapor assay; doses not reported; purity unknown | Milman *et al.* 1988 |
| *S. typhimurium* | 20% (unstabilized) | | – | Vapor assay; S9 from rat and hamster; no stabilizers | McGregor *et al.* 1989 |

| Test system/endpoint | LEC/HIC | Without activation | With activation | Comments | References |
|---|---|---|---|---|---|
| TA98, TA100 | | | | | |
| *S. typhimurium* TA98, TA100 | 10,000 µg/plate (oxirane-stabilized) | – | – | Preincubation assay; no stabilizers | McGregor *et al.* 1989 |
| *S. typhimurium* TA1535, TA100, TA98 | 5% (oxirane-stabilized ) 0.63% (TA1535) | TA1535 +<br>TA100 +<br>TA98 – | TA1535 +<br>TA100 +<br>TA98 – | Vapor assay; toxic at 2.5% in one assay; contained stabilizers (epoxybutane and epichlorohydrin); mutagenic but at lower concentration | McGregor *et al.* 1989 |
| *S. typhimurium* BAL13 | 190 µg/mL | – | – | Forward mutation assay (ara test); no stabilizers | Roldan-Arjona *et al.* 1991 |
| *S. typhimurium* YG7108 | 1,000 µg/mL | + | | Metabolically competent strain microcolony assay/revertants; purity ≥ 99.5% | Emmert *et al.* 2006 |
| *Escherichia coli* K12 | 0.9 mM (analytical grade) | _ | + | Revertants at arg56; purity unknown | Greim *et al.* 1975 |
| *Escherichia coli* PQ37 | | _ | _ | SOS chromotest; purity unknown; doses not reported | Von der Hude *et al.* 1988 |
| *Escherichia coli* PQ37 | 7,325 µg/mL | _ | _ | SOS chromotest; no stabilizers | Mersh-Sundermann *et al.* 1989 |

Sources: EPA 2011a, IARC 2014; if additional detail was needed, primary paper was reviewed.
+ = positive, (+) = weak positive, – = negative.

To return to text citing Table C-1, click here.

**Table C-2. Studies of trichloroethylene in non-mammalian eukaryotes**

| Test system/ endpoint | LEC/HIC | Without activation | With activation | Comments | References |
|---|---|---|---|---|---|
| **Gene conversion** | | | | | |
| *Saccharomyces cerevisiae* | Strain D7: 1970<br>Strain D4: 2900 | | +<br>– | CYP content 5-fold greater in D7; high cytotoxicity at 22 mM; purity unknown | Callen *et al.* 1980 |
| *S. cerevisiae* D7 | 2900 | – | – | Both stationary and log phase/production of phototropic colonies; purity unknown | Koch *et al.* 1988 |
| *S. cerevisiae* D7 | 2600 | – | + | Test sample without stabilizers | Bronzetti *et al.* 1978 |
| **Recombination and mitotic crossover** | | | | | |
| *S. cerevisiae* D7 | 1970 | | + | Purity unknown | Callen *et al.* 1980 |
| *Aspergillus nidulans* yA2/+ strain 35/17 | 3660 (quiescent)<br>90 ppm (growth-mediated | –<br>– | | Gene crossover; tested both quiescent and grown-mediated (vapor) | Crebelli *et al.* 1985 |
| **Mitotic aneuploidy** | | | | | |
| *S. cerevisiae* D61.M | 725 | + | + | Loss of dominant color homolog, purity unknown | Koch *et al.* 1988 |
| **Gene mutation** | | | | | |
| *S. cerevisiae* D7 | 1300 | – | + | Reverse mutation<br>Test sample without stabilizers | Bronzetti *et al.* 1978 |
| *S. cerevisiae* D7 | 1970 | | + | Reverse mutation, log phase, purity unknown | Callen *et al.* 1980 |
| *S. cerevisiae* D7 | 725 | – | (+) | Reverse mutation, log phase and stationary<br>Purity unknown | Koch *et al.* 1988 |
| *A. nidulans* haploid strain 35 | <br>100 ppm<br>13 ppm | <br>–<br>+ | | Forward mutation, vapor, no stabilizers<br>Quiescent<br>Growth-mediated | Crebelli *et al.* 1985 |
| *Schizosaccharomyces pombe* P1 | 3280 (stationary)<br>13,140 (growing) | –<br>– | –<br>– | Forward mutation.<br>Negative with (technical grade) and without stabilizers (pure) | Rossi *et al.* 1983 |

Sources: EPA 2011a, IARC 2014; if additional detail was needed, primary paper was reviewed.
LEC/HIC = lowest effective concentration/highest ineffective concentration, treatment concentration µg/ml unless otherwise noted.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

To return to text citing Table C-2, click here.

**Table C-3. *In vitro* studies of cytogenetic effects of trichloroethylene in mammalian (including human) cells**

| Endpoint<br>Test system | LEC/HIC | Without activation | With activation | Comments | References |
|---|---|---|---|---|---|
| **Gene mutation** | | | | | |
| Mouse lymphoma<br>L5178Y *tk* locus | 146 µg/mL | – | + | ≥ 99% purity | Caspary *et al.* 1988 |
| Human lymphoblastoid TK6 cells | 600 µg/mL | – | – | No stabilizers | Caspary *et al.* 1988 |
| **Micronucleus induction** | | | | | |
| Chinese hamster ovary-$K_1$ cells | 150 [0.8–1.4 ppm] | + | | Dose-dependent significant increase | Wang *et al.* 2001 |
| Primary culture<br>rat kidney cells | 16.5 | + | | Purity unknown<br>Dose-dependent significant increase | Robbiano *et al.* 2004 |
| Primary culture<br>human kidney cells | 16.5 | + | | Purity unknown<br>Dose-dependent significant increase | Robbiano *et al.* 2004 |
| Human hepatoma HepG2 cells | 0.5 mM [65.7 µg/mL] | + | | ≥ 99.5 % purity | Hu *et al.* 2008 |
| Human lymphocytes | 6 mM | – | | Cytokinesis-block assay<br>Purity unknown | Kumar *et al.* 2009 |
| **Chromosomal aberrations** | | | | | |
| Chinese hamster lung cells | 1000 µg/mL | – | – | Purity unknown | Sofuni *et al.* 1985 |
| Chinese hamster ovary cells | 14,900 µg/mL | – | – | No stabilizers | Galloway *et al.* 1987 |
| Human lymphocytes | 6 mM | – | | Purity unknown | Kumar *et al.* 2009 |
| **DNA strand breaks** | | | | | |
| Human hepatoma HepG2 cells | 0.5 mM [65.7 µg/mL | + | | Comet assay<br>≥ 99.5 % purity | Hu *et al.* 2008 |
| Primary rat kidney cells | 130 | + | | Comet assay<br>Purity unknown<br>Dose-dependent significant increase | Robbiano *et al.* 2004 |
| Primary culture | 130 | + | | Comet assay | Robbiano *et al.* 2004 |

| Endpoint<br>Test system | LEC/HIC | Without activation | With activation | Comments | References |
|---|---|---|---|---|---|
| human kidney cells | | | | Purity unknown<br>Dose-dependent significant increase | |
| **Sister chromatid exchange** | | | | | |
| Chinese hamster ovary cells | 9 | | – | Purity unknown<br>1 hr (vapor) | White *et al.* 1979 |
| Chinese hamster ovary cells | +S9: 401 µg/mL<br>–S9: 700 µg/mL | (+) | + | ≥ 99% purity | Galloway *et al.* 1987 |
| Human lymphocytes | 178 µg/mL | + | | No stabilizers | Gu *et al.* 1981 |
| **UDS (DNA repair)** | | | | | |
| Rat hepatocytes, phenobarbital-induced | 368 | + | | Purity unknown | Costa & Ivanetich 1984 |
| Rat primary hepatocytes | 130 ppm vapor (2.5%)<br>0.1% conventional | – | | Vapor and conventional method<br>Low and high levels of stabilizers<br>3 and 18 hrs exposure; results all negative; cytotoxic | Shimada *et al.* 1985 |
| Rat primary hepatocytes | 2.5% (without stabilizer)<br>5.0% (with stabilizer) | – without stabilizers<br>– with stabilizers | | Vapor (130)<br>Tested with low and high levels of stabilizers | Shimada *et al.* 1985 |
| Rat primary hepatocytes | 368 mg/mL (without stabilizer)<br>14.5 mg/mL (with stabilizer) | – without stabilizers<br>+ with stabilizers | | Stabilized sample tests used vapor phase exposure | Williams *et al.* 1989 |
| $B6C3F_1$ mouse primary hepatocytes | NR | + | | Purity unknown; contained stabilizers | Milman *et al.* 1988 |
| Rat primary hepatocytes | NR | – | | Purity unknown; contained stabilizers | Milman *et al.* 1988 |
| Human lymphocytes | 2.5 µl/mL | (+) | | No stabilizers | Perocco and Prodi 1981 |

| Endpoint<br>Test system | LEC/HIC | Without activation | With activation | Comments | References |
|---|---|---|---|---|---|
| **Cell transformation** | | | | | |
| RLV/Fischer rat F1706 embryo cells | 144 | + | | 99.9% pure | Price *et al.* 1978 |
| Syrian hamster embryo cells | 25 | (+) | | Purity unknown | Amacher and Zelljadt 1983 |
| BALB/C-3T3 mouse cells | 250 | (+) | | Purity unknown | Tu *et al.* 1985 |

Sources: EPA 2011a, IARC 2014; if additional detail was needed, primary paper was reviewed.
LEC/HIC = lowest effective concentration/highest ineffective concentration; concentration in µg/ml unless otherwise noted.
**P* < 0.05, ***P* < 0.01, ****P* < 0.001. NR = not reported, + = positive, (+) = weak positive, – = negative.

To return to text citing Table C-3, click here.

**Table C-4. Studies of DNA and protein binding in mammalian cells or rodents treated with trichloroethylene**

| Endpoint/ Test system | LED/HID | Without activation | With activation | Comments | References |
|---|---|---|---|---|---|
| ***In vitro*** | | | | | |
| Covalent binding calf thymus DNA | 131 | | + | No stabilizers | DiRenzo *et al.* 1982 |
| Covalent binding calf thymus DNA | 340 | – | + | No stabilizers | Bergman 1983 |
| Covalent binding calf thymus DNA | 13 | | + | No stabilizers | Miller and Guengerich 1983 |
| Covalent binding rat hepatocyte DNA | 13 | + | | No stabilizers | Miller and Guengerich 1983 |
| Covalent binding mouse hepatocyte DNA | 13 | + | | No stabilizers | Miller and Guengerich 1983 |
| Covalent binding NMRI mouse DNA | 67 | | | Tissues: spleen, lung, kidney, pancreas, testis and brain<br>i.p. × 5; purity ≥ 99% (no stabilizers)<br>Metabolic incorporation of $^{14}C$ into nucleotides observed | Bergman 1983 |
| Covalent binding calf thymus DNA | 3.2 | | + | Purity unknown | Mazzullo *et al.* 1992 |
| Covalent binding salmon sperm DNA | 270 | – | + | No stabilizers | Banerjee and Van Duuren 1978 |
| Protein binding microsomal protein<br>Sprague-Dawley, Osborne-Mendel, and Fischer 344 rats | | + | | Liver, lung stomach, kidney<br>Sprague Dawley-rats had higher binding levels than Osborne-Mendel and Fischer 344 rats<br>Binding was greater for males than females in Osborne-Mendel rats<br>No stabilizers | Banerjee and Van Duuren 1978 |
| Protein binding microsomes<br>$B6C3F_1$ mouse | | + | | Liver, lung stomach, kidney<br>Binding was greater in mouse than rat in same study<br>Binding was greater in male than female mice<br>No stabilizers | Banerjee and Van Duuren 1978 |

| Endpoint/ Test system | LED/HID | Without activation | With activation | Comments | References |
|---|---|---|---|---|---|
| Protein binding microsomes<br>Osborne-Mendel rat | | + | | Liver and lung microsomes<br>Binding to TCE oxide<br>No stabilizers | Miller and Guengerich 1983 |
| Protein binding microsomes<br>$B6C3F_1$ mouse | | + | | Liver microsomes<br>Binding to TCE oxide<br>No stabilizers | Miller and Guengerich 1983 |
| Protein binding microsomes<br>Human | | + | | Liver microsomes<br>Binding to TCE oxide<br>No stabilizers | Miller and Guengerich 1983 |
| ***In vivo*** | | | | | |
| Protein binding<br>Osborne-Mendel rat (male) | 10 ppm | + | | Liver and kidney (measured reactive metabolite)<br>inh. 6 hr (10 or 600 ppm)<br>Purity > 99.9% | Stott *et al.* 1982 |
| Protein binding<br>$B6C3F_1$ mouse (male) | 10 ppm | + | | Liver and kidney (measured reactive metabolite)<br>inh. 6 hr (10 or 600 ppm)<br>Purity > 99.9%<br>Mouse greater binding than rat all doses, both tissues | Stott *et al.* 1982 |
| DNA from BALB/c mouse | 0.76 | (+) | | Liver, kidney, lung, stomach<br>i.p. × 1<br>Purity unknown | Mazzullo *et al.* 1992 |
| DNA from Wistar rat | 0.76 | (+) | | Liver, kidney, lung, stomach<br>i.p. × 1<br>Purity unknown | Mazzullo *et al.* 1992 |
| Covalent binding<br>NMRI mouse DNA | 67 | – | | Spleen, lung, kidney, pancreas, testis, brain<br>i.p. × 5<br>Purity ≥ 99%<br>Metabolic incorporation of $^{14}C$ into nucleotides was observed | Bergman 1983 |
| Covalent binding<br>NMRI mouse RNA | 67 | – | | Spleen, lung, liver, kidney, pancreas, testis, brain<br>i.p. × 5 | Bergman 1983 |

| Endpoint/ Test system | LED/HID | Without activation | With activation | Comments | References |
|---|---|---|---|---|---|
| | | | | Purity ≥ 99%<br>Metabolic incorporation of $^{14}C$ into nucleotides observed | |

Sources: EPA 2011a, IARC 2014; if additional detail was needed, primary paper was reviewed; studies considered to be inconclusive are not included here.
Exposure *in vitro*, µg/mL, unless otherwise indicated; *in vivo*, i.p. = intraperitoneal injection in mg/kg bw; inh. = inhalation, doses in ppm.
+ = positive, (+) = weak positive, – = negative.

To return to text citing Table C-4, click here.

**Table C-5. *In vivo* studies of cytogenetic effects of trichloroethylene in rodents**

| Test system/ endpoint | LED/HID[1] | Results | Comments | Reference |
|---|---|---|---|---|
| **Gene mutation** | | | | |
| NMRI-Hans/BGA mouse (male) | 3400 | – | Dominant lethal<br>inh. 24 hr × 1; no stabilizers | Slacik-Erben *et al.* 1980 |
| *Lac Z* transgenic mouse (male and female) | 3144 | – | Lung, liver, spleen, kidney, testicular germ cells<br>No base changes or small deletions<br>inh. 6 hr/d × 6 d; no stabilizers | Douglas *et al.* 1999 |
| **Chromosomal aberrations** | | | | |
| C57BL/6J mouse (male) | 9800 | _ | Splenocytes<br>inh. 6 hr × 1; no stabilizers | Kligerman *et al.* 1994 |
| Sprague-Dawley CD rat (male) | 960 | _ | Peripheral blood lymphocytes<br>inh. 6 hr; no stabilizers | Kligerman *et al.* 1994 |
| Sprague-Dawley CD rat (male) | 960 | _ | Peripheral blood lymphocytes<br>inh. 6 hr × 4; no stabilizers | Kligerman *et al.* 1994 |
| CD-1 mouse | 1000 | – | Bone-marrow cells<br>p.o. × 1; purity unknown | Loprieno and Abbondandolo 1980 |
| **Micronucleus induction** | | | | |
| Mouse | 750 | + | Bone-marrow erythrocytes<br>p.o. × 2; no stabilizers | Duprat and Gradiski 1980 |
| B6C3F$_1$ mouse (male) | 2500 | – | Bone-marrow erythrocytes<br>i.p. × 3; no stabilizers | Shelby *et al.* 1993 |
| C57B1/6J mouse (male) | 565 | – | Spermatocytes<br>inh. 6 hr/d × 5 d; no stabilizers | Allen *et al.* 1994 |
| CD-1 mouse (male) | 460 | + | Bone-marrow erythrocytes, correlated with urine TCOH<br>i.p. × 1; purity unknown | Hrelia *et al.* 1994 |
| C57BL/6J mouse (male) | 9800 | – | Splenocytes<br>inh. 6 hr × 1; no stabilizers | Kligerman *et al.* 1994 |

| Test system/ endpoint | LED/HID[1] | Results | Comments | Reference |
|---|---|---|---|---|
| Sprague-Dawley CD rat (male) | 5 | + | Bone-marrow erythrocytes<br>Results dose-dependent<br>inh. 6 hr × 1; no stabilizers | Kligerman *et al.* 1994 |
| Sprague-Dawley CD rat (male) | 960 | – | Bone-marrow erythrocytes<br>inh. 6 hr × 4; no stabilizers | Kligerman *et al.* 1994 |
| Sprague-Dawley CD rat (male) | 5000 | – | Bone marrow erythrocytes<br>inh. 6 hr × 1; purity 99.97% | Wilmer *et al.* 2014 |
| Sprague-Dawley CD rat (male) | 8800 | – | Peripheral blood lymphocytes<br>inh. 6 hr × 1; no stabilizers | Kligerman *et al.* 1994 |
| Sprague-Dawley CD rat (male) | 960 | – | Peripheral blood lymphocytes<br>inh. 6 hr × 4; no stabilizers | Kligerman *et al.* 1994 |
| Sprague-Dawley CD rat (male) | 3591 | + | Kidney cells<br>p.o. × 1; no stabilizers | Robbiano *et al.* 2004 |
| **Sister chromatid exchange** | | | | |
| Sprague-Dawley CD rat (male) | 8800 | – | Peripheral blood lymphocytes<br>inh. 6 hr × 1; no stabilizers | Kligerman *et al.* 1994 |
| Sprague-Dawley CD rat (male) | 960 | – | Peripheral blood lymphocytes<br>inh. 6 hr × 4; no stabilizers | Kligerman *et al.* 1994 |
| C57BL/6J mouse (male) | 9800 | – | Splenocytes<br>inh. 6 hr × 1; no stabilizers | Kligerman *et al.* 1994 |
| **DNA single-strand breaks** | | | | |
| $B6C3F_1$ mouse (male) | 2000 | – | Liver<br>DNA single strand breaks<br>i.p. × 1; no stabilizers | Parchman & Magee 1982 |
| NMRI mouse (male) | 790<br>1300 | + (kidney, liver)<br>− (lung) | Kidney, liver, lung<br>DNA single strand breaks<br>(alkaline unwinding)<br>i.p. × 1; no stabilizers | Walles 1986 |
| $B6C3F_1$ mouse (male) | 1500 | + | Liver | Nelson and Bull 1988 |

| Test system/ endpoint | LED/HID[1] | Results | Comments | Reference |
|---|---|---|---|---|
| | | | DNA single strand breaks<br>(alkaline unwinding)<br>p.o. × 1; no stabilizers | |
| Mouse spot test | 350 | – | DNA alterations; treat female dam and evaluate embryos; no stabilizers<br>i.p. × 1 | Fahrig 1977 |
| Sprague-Dawley rat (male) | 3000 | + | Liver<br>(alkaline unwinding)<br>p.o. × 1; no stabilizers | Nelson and Bull 1988 |
| Sprague-Dawley CD rat (male) | 3591 | + | Kidney<br>DNA strand break (comet assay)<br>inh. × 1; no stabilizers | Robbiano *et al.* 2004 |
| Sprague-Dawley CD rat (male) | 200 ppm | – | Kidney<br>DNA strand break (comet assay)<br>inh. × 1; purity 99.5% | Clay *et al.* 2008 |
| **UDS (DNA repair)** | | | | |
| Fisher 344 rat (male) | 1000 | – | Primary hepatocytes<br>p.o. × 1; purity unknown | Mirsalis *et al.* 1989 |
| B6C3F$_1$ mouse (male and female) | 1000 | – | Primary hepatocytes<br>p.o. × 1; purity unknown | Mirsalis *et al.* 1989 |
| CD-1 mouse (male) | 1000 | – | Primary hepatocytes<br>p.o. × 1; no stabilizers | Doolittle *et al.* 1987 |

Sources: EPA 2011a, IARC 2014; if additional detail was needed, primary paper was reviewed.
Exposure: i.p. = intraperitoneal injection, p.o. = oral, both in mg/kg bw; inh. = inhalation, doses in ppm.
[1]LED, lowest effective dose; HID, highest ineffective dose.

To return to text citing Table C-5, click here.

**Table C-6. Studies of cytogenetic effects in peripheral blood lymphocytes from TCE-exposed workers**

| Reference | Population | Exposure Group | Findings | Comments |
|---|---|---|---|---|
| Rasmussen *et al.* 1988<br>Denmark | 15 metal degreaser workers exposed to TCE > 20 hr/wk<br>669 controls from population-based study and survey of parents with offspring with stable chromosomal abnormalities in same geographical location | Exposed<br>Controls<br><br>Exposed<br>Controls<br><br>Exposed<br>Controls | *CA: breaks*<br>1.90 (1.22−2.84)<br>0.85 (0.66−1.08)***<br><br>*CA: other*<br>1.35 (0.79−2.16)***<br>0.15 (0.08−0.27)<br><br>*CA: hyperdiploid*<br>0.79 (0.38−1.46)*<br>0.24 (0.15−0.38) | 15 workers identified from a total of 116 workers<br>Control population may not be comparable to workers although the large size may reduce any potential selection bias<br>Other chromosomal aberrations include translocations, deletions, and inversions. |
| Seiji *et al.* 1990<br>Japan | 38 TCE-exposed (22 M, 16 W) 7 ppm<br>51 controls (26 M, 25 W) matched on age, sex, smoking habits, and geographical location | *Men*<br>Exposed smoker (8)<br>Control smokers (7)<br>Exposed non-smoker (14)<br>Control non-smoker (19)<br>*Women*<br>Exposed non-smokers (16)<br>Control non-smoker (25) | *SCE*<br>7.06 ± 1.38**<br>5.10 ± 1.16<br>6.46 ± 1.25<br>5.78 ± 1.64<br><br>6.15 ± 1.34<br>6.25 ± 1 42 | Workers TCE synthesis and degreasers<br>TCE exposure levels (ppm) were higher in women (3−32 ppm) than men (2−10 ppm); duration was shorter in women (~70 months) than men (120 months)<br>No independent effect of smoking |
| Nagaya *et al.* 1989<br>Japan | 22 TCE-exposed workers (~30 ppm)<br>22 workers without exposure to solvents and matched on age, and sex, and smoking habits. | Exposed<br>Controls | *SCE*<br>7.7 ± 1.3<br>8.0 ± 1.4 | Employment duration 0.7−34 years, mean 9.7 years<br>Estimated exposure 30 ppm, based on urinary total trichloro compounds, but large range in exposure levels. |
| Gu *et al.* 1981 (Cited from IARC 2014) | 6 TCE-exposed workers<br>9 controls | Exposed<br>Controls | *SCE*<br>9.045 ± 4.898<br>7.910 ± 2.890 | Exposure assessed by measurement of TCE and metabolite (U-TCA) in blood |

CA = chromosomal aberrations; SCE = sister chromatid exchange; TCE = trichloroethylene; U-TCA = urinary trichloroacetic acid.
* $P < 0.05$, $\chi^2$-test (Rasmussen *et al.*); ** $P < 0.01$ (*t*-test compared with concurrent male controls for Seiji *et al.*); ***$P < 0.001$, $\chi^2$-test (Rasmussen *et al.*).

To return to text citing Table C-6, click here.

# Appendix D: Human Cancer Study Tables

This appendix contains background information related to the cancer assessment on trichloroethylene in humans including detailed (1) data information on study design, methods, and findings for human cancer studies (Tables D-1 to D-3) and (2) detailed information on the quality assessment of the individual studies (Table D-4 to D-6) and (3) studies included in several meta-analyses (Table D-7).

### *Methodologies and study characteristics of the selected epidemiologic studies and identification of cancer endpoints*

The data from the 16 cohort studies, which include two nested case-control studies (Table D-1), 7 kidney case-control studies, including one that reported on liver cancer (Table D-2), and 11 NHL or related subtypes case-control studies (Table D-3), which includes one pooled study and the three constituent studies were systematically extracted from relevant publications and are summarized in the tables below. The cohort studies are organized according to several broad occupational groups related to the exposure scenarios or occupations similar to Table 3.1, and the case-control studies are organized similar to Tables 3.2 and 3.3.

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**Abbreviations used in Tables D-1, D-2, D-3, D-4a,b, D-5a,b, D-6a,b**

BMI = body mass index
CAREX = CARcinogen Exposure (Canada)
CLL = chronic lymphocytic lymphoma
DLBCL = diffuse large B-cell lymphoma
DMV = Department of Motor Vehicles
F = female(s)
FL = follicular lymphoma
GST = glutathione-S-transferase
HCL = hairy-cell leukemia
HIV = human immunodeficiency virus
HL = Hodgkin lymphoma
HP = Hadnot Point (Camp Lejeune)
HR = hazard ratio
HWE = healthy worker effect
ICD = International Classification of Diseases
ICDA = International Classification of Diseases-Adjusted
IQR = interquartile ratio

JEM = job exposure matrix
JP4 = jet propellant-4
JTEM = job-task exposure matrix
LHC = lymphohematopoietic cancer(s)
M = male(s)
MIS = Multicentre Italian Study
MM = multiple myeloma
N = number
NAS = National Academy of Science
NCI = National Cancer Institute
NDI = National Death Index
NHL = non-Hodgkin lymphoma
NIOSH = National Institute for Occupational Safety and Health
NOCCA = Nordic Occupational Cancer
NR = not reported
OR = odds ratio
OSHA = Occupational Safety and Health Administration
PAH = polycyclic aromatic hydrocarbon
PCBs = polychlorinated biphenyls
PCE = perchloroethylene (tetrachloroethylene)
PEL = permissible exposure limit
Perc. = perchloroethylene (tetrachloroethylene)
PGDP = Paduca Gaseous Diffusion Plant
PPM = parts per million
RCC = renal-cell cancer
RDD = random-digit dialing
REAL = Revised European-American Lymphoma classification
RR = relative risk
SEER = Surveillance, Epidemiology and End Results Program (US National Cancer Institute)
SES = socioeconomic status
SIR = standardized incidence ratio
SLL = small cell lymphocytic lymphoma
SMR = standardized mortality ratio
SRR = standardized rate ratio
SSA = Social Security Administration
SSFL = Santa Susanna Field Laboratory
SSN = Social Security number
TCA = trichloroacetic acid
TCE = trichloroethylene
TT = Tarawa Terra (Camp Lejeune)
TWA = time-weighted average
U-TCA = urine trichloroacetic acid
μg/L = micrograms/liter
VOC = volatile organic compounds
W = women
WHO = World Health Organization

Yr = year(s)

## Table D-1. Study descriptions and methodologies: cohort studies of trichloroethylene exposure

| **Hansen *et al.* 2013** | |
|---|---|
| **Related References** | **Geographic Location** |
| Anttila *et al.* 1995, Axelson *et al.* 1978, Axelson *et al.* 1994, Hansen *et al.* 2001, Tola *et al.* 1980 | Sweden, Finland, Denmark |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: All workers provided with urine TCA monitoring in Sweden (1955–1975), Finland (1965–1982), and Denmark (1947–1989) ≥ 1 U-TCA measurement<br>Exposed cohort: 5553 workers (3776 men; 1777 women); total 154,778 person-yr of observation<br>Follow-up: Sweden, 1958–2003; Finland, 1967–2004; Denmark, 1968–2008<br>Loss to follow-up: 0.1% | National rates (Sweden, Finland, Denmark)<br>***All-cause and all-cancer mortality/incidence***<br>All-cause incidence (SIR): NR<br>All-cancer incidence (SIR) = 1.06 (0.99–1.13); 997 |
| **Study Design and Analytical Methods/ Control for Confounding** | |
| Pooled and extended analysis of three historical cohort cancer incidence (registry) studies<br>External analysis (by sex, age, and calendar period) with 10- and 20-year exposure lagging; Internal analysis by U-TCA category (average level) using Cox regression to estimate hazard rate ratios adjusted for age, sex, calendar period, country; Indirectly evaluated potential confounding by smoking and alcohol consumption by calculating combined SIR of smoking- or alcohol-related cancers).<br>Additional analyses in earlier updates for the 3 cohorts: Swedish study evaluated risk (SIR, SMR) of U-TCA stratified by exposure time (< and > 2 years). Danish study also evaluated cancer risk by period of first employment, duration of employment, mean and cumulative exposure (air calculated from U-TCA) with 10- and 20-year lagging and stratified by sex. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| Mean/median urine TCA levels (mg/L)<br>Mean Median % samples > 50 mg/L<br>Sweden: 28.2 ± 39 13.0 17.7<br>Finland: 30.3 ± 82 9.2 13.3<br>Denmark: 39.2 ± 78 15.0 20.7<br>No data on cumulative exposure or exposure duration; Mean duration of employment: 5.5 yr (Sweden) and 6.3 (Denmark), NR for Finland~ 81 of Swedish cohort with < 20 ppm ambient TCE<br>Finland: Estimated TCE exposures were approximately 4 ppm (median) and 6 ppm (mean). Denmark: Overall calculated air concentrations (urinary TCA to air) =1-2 ppm (65 mg/m$^3$) mean, 3.53 ppm (19 mg/m$^3$) median | Individual Urine TCA measurements (national surveillance program); Most (65%–66%) of the first U-TCA samples were taken after 1970. Few measurements (usually 2 or 3) were available for each individual. Employment history was available in the Denmark cohort.<br>Co-exposures (Finland)<br>TCA Perc TCE<br>Urine (μmol/L) 48–53 NR NR<br>Air (ppm) 6 avg < 50 79 avg<br>Blood (μmol/L) NR 0.4–0.7 20–25 |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| NR | Personal identification number linked to Central Person Registers to ascertain vital status; linkage to national cancer registries. ICD-7 (modified). |

| **Raaschou-Nielsen *et al.* 2003** | |
|---|---|
| **Related References** | **Geographic Location** |
| Raaschou-Nielsen *et al.* 2001, Raaschou-Nielsen *et al.* 2002; Note: cohort partly overlaps that of Hansen *et al.* 2001. | Denmark |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: All male and female blue-collar workers employed ≥ 3 months in 347 companies using TCE with < 200 employees; Potentially higher exposed workers had > 1 year duration of employment and were first employed before 1980.<br>Potentially exposed cohort: 40,049 blue-collar workers in 347 TCE-using companies; 588,047 person-yr of exposure (men), 118,270 person-yr (women); 14,360 with potential higher exposure to TCE; TCE-using companies identified via Danish Institute for Occupational Health, Danish Product Registry, dry cleaning survey and files of main TCE producer.<br>Follow-up: 1968–1997<br>Loss to follow-up: NR, "Virtually complete" | Danish population<br>***All-cause and all-cancer mortality/incidence***<br>All cause incidence (SIR): NR<br>All-cancer incidence:<br>SIR: 1.08 (1.04–1.12); 2,620 (men)<br>SIR: 1.23 (1.14–1.33); 624 (women) |
| **Study Design and Analytical Methods/ Control for Confounding** | |
| Historical cohort incidence (registry) study; External SIR analysis, adjusted for sex, age, and calendar year, by lag time, calendar period, duration of employment, size of company; Separate analysis on potential high exposure by the same variables; No analysis for potential confounding from co-exposure or lifestyle factors; Sensitivity analysis on excluded workers (less than 3 months employment) | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| All workers in Danish TCE measurement registry: (Raaschou-Nielsen *et al.* 2001, 2002)<br>1960–1964: mean U-TCA = 58 mg/L<br>1960s: mean air TCE = 318 mg/m$^3$<br>1980–1985: mean U-TCA = 14 mg/L<br>1980s: mean air TCE = 75 mg/m$^3$<br>Co-exposures NR, Industries include iron and metal (> 50%), electronics, painting, printing, chemicals, dry cleaning | Potentially exposed workers identified from Central Population Registry (1968 on) and Danish Pension Fund (compulsory membership since 1964).<br>Job title and individual employment history (duration and year of first employment) obtained from Danish Pension Fund. Size of company also used as a surrogate for prevalence of TCE. 81%, 51% and 19% of the blue-collar workers in small (< 50) medium (50–100) and large (> 100) companies, respectively, estimated to be exposed to TCE.<br>No exposure data on individual workers |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| NR | Danish Cancer Registry<br>Modified ICD-7 |

| **Vlaanderen *et al.* 2013** | |
|---|---|
| **Related References** | **Geographic Location** |
| Kauppinen *et al.* 2009, Pukkala *et al.* 2009 | Denmark, Finland, Iceland, Norway, Sweden |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: Kidney cancer: 44,708 M, 31,422 F; Liver cancer: 14,702 M, 9,194 F; NHL: 36,487 M, 32,767 F; MM 187,777 M, 16,757 F | Referents: Kidney cancer: 223,540 M, 157,110 F; Liver cancer: 73,510 M, 45,970 F; NHL: 182,435 M, 163,835 F; MM: 93,885 M, 83,785 F |
| Eligibility criteria (cohort): All men and women aged 30–64 years old participating in the 1960, 1970, 1980–1981 and/or 1990 censuses in participating countries and alive on Jan 1 of year following the census<br>Cohort: Nordic Occupational Cancer Cohort (NOCCA): 45 years of cancer incidence and follow-up for 15 million people<br>Case identification and ascertainment: Linkage to cancer registries (incident cases) and followed by linkage to population registries | Referent eligibility criteria: Randomly selected from Nordic Occupational Cancer (NOCCA) database; alive and free of cancer<br>Matching criteria: Age (+/- 1 yr), sex, country; 5 controls per case and without cancer at time of case diagnosis |
| Follow-up: date of 1st entry into census to emigration, death or end of 2003 (Norway), 2004 (Iceland), 2005 (Sweden, Finland) | |
| **Study Design and Analytical Methods** | |
| Cancer registry and census record linkage study (Pukkala *et al.* 2009); Nested case-control design; Analysis of hazard ratio by exposure to TCE using conditional logistic regression for tertiles of cumulative exposure and continuous cumulative exposure (spline or linear); Non-exposed participants as internal controls; 1-, 5-, 10- and 20-year lagging explored but had minimal effect and thus unlagged models used. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| Levels: NR. Overall prevalence of exposure to TCE low (5%)<br><br>High estimated levels of exposure to TCE were found in shoe and leather industry workers, mechanics, laundry and smelting workers.<br><br>Moderate correlation between TCE and tetrachloroethylene (r = 0.58–0.63), chlorinated hydrocarbons (r = 0.56–0.61) and 1,1,1-trichloroethane (r = 0.37–0.43); No association between TCE and benzene and ionizing radiation | Census questionnaire data was used to construct country-specific and calendar time-specific quantitative JEM for 29 agents for NOCCA.<br>Person-yr of exposure started at age 20 or age at first job until death, emigration, cancer diagnosis or age 65. Assume same exposure between census reports. Exposures before 1st census report assumed same since age of first entry into cohort.<br>Cumulative exposure = prevalence × level of exposure by calendar year × lifetime employment duration. High exposure = exposure to levels > 90th percentile of cumulative exposure or average intensity × prevalence. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| NR | ICD-7; NHL 200+202, MM 203 |

| **Boice *et al.* 2006** | |
|---|---|
| **Related References** | **Geographic Location** |
| Overlaps cohort of Ritz *et al.* 1999 and Zhao *et al.* 2005 (see above) | Los Angeles (USA) |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: male Rocketdyne rocket engine testing workers employed ≥ 6 months from Jan 1, 1948 on and with adequate work histories and identifying data<br>Exposed cohort: 1,111 test stand mechanics with any estimated exposure to TCE or hydrazine<br>Total cohort: 8,372 Rocketdyne Aerospace workers (7,083 M, 1289 F) at the SSFL facility; 1,651 were test stand mechanics<br>Follow-up: 1948–1999; ~88% of test stand mechanics were followed for over 20 years.<br>Loss to follow-up: 0.4% test stand mechanics | External: US population<br>Internal: Hourly non-administrative Rocketdyne workers at SSFL and adjacent facilities<br>***All-cause and all-cancer mortality/incidence***<br>All-cause mortality: SMR = 0.87 (0.78–0.96); 391<br>All-cancer mortality: SMR = 1.00 (0.83–1.19); 121 |
| **Study Design and Analytical Methods/ Control for Confounding** | |
| Historical cohort mortality study; External (all cancers) adjusted for age, race, calendar year. Internal analysis (selected cancers including kidney but not NHL or liver cancer) using Cox proportional hazard models, adjusting for date of birth, year of hire, pay type (surrogate for SES) and exposure to hydrazine (for TCE analyses and TCE for hydrazine analyses) for any exposure, duration of employment with potential exposure to TCE or hydrazine, and number of engine test flushes using TCE. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| No quantitative exposure assessment<br>TCE used for engine flush to mid 1960s, used as utility solvent to 1974. Approx. 58% exposed to TCE during engine flushing/cleaning (high exposure); Approx. 42% exposed to TCE during utility cleaning (lower exposure)<br>Co-exposures: hydrazine, mixed solvents, rocket fuels, oxidizers, exhaust gases, other chemicals, radiation<br>8.4% (N = 121) exposed to both hydrazine and TCE | Qualitative exposure assessment to TCE; Walk-through surveys and veteran employees' assessments used to determine dates that TCE was used at test strands as a utility solvent or to flush engines. Comprehensive job history based on dates and job titles used to assign workers to specific test stands.<br>Workers assigned to (1) duration of employment for potential exposure to TCE and (2) duration (test years) of exposure to TCE from engine flush, which was weighted by number of engine tests per year accounting for the number of workers that year. |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| Smoking history (pack-yr) among subsample of 600 workers | SSA, California death index, NDI, state vital records, Pension Benefit Information Files, Medicare and Medicaid Services data, company personnel, pension and retirement records<br>ICD in use at time of death |

| **Zhao *et al.* 2005** | |
|---|---|
| **Related References** | **Geographic Location** |
| Morgenstern *et al.* 1997, Ritz *et al.* 1999. Members of cohort also part of separate larger mortality cohort study of Boice *et al.* 2006. | Los Angeles, California |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: Male workers at Rocketdyne aerospace facility 1950–1980 with ≥ 2 years' employment and no radiation exposure<br>Exposed cohort: 6,107 male aerospace workers at the Santa Susana Field Laboratory (SSFL); mortality: 6,044; incidence: 5,049 workers; TCE-exposed workers (greater than intensity score 3): mortality 2,648; incidence 2,236<br>Total cohort: 55,000 Rockwell/Rocketdyne aerospace workers<br>Follow-up: 1950–2001 (mortality)<br>1988–2000 (incidence)<br>Average follow-up 29 yrs<br>Loss to follow-up: < 1% for mortality | Mortality: US population<br>Incidence: California and 8 other state incidence rates<br>Internal analysis: Low TCE exposure category |
| | ***All-cause and all-cancer mortality/incidence*** |
| | All-cause and all cancer mortality (SMR): NR<br>All-cause and all cancer incidence (SIR): NR |
| **Study Design and Analytical Methods/Control for Confounding** | |
| Historical cohort mortality/incidence study; internal analyses; proportional hazards modeling with fixed and time-dependent variables; multivariate models for cumulative exposure (low, medium, and high exposure intensity) in lagged and unlagged analyses included pay type (surrogate for SES), time since first employment (surrogate for survival), age and co-exposures to other chemicals | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| Limited quantitative exposure assessment<br>Co-exposures: hydrazine, PAH, benzene (early years), mineral oil, gasoline, fuel oils | Semi-quantitative JEM developed by industrial hygienists based on walk-through surveys; employees' assessments, job task manuals, review of company records for TCE, hydrazine, PAH, mineral oil; Work histories for each individual linked to JEM to generate calendar time-dependent intensity scores for each chemical exposure for each worker. Individual cumulative intensity scores (low/medium/high) based on estimated intensity of exposure in job/task × time in job. |
| | 1% workers missing job description; 3% workers with insufficient job description – exposure imputed from job title |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |

| **Zhao *et al.* 2005** | |
|---|---|
| Smoking data for subsample of 200 workers with medical questionnaire data | Mortality: ICD 9 and 10; underlying and contributing causes of death<br>Incidence: California Cancer Registry and 8 other state cancer registries. ICD-O (incidence). Reports all lymphohematopoietic cancers (excluding CLL) only, not NHL |

| **Lipworth *et al.* 2011a** | |
|---|---|
| **Related References** | **Geographic Location** |
| Boice *et al.* 1999 (errata published in Boice and McLaughlin 2001); Marano *et al.* 2000 | Burbank, CA (USA) |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: All aircraft manufacturing workers employed ≥ 1 year from 1960<br>Exposed cohort: 5,443 M+F (180,704 person-yr)<br>Total cohort: 77,943 Aircraft mfg. workers at Lockhead Martin (Burbank)<br>Follow-up: 1960–2008 or age 95 (avg 32 yr)<br>Loss to follow-up: 1.7% total cohort | California (white workers) and USA (non-white workers)<br>***All-cause and all-cancer mortality/incidence***<br>All-cause mortality: SMR: 0.91 (0.88–0.93); 4,070<br>All-cancer mortality: SMR: 0.92 (0.86–0.97); 986 |
| **Study Design and Analytical Methods/ Control for Confounding** | |
| Historical cohort mortality study; External analysis: adjusted for age, sex, and calendar period; Internal analyses: Cox proportional hazard models for specific cancer by duration of exposure and exposure pattern adjusting for age, date of birth, date of hire, termination date, sex, and race; No control for potential confounding from co-exposures and lifestyle factors | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| No quantitative exposure assessment<br>TCE used for vapor degreasing up to 1966, replaced by tetrachloroethylene<br>Approx. 12% workers with routine TCE exposure, 30% routine or intermittent TCE exposure<br>Co-exposures: PCE, chromate, mixed solvents (including methyl ethyl ketone, alcohols, petroleum distillates, 1,1,1-trichloroethane, methylene chloride, methyl isobutyl ketone, acetone, toluene, xylene, freons), cutting fluids, lubricants | Qualitative JEM; Occupational job groups developed by industrial hygienists based on walk-through survey, veteran employee interviews and historical industrial hygiene surveys and reports<br>Individuals classified as ever/never, routine, or intermittent exposure to TCE and co-exposures (PCE, and mixed solvents) (Boice *et al.* 1999) and by duration of potential exposure to each substance (Lipworth *et al.* 2011a) |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| NR | California death files, National Death Index, state vital statistics records, vital records search company; Pension Benefit Information Files, Social Security Death Index, Health Care Financing Administration beneficiary files, California DMV, work and pension records<br>Nosologist coded cause of death from death certificates using ICD in use at time of death, underlying cause of death. |

| **Radican *et al.* 2008** | |
|---|---|
| **Related References** | **Geographic Location** |
| Spirtas *et al.* 1991, Stewart *et al.* 1991, Blair *et al.* 1998 (mortality and incidence) | Utah (USA) |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: employed ≥ 1 year 1952–1956<br>Exposed cohort: 7,204 (6,153 men, 1,051 women) TCE-exposed workers<br>Total cohort: 10,730 male and 3,725 female civilian aircraft maintenance workers (at Hill Force military base)<br>Follow-up: mortality1991–2000; incidence 1973–1990<br>Loss to follow-up: NR | USA (mortality; Radican *et al.* 2008) and Utah cancer registry (Blair *et al.* 1998)<br>Non-chemical-exposed workers (internal analysis)<br>***All-cause and all-cancer mortality/incidence***<br>Radican *et al.* 2008 (internal analysis)<br>All-cause mortality HR = 1.04 (0.98–1.11); 3,628<br>All-cancer mortality HR = 1.12 (0.96–1.30); 729 |
| **Study Design and Analytical Methods/Control for Confounding** | |
| Historical cohort mortality/incidence study; Internal analyses (External analysis reported for 1990 follow-up for mortality only.)<br>2000 follow-up (mortality): Cox proportional hazards model, using age as variable and adjusting for race, stratified by sex and considering calendar year; 1990 follow-up (mortality and incidence): Poisson multivariate regression analysis adjusted for age, calendar year and sex. Both models were used to evaluate TCE exposure-response by cumulative exposure and exposure patterns (mortality only). Separate analysis for other chemical exposures, no multivariate analysis controlling for potential confounding from exposure to other substances or lifestyle factors. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Level and Co-Exposures*** | ***Exposure Assessment*** |
| No quantitative exposure (air) assessment specific for TCE, but air measurements available on vapor degreasing and other solvents. Estimated TCE exposures were:<br>Peak / Low level<br>1939–54: 600 / 10<br>1955–67: 400 / 10<br>1968–78: 200 / 0<br>1979–83: 0 / 0<br>Cherrie *et al.* (2006) estimated long-term exposure as 50 ppm and short term up to 600 ppm. The NAS concluded the cohort had a modest number of highly exposed (~ 100 ppm) but most were exposed to low TCE concentrations (~10 ppm).<br>Co-exposures: Ever/never exposure for 1,1,1-trichloroethane, methylene chloride, carbon tetrachloride, freon, isopropyl alcohol, acetone, ketone, toluene, methyl ethyl ketone, *o*-dichlorobenzene, perchloroethylene, chloroform, Stoddard solvent, xylene styrene, JP4 gasoline, metal fumes/dust, silica, zinc chromate, nitroglycerine, solder flux | All exposures: Walk-through surveys; veteran employee assessment; individual work and job histories from personnel records; Process descriptions were used to develop ever vs. never exposure to 21 solvents and chemicals for each job -department combination.<br>TCE: Semi-quantitative individual exposure assessment, calendar year specific; Detailed job task descriptions used to develop exposure score for each job based on relative exposure intensity for each calendar period, frequency of use and duration of use. Cumulative exposure (unit-years) was the sum of exposure scores × job duration across jobs (Stewart *et al.* 1991). Workers also assigned to patterns or types of exposure (e.g., low level, peak, continuous or intermittent). |

| **Morgan *et al.* 1998** | |
|---|---|
| **Related References** | **Geographic Location** |
| Wong and Morgan 1990 | Arizona (USA) |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: All male and female aircraft manufacturing workers employed ≥ 6 months 1950–1985<br>Exposed cohort: 4,733 (2,555 men; 2,178 women)<br>Total cohort: 20,508 aircraft manufacturing workers at the Hughes Aircraft Manufacturing Site<br>Follow-up: 1950(?)–1993 (approx. 66% followed for > 20 yr)<br>Loss to follow-up: 0.1% excluded due to missing data (not clear if vital status or other data) | External analysis: NR (assume U.S. population)<br>Internal analysis: 11,187 male and 4,588 female unexposed workers; peak exposure – used unexposed and low exposed workers as the reference group. |
| | ***All-cause and all-cancer mortality/incidence*** |
| | All-cause mortality: SMR: 0.84 (0.79–0.90); 917<br>All-cancer mortality/incidence:<br>SMR: 0.92 (0.81–1.03); 270 |
| **Study Design and Analytical Methods/ Control for Confounding** | |
| Historical cohort mortality study; External (SMR) analysis for TCE-exposed cohort, low and high exposure for multiple cancer sites; Internal analyses using Cox proportional hazards adjusting for age at hire, and sex used to evaluate cumulative (low and high) and peak exposure and selected cancer sites. No control for potential confounding from co-exposures and lifestyle habits | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| Limited quantitative exposure levels available, especially before 1975. Before 1981, plant had contaminated well water estimated between 730 and 2,200 ppb TCE for showers and drinking.<br>High exposure = work on degreaser machines using TCE (estimated to be 50 ppm; medium exposure = jobs near degreasing area (occasional contact); low exposure = jobs away from degreaser work<br>TCE used for vapor degreasing 1952–1977<br>Co-exposures: NR | Semi-quantitative individual JEM based on veteran employees' plus company industrial hygienists' exposure rankings. Jobs classified into no, low, medium, high exposure scores.<br>Cumulative exposure score (low, high) = exposure category × duration of exposure. Peak exposure = jobs with medium and high exposure.<br>Medium/low exposures may be misclassified. |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| NR | SSA; NDI; State death certificates; ICD-7, 8 or 9 in use at time of death |

| **Bahr *et al.* 2011** | |
|---|---|
| **Related References** | **Geographic Location** |
| None | Kentucky (USA) |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: All (6,766) workers with complete exposure/job histories employed between 1952 and 2003.<br>Exposed male cohort: 5,535 male uranium enrichment workers employed at the Paducah Gaseous Diffusion Plant (PGDP).<br>Total cohort: 6,820 uranium employment workers<br>Follow-up: 1995–2004<br>Loss to follow-up: NR | U.S. population for mortality and NCI prevalence data for NHL incidence<br>Kentucky cancer registry (NHL cases only) |
| | ***All-cause and all-cancer mortality/incidence*** |
| | All-cause mortality (SMR)<br>Total cohort: 0.76 (0.72–0.79); 1,638 deaths<br>Male cohort: 0.76 (0.72–0.79); 1,340 deaths<br>All-cancer mortality: NR |
| **Study Design and Analytical Methods/Control for Confounding** | |
| Historical cohort mortality study: External (SMR) and internal (SRR) analysis using NIOSH life table analysis system.<br>Regional adjustment made for lung cancer and leukemia. Indirect adjustment for smoking using age-adjusted-race- and gender-specific cancer rates and population-based smoking prevalence rates that were extrapolated back to 1953. Incidence and mortality combined data used for NHL only. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| No quantitative exposure assessment<br>Co-exposures not identified | JEM based on discussions with current and past employees, job title and work history used to rank each job title with likelihood of exposure to TCE (5 categories). Work histories were linked with JEM to classify workers as ever/never exposed and into 4 exposure groups but number of workers in each subgroup is unclear. Not calendar-year specific. |
| | Missing exposure data for 54 workers |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| NR | Source of vital status data NR; nosologist coded cause of death on death certificates not otherwise coded, using ICD version in use at time of death.<br>Incidence cases of NHL: Kentucky cancer registry |

| **Yiin *et al.* 2009** | |
|---|---|
| **Related References** | **Geographic Location** |
| None | Tennessee, US |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: hired before 1985, employed 30 days or longer.<br>Total cohort: 47,941 Uranium enrichment (gaseous diffusion) plant workers; TCE-exposed NR<br>Cases: 98 multiple myeloma deaths<br>Follow-up: 1985 - 1998<br>Loss to follow-up: NR | 419 controls (219 deaths) 5:1 controls to cases, matched on age, sex, race<br>Selected by incidence density sampling from risk set of all workers at risk of mortality from multiple myeloma; |
| | ***All-cause and all-cancer mortality/incidence*** |
| | Not applicable |
| **Study Design and Analytical Methods/ Control for Confounding** | |
| Nested case-control mortality study.<br>Conditional logistic regression (univariate and and multivariate analyses focusing on ionizing radiation dose adjusted for external radiation, X-rays, and TCE, mercury, and nickel as potential confounders; 15 year lagging. Also conducted separate analyses for TCE and other chemicals. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| Historical area air monitoring data available but inadequate information (e.g. building work location) to link to employees.<br>Estimated cumulative exposure levels to TCE (mean); 183.8 cases, and 113.4 controls (units not reported). | Exposure to TCE, mercury, nickel: modified job-exposure matrix using site records to identify exposure activities for TCE and other chemicals. Mean air levels estimated for each activity by decade. Activities associated with dept. based on workforce information. |
| Internal and external radiation dose estimated: average cumulative exposure = 0.026 mGy cases, 0.012 mGy controls<br>Other exposures: Mercury and nickel | Cumulative exposure scores (ranks) based on estimated exposure level for activity, employment duration (days) in dept. associated with exposure activity, and fraction of the day in exposure activity work area based on expert assessment (industrial hygienists). |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| NR | Source of mortality data NR<br>ICD-8 203; underlying and contributory cause of death |

| **Ritz 1999** | |
|---|---|
| **Related References** | **Geographic Location** |
| None | Ohio (USA) |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: All white males employed from 1951 and 1972 for ≥ 3 months with chemical exposure data and monitoring data for radiation (N = 3,814)<br>Exposed cohort: 2,971 (of 3,814 eligible) white male uranium processing workers<br>Follow-up: 1951–1989; mean length: 31.5 years<br>Loss to follow-up: NR | U.S. population; NIOSH-CORPS reference data (Zahm *et al.* 1992)<br>***All-cause and all-cancer mortality/incidence***<br>Total cohort only: mortality (SMR)<br>All-cause mortality: 0.84 (0.79–0.90); 1,045 deaths<br>All-cancer mortality: 1.10 (0.99–1.23) 328 deaths |
| **Study Design and Analytical Methods/Control for Confounding** | |
| Historical cohort mortality study; external (SMR) adjusted for age and calendar year. Internal (risk-set) analyses by level (category) and duration of exposure in l5 lagged and unlagged analyses using conditional Cox proportional hazards modeling matching by age to index case age, and adjusting for time since first hired, pay status (surrogate for SES), using time since first hired (surrogate for healthy worker survival effects, radiation dose and exposure to other chemicals). | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| No quantitative exposure assessment<br>Only 6% of cohort had moderate exposure and no workers had heavy exposure.<br>Co-exposures: cutting fluids, kerosene, carbon, (approx. 50% TCE-exposed workers exposed to cutting fluids, some to kerosene or carbon.) and external and internal radiation (badge dosimetry, urine, area monitoring) (mainly uranium and thorium isotopes)<br>287 workers excluded because of missing radiation exposure data. | JEM based on in-plant industrial hygiene assessment by hygienists, veteran workers, engineers in 1970s and 1980s to estimate probability of chemical exposures by job title and department.<br>Workers classified by estimated exposure level categories (light, moderate, heavy) and exposure duration. |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| Smoking history available for approx. 20% subsample of workers from 1968; used to indirectly estimate smoking prevalence by exposure status among workforce. | Social Security Administration (prior to 1979)<br>National Death Index<br>Internal analysis: ICD-9 codes |

| **Silver *et al.* 2014** | |
|---|---|
| **Related References** | **Geographic Location** |
| Fleming *et al.* 2013, Clapp and Hoffman 2008 | New York State, US |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: Workers with 91 or more days of employment 1969 – 2001; contract and foreign national workers (or without SSN) excluded<br>Exposed cohort: 3113 ever exposed to TCE<br>Total cohort: 34,494 (24,037 men, 10,457 women) employed a microelectronics business facility; hourly workers -=15447 M and 8934W.<br>Follow-up: 1969 – 2009; average 25.7 years (total cohort)<br>Loss to follow-up: NR | US mortality rates, NY State mortality rates (excluding New York City)<br>***All-cause and all-cancer mortality/incidence***<br>All-cause mortality: SMR (all hourly workers)<br>M: 0.76 (0.73-0.78) 3571; F: 0.73 (0.68-0.79) 823<br>All-cancer mortality: SMR (all hourly workers)<br>M: 0.83 (0.78-0.88) 1005; F: 0.86 (0.76-0.96) 291 |
| **Study Design and Analytical Methods/ Control for Confounding** | |
| Historical cohort mortality study. External analyses: SMR for all workers only calculated using NIOSH life table analysis system (race, sex, and calendar year) and Poisson distribution.<br>Internal (conditional forward Cox regression) analyses for workers exposed to TCE, tetrachloroethylene, methylene chloride, lead, or classes of agents, by cumulative probability of exposure or duration of exposure; analyses controlled for age in risk set selection. Univariate models included sex, paycode and chemical exposure. Multivariate models included those variables with significant findings in univariate models and birth cohort, time since last exposure (healthy worker survivor), employment duration prior to 1966, and hire era. No control for other potential confounders. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| Trichloroethylene was used from 1969 to 1987. Some sampling of levels available from 1980 to 1984 which was not thought to be representative of earlier time periods (levels NR).<br>Lead, tetrachloroethylene, methylene chloride, methyl chloroform, classes of chlorinated and other hydrocarbons, acids, bases used in plant. Information on co-exposures not reported. | Company industrial hygiene monitoring and related records, veteran employees' information and expert assessment used to identify dept. in which chemical agents were used over time.<br>Individual work history linked to dept.-year exposure matrix. Cumulative exposure score for each worker assigned by (i) extent of chemical use based on depart. (none, intermittent, routine), (ii) employment duration in dept. (iii) potential of exposure based on broad job category within department (processing vs. clerical or administrative), and (iv) chemical usage in dept.-during time period. |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| NR | State vital records or NDI; ICD code in use at time of death |

| **Henschler *et al.* 1995** | |
|---|---|
| **Related References** | **Geographic Location** |
| None | Germany |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: All workers exposed to TCE ≥ 1 year 1956–1975<br>Exposed cohort: 169 (of eligible 183) male cardboard manufacturing workers exposed to TCE men (5,188 person-yr)<br>Total cohort: 169 TCE exposed and 190 unexposed workers (6,100 person-yr); Median age 59 years for exposed and 62 for unexposed<br>Follow-up: 1956–1992; Average follow-up greater than 30 years for both exposed and unexposed; (Note: 2 exposed cases identified outside follow-up period, included in additional analysis)<br>Loss to follow-up: 7.7% (169 of 183 analyzed) includes refusals, unable to participate, loss to follow-up) for exposed cohort; NR for unexposed workers. | External analysis: local population (mortality) Danish and German Democratic Republic cancer rates (renal-cell cancer incidence)<br>Internal analysis: 190 workers in factory not exposed to TCE matched as group for age and physical activity; excluding office workers |
| | ***All-cause and all-cancer mortality/incidence*** |
| | All-cause mortality<br>Exposed: SMR = 0.68 (0.48–0.93); 50 deaths<br>Unexposed: SMR = 1.03 (0.77–1.35); 52 deaths<br>All-cancer mortality:<br>Exposed: SMR = 0.96 (0.51–1.67); 15 deaths<br>Unexposed: SMR =1.16 (0.65–1.91): 15 deaths<br>All cause and all cancer incidence not reported |
| **Study Design and Analytical Methods/Control for Confounding** | |
| Historical cohort mortality and incidence study (renal cancer); external and internal analysis (Mantel-Haenszel test statistics ignoring age stratification) | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| No quantitative air levels or urine measurements of TCE. Subanaesthetic symptoms usually associated with TCE concentrations above 37 ppm; Cherrie *et al.* (2001) estimate peak exposures were > 2000 ppm with average long-term exposure 10 to 225 ppm. In cold degreasing process, estimated average chronic exposure was ~100 ppm.<br>Long exposure periods (17.8 months)<br>TCE used from 1956–1975.<br>Cardboard machine area cleaned with TCE every 2 weeks for 4–5 hour, open system, and poor ventilation and presumed high exposure, odor recorded and sweet taste in mouth and adverse effects (headache, dizziness, vertigo).<br>TCE used in locksmith's and electrical workshop for degreasing metal parts and involved "continuous exposure" at lower levels than in cardboard machine area without personal protective equipment.<br>Other solvents, including halogenated and non-halogenated hydrocarbons, pentachlorophenol, 1,1,1-trichloroethane, tetrachloroethane used in "negligible" | Walk-through survey and employee interview used to identify three locations of exposure: cardboard machine area, locksmith's area and electrical workshop areas. TCE also used for general cleaning purpose to clean floors, clothes, and hands.<br>Individual employee questionnaire on job history, tasks, materials used. |

| **Henschler *et al.* 1995** | |
|---|---|
| amounts compared to TCE from 1967. | |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| Smoking, alcohol, intake diuretics, body weight, height, blood pressure (individual employee questionnaire) | Mortality: vital status from medical, personnel and pension depts, relatives' interview; cause of death from hospital or physician records, not based on death certificates (ICD-9).<br>Incidence: hospital and physician records; Physical examination by abdominal sonography; Renal tumors histologically confirmed. |

| **Greenland *et al.* 1994** | |
|---|---|
| **Related References** | **Geographic Location** |
| None | Massachusetts (USA) |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria ("cohort"): 1,821 white males at electrical manufacturing plant (transformers, plastics, ordnance systems) employed before 1984, terminated working after 1946, 21–90 years old, date of death benefit claims between 1969–1984 with insurance death records and exposure information; (total # NR)<br>Cases: 512 cancer deaths, 15 NHL and Hodgkin lymphoma combined, 12 kidney, 9 liver cancers<br>Follow-up: Workers who died between 1969–1984<br>Loss to follow-up: NR | Controls: 1,202 non-cancer deaths "unrelated to exposures under study" (primarily circulatory (78%), respiratory (10%), injury (6%), and other causes (6%) |
| | ***All-cause and all-cancer mortality/incidence*** |
| | All-cause mortality: SMR: NR |
| **Study Design and Analytical Methods/ Control for Confounding** | |
| Nested case-control analysis among workers at a plant with death benefit claims<br>Separate analyses by specific exposure for cancers with more than 8 cases that adjusted for age and date of death, and covariates (related to employment that changed the risk estimate by > 20%); No multivariate control for potential confounding from co-exposures or lifestyle habits | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| No industrial hygiene data<br>TCE used 1930–1977<br>NAS (2006) noted low likelihood of TCE potential exposure among subjects.<br>30 chemicals with carcinogenic potential identified; 6 selected with large volume or number of jobs in addition to TCE: Pyranol (PCBs and trichlorobenzene), benzene, other solvents, machining fluids, asbestos, resins (mostly phenol formaldehyde, polyvinyl resin) | Interviews with employees and combination of job titles and department and building used by industrial hygienist to construct qualitative JEM for seven exposures. JEM combined with work history to assign exposure to TCE to each individual (ever/never exposure). |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| NR | Death records in company pensions system; subset of death certificate diagnoses for cancers with less than 90% confirmation rate verified using hospital records.<br>ICDA-8 (combined NHL and Hodgkin lymphomas only) |

| **Wilcosky *et al.* 1984** | |
|---|---|
| **Related References** | **Geographic Location** |
| Arp *et al.* 1983, McMichael *et al.* 1976, McMichael *et al.* 1974 | Ohio (USA) |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria (exposed cohort): 6,678 current and retired rubber manufacturing workers 40–84 years old in 1964 exposed to selected solvents > 1 year.<br>Cases: Deaths for cancers in excess in cohort study (McMichael *et al.* 1976); NHL (ICD 200): stomach (30), prostate (333), lymphosarcoma and reticulum cell sarcoma (9) and lymphatic leukemia (10)<br>Follow-up: 1964–1974<br>Loss to follow-up: NR | Controls: 20% age-stratified sample of cohort<br>***All-cause and all-cancer mortality/incidence***<br>N/A<br>All-cancer mortality/incidence: N/A<br>SMR: N/A<br>SIR: N/A |
| **Study Design and Analytical Methods/Control for Confounding** | |
| Nested case-control study; separate age-adjusted analyses stratified by race for any vs. no exposure to each of 20+ solvents; No adjustment for potential confounding from co-exposure or lifestyle factors | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| No quantitative exposure assessment or industrial hygiene measurements available<br>Co-exposures: 25 solvents identified in different processes | Review of product specifications for solvents authorized for use in specified processes and operations by calendar year used to develop JEM. It is not known whether the solvents were actually used. Work histories constructed from job title/dept. (company records) and linked to JEM.<br>Exposure defined as ever/never work in a process area where one or more of 25 solvents (including TCE) authorized for use. |
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| NR | Death certificates; ICD-8 (coded by nosologist) |

| **Bove *et al.* 2014** | |
|---|---|
| **Related References** | **Geographic Location** |
| None | Camp Lejeune, NC, Camp Pendleton, CA (USA) |
| **Population Characteristics** | |
| ***Exposed Cohort and Ascertainment*** | ***Reference Population*** |
| Eligibility criteria: All Marine and Navy personnel on active duty and stationed at Camp Lejeune between April 1975–December 1985<br>Exposed cohort: 154,932 M+F stationed at Camp Lejeune; 97% under the age of 55 and less than 6% had died by the end of the study.<br>Follow-up: 1979–2008<br>Loss to follow-up: 1.3% Camp Lejeune, 1.5% Camp Pendleton | Eligibility criteria: All Marine and Navy personnel on active duty April 1975–December 1985 and stationed at Camp Pendleton, CA any time during this period.<br>"Unexposed cohort": Camp Pendleton<br>***All-cause and all-cancer mortality/incidence***<br>All-cause mortality: SMR: 0.83 (0.81–0.84); 8,964<br>All-cancer mortality: SMR: 0.85 (0.80–0.90); 1,078 |
| **Study Design and Analytical Methods/Control for Confounding** | |
| Retrospective cohort study using ecological exposure assessment; Two types of analyses:<br>Evaluation of contaminated water comparing the exposed (Camp Lejeune) and non-exposed population (Camp Pendleton): Hazard Ratio using Cox extended regression models with age and time as a variable that compared mortality rates (SMR) between the 2 cohorts. SMR were calculated using Life Table Analysis System that adjusted for age, sex, and calendar period and accounted for latency.<br>Evaluation of individual water contaminants within the Camp Lejeune cohort: Evaluation of exposure response relationships of cumulative exposure (untransformed, log10 transformed and continuous) for each contaminant using Cox extended regression adjusting for age, and accounting for latency. Other analyses included duration of exposure and restricted cubic spline.<br>Models were adjusted for sex, race, and education. Other variables considered in the model (did not change risk estimates by 10%) include marital status, birth cohort, date of death, duty occupation. Smoking was considered by subtracting the log HR among smoking-related diseases from the log HR of disease of interest. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-Exposures*** | ***Exposure Assessment*** |
| Two of the eight drinking water systems at Camp Lejeune were contaminated with solvents based on sampling data from 1980 to 1984.<br>Tarawa Terrace (TT): Contaminated by off-base dry-cleaning business: Primarily contaminant PCE<br>Estimated mean level (µg/L): TCE 3.1; PCE 75.7<br>Hadnot Point (HP): Contaminated by on-base sources (underground storage tank, industrial spills): Primarily contaminant TCE (up to 1,400 µg/L)<br>Estimated mean levels (µg/L): TCE: 358.7, PCE 14.7, Vinyl Chloride: 24, Benzene: 5.4<br>TCE and PCE highly correlated with each other<br>Overall cumulative exposure (µg/L months) for TCE, mean = 6,369, median = 5,289, 20% were exposed to levels between 7,700 and 39,745. Potential daily exposure from HP could be as high as 3.6 mg/day (showering and drinking water). | TCE and other contaminant levels: Historical reconstruction using historical samples, and modeling based on water fate and distribution modeling.<br>TT water system served on-base houses and HP mainly served bachelor quarters.<br>Each individual at Camp Lejeune was assigned an estimated average contaminant concentration in the drinking water system serving their residence for the period of their residence. Several sources were used to determine the individual residence. Probability and matching were used to link married cohort members to base housing.<br>Cumulative exposure (ug/L-months) was calculated using the estimated monthly average contaminants, in the water serving the individual residence and occupancy dates. No information on water consumption. |

| **Bove *et al.* 2014** | |
|---|---|
| ***Assessment: Other Exposures*** | ***Disease Assessment*** |
| Tetrachloroethylene<br>1,2-Dichloroethylene<br>Vinyl chloride | Multiple sources (such as Social Security, Death Master File, National Death Index) used to determine vital status. |

**Table D-2. Study descriptions and methodologies: case-control studies of trichloroethylene exposure and kidney cancer.**

| **Brüning *et al.* 2003** | |
|---|---|
| **Related References** | **Geographic Location** |
| (Vamvakas *et al.* 1998) (same area but no overlap) | Arnsberg and 30 km surrounding area, Germany |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 134 RCC (113 incident, 21 deceased) | Referents: 401 |
| Case eligibility criteria: People with nephrectomy 1992 to 2000 from urology department serving the area (1 hospital) | Referent eligibility criteria: People in hospital for surgery or geriatrics without dementia or diagnosis of cancer |
| Participation rate: 83% cases, controls NR | Matching criteria: sex, age (5 yr) 3:1 ratio (frequency-matched) |
| **Study Design and Analytical Methods** | |
| Hospital-based: Conditional logistic regression for three types of exposure assessments, and for duration and time since first and last exposure for self-assessed exposure<br>Adjusted for sex, age (from matching), and smoking | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| Levels NR but estimated to be 400 to 600 ppm during hot dipping and > 100 ppm overall (Cherrie *et al.* 2001).<br>Arnsberg area is a small geographical area with large number of companies in the metal process industries. TCE use was widespread and only two solvents were used in the industry. Exposure prevalence among controls varied by exposure assessment: Very high (for jobs associated with TCE exposure) using CAREX (80%) to 10% using self-reported exposure.<br>Regulatory measures were enforced starting in the 1980's. | Interview questionnaire (as used by Vamvakas *et al.* 1998) (approx. 16% proxies for deceased cases used, no proxies for controls); No information on whether interviewers blinded to case status<br>Exposure assessed via three methods: (1) job/industry (ever and longest held) associated with exposure using CAREX database (which is based on expert assessment) and applying JEM, (2) agent-specific (not specific for TCE) using British JEM (duration, probability, and intensity) for jobs held for > 1 year, (3) self-assessed frequency and duration of exposure to TCE and narcotic symptoms (comparable to Vamvakas *et al.* (1998) exposure assessment). |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Questionnaire/interview: Smoking, BMI, analgesics use. Cases and controls similar with respect to obesity (BMI > 30), analgesics use, sex, and age. | Histologically confirmed |

| **Vamvakas *et al.* 1998** | |
|---|---|
| **Related References** | **Geographic Location** |
| None (same area but no overlap with Brüning *et al.* 2003) | Arnsberg (city), Germany |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 58 RCC | Referents: 84 |
| Case eligibility criteria: People with nephrectomy between 1987 and 1992 at a county hospital | Referent eligibility criteria: Accident patients at 3 nearby hospitals (not the same hospital as cases) in 1993 without kidney cancer (sonograph) |
| Participation rate: 87% cases, 75% controls | Matching criteria: None |
| **Study Design and Analytical Methods** | |
| Hospital-based: Multivariate logistic regression by exposure category (no, low, medium, high). Stratified by age analysis (Mantel-Haenszel). Adjusted for age, gender, smoking, blood pressure, and diuretic intake. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| Levels NR but estimated to be 400 to 600 ppm during hot dipping and > 100 ppm overall (Cherrie *et al.* 2001).<br>Arnsberg area is a small geographical area with a large number of companies doing metal and electronics work. TCE use was widespread and one of only two solvents (other was carbon tetrachloride) used in the industry.<br>Most subjects were involved in metal degreasing, without personal protective equipment. According to walkthrough surveys and interviews with employees and health professionals, degreasing procedures were done in open conditions above 60°C, and TCE was used to clean arms and hands, cloths, floors, etc. | Interview using structured questionnaire (not blinded) by physician on occupational history and exposure to multiple substances with subject or proxy. Follow-up info on exposure to TCE and tetrachloroethylene; Detailed info obtained from employer liability insurance.<br>Exposure level based on combination of exposure duration and frequency and severity of acute prenarcotic symptoms. |
| ***Assessment of potential confounders c*** | ***Disease Assessment*** |
| Interview: smoking, alcohol consumption, BMI, blood pressure, diuretics intake, and exposure to other known carcinogens – asbestos, cadmium, gasoline and/or other petroleum products. Cases and controls similar with respect to alcohol consumption, BMI, percentage of males | Histologically re-confirmed (double blind). All cases arose from tubule epithelium. |

| **Pesch *et al.* 2000a** | |
|---|---|
| **Related References** | **Geographic Location** |
| Pesch *et al.* 2000b | Germany |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 935 RCC (570 males and 375 females) | Referents: 4,298 |
| Case eligibility criteria: German nationals (no age limit) from large hospitals 1990–1995 | Referent eligibility criteria: German nationals randomly selected from local residency registers |
| Participation rate: 88% cases, 71% controls | Matching criteria: Region, sex, age (5 yr) (1:4) |
| **Study Design and Analytical Methods** | |
| Population-based: Conditional logistic regression adjusting for smoking (pack-years) and matching variables (region, sex, age) for exposure index (medium, high, substantial) using the low-exposure group as the reference. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| NR; no information on the types of job exposed to TCE<br>Prevalence of substantial TCE exposure was low among cases (4% to 10%) and varied by type of JEM.<br>Includes the Arnsberg and other regions; NAS (2006) estimated that most subjects had minimal contact with TCE averaging concentration of 10 ppm or less. | Interview using structured questionnaires; Exposure assessed using two JEM (British, German) and a job task-exposure matrix (JTEM), which provided an expert assessment of probability of exposure and intensity to a given agent.<br>Life-time exposure (exposure index) was the product of probability, duration and intensity of exposure summarized across jobs for both JEM and JTEM. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Questionnaire/interview: various measures of smoking, socioeconomic status, analgesics use, and BMI. SES was an independent risk factor for kidney cancer among women. Cases and controls did not differ in BMI, education, age, region, and smoking status and analgesics use. | Histologically (95%) or sonographically (5%) confirmed |

| **Moore *et al.* 2010** | |
|---|---|
| **Related References** | **Geographic Location** |
| Brennan *et al.* 2008, Hung *et al.* 2007 | Central and Eastern Europe (7 centers, 4 countries) |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 1,097 RCC | Referents: 1,476 |
| Case eligibility criteria: Cases at participating hospitals 1999–2003; living in area for at least 1 yr. | Referent eligibility criteria: Inpatients or outpatients with non tobacco-related conditions at same hospitals without cancer or genitourinary disorders (except benign prostate hyperplasia) |
| Participation rate: NR | Matching criteria: age, sex, study center |
| **Study Design and Analytical Methods** | |
| Hospital-based: Unconditional logistic regression evaluating ever and categories of different exposure metrics: duration (hr, yr), average intensity and cumulative for all subjects and for subjects with high confidence exposure assessment; Lagged analysis: Analyses were lagged and controlled for sex, age, study center; residence, smoking BMI, and history of hypertension considered but did not affect risk estimate. Analysis by GST genotypes. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| Chlorinated and other solvents<br>Intensity and prevalence of occupational exposures have been higher in central and eastern Europe than other industrial areas.<br>Estimated median exposure and interquartile range (IQR)<br>Cumulative exposure (ppm-yr): IQR = 0.77–2.87 for controls, median = 1.95; IQR = 0.83–7.25 for cases<br>Average intensity (ppm): IQR = 0.08–0.16 for controls, median = 0.08; IQR = 0.08–0.44 for cases | In-person interviews using structured and occupational specific and detailed questionnaires (e.g., tasks, working environment time on each task) for lifetime jobs held at least 1 year. Expert assessment (blinded) by exposure assessment teams (with knowledge of plants in their study area) coded jobs for exposure to specific agent and assessed the frequency, confidence, intensity of exposure. Cumulative exposure defined as product of intensity, duration, and frequency of exposure. Confidence = expected percent of workers exposed in a given job (possible, probable, definite).<br>Assessment of organic exposures were reevaluated at a later date blinded to the previous assessment and disease status. For TCE, the agreement was 83% in 1 country and 100% in 2 countries (not done in the 4th country because of unlikely exposure to TCE). |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Interviews: Lifestyle factors, especially tobacco consumption, anthropometric measures 1 year before diagnosis, and personal and familial medical history | Histologically confirmed by study experts using standard confirmation and disease classification. ICD-0-2, Code C.64 |

| **Charbotel *et al.* 2006, Charbotel *et al.* 2009** | |
|---|---|
| **Related References** | **Geographic Location** |
| Fevotte *et al.* 2006 | Arve valley, France |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 86 cases RCC (19 deceased), 67% men | Referents: 326 (7 deceased); 70% men |
| Case eligibility criteria: Deceased or living identified retrospectively from medical (urology and oncology) practitioners 1993–2003 | Referent eligibility criteria: Patients (without kidney cancer or disease or urinary tract cancer) randomly selected from the same practitioners as cases |
| Participation rate: Cases 74%; controls 78%; follow-up questionnaire sent to non-participants | Matching criteria: Age, gender (matched 4:1) |
| **Study Design and Analytical Methods** | |
| Hospital-based: Multivariate analysis using variables with 10% differences (4 classes of smoking and 3 classes of BMI) between cases and controls; Analysis performed for ever, cumulative exposure, and combined cumulative & peak exposure. Additional analyses for higher TWA exposure thresholds (35, 50 and 75 ppm) and for and co-exposure to cutting, petroleum and/or other mineral oils (Charbotel *et al.* 2009); Sensitivity analysis to assess sources of misclassification (proxy, older patients, jobs with high confidence) | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| Region has high prevalence and high degree of exposure to TCE because of its use as a degreaser in the widespread screw-cutting industry.<br>Estimated TCE concentrations associated with quantitative ranking: low = 5–150 ppm-yr; medium = 155–335 ppm-yr; high = > 335 ppm-yr. Among controls the median exposure for low, medium and high categories = 60, 252, and 630 ppm, respectively. Among cases median exposure = 30, 300, and 885 ppm, respectively.<br><br>Co-exposure to cutting oils, petroleum oils, and other mineral oils | Telephone interviews using medical and occupational questionnaires, with subject or next of kin, focusing on screw-cutting industry (TCE used); Exposure to TCE and other substances assigned using expert and task exposure matrix (JTEM) for screw-cutting industry. Exposure to TCE was semi-quantitative; ranked categories. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Questionnaire: familial kidney disease and medical history, such as kidney stones, infection, chronic dialysis, hypertension and use of drugs (anti-hypertensive drugs, diuretics, and analgesics); BMI, lifestyle considered smoking habits (pack-years) and coffee consumption. No significant differences in most of these characteristics were found in univariate analysis except for BMI and smoking. | Mainz classification; histologically confirmed |

| **Christensen *et al.* 2013** | |
|---|---|
| **Related References** | **Geographic Location** |
| Siemiatycki 1991 | Montreal Canada |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 177 RCC; 48 liver cancer | Referents: 533 population controls; 1,999 cancer controls for kidney cancer and 1,834 for liver cancer |
| Case eligibility criteria: Male Canadian citizens, ages 35–70, incident cases 1979–1985 identified from 18 major hospitals | Referent eligibility criteria: Population controls randomly selected from electoral records. Cancer controls - no more than 20% of one cancer, excluded lung and contiguous sites for the index cancer; Specific cancers not reported. |
| Participation rate: 82% cases, 72% controls (total study population) | Matching criteria: Age, sex |
| **Study Design and Analytical Methods** | |
| Hospital and population-based: Unconditional logistic regression using each type of control and pooled (weighted) controls and controlling for SES, ethnicity, interview type (self or proxy), smoking, coffee, alcohol; Risk calculated for any and substantial exposure. Exposures occurring 5 years before diagnosis were excluded. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| NR<br>Exposure prevalence to TCE: ≤ 2% of cancer controls or population controls had substantial exposure and 3% had any exposure.<br>Occupations considered to have the highest exposure were mechanics and repairmen, metal machining occupations, electrical and electronics and metal shaping and formulation. | In person interviews (with subject or proxy) obtaining detailed information on lifetime occupational history and duration in 13 specific occupations/industries and seven jobs with specific exposures. Proxy interviews were done for 12% of population controls and 14% of kidney cancer cases.<br>Expert (team) assigned exposures based on reported job histories for close to 300 substances and rated the confidence, frequency, and intensity of each exposure. Assessor blinded to case-control status. Substantial exposure based on duration, frequency, confidence, and concentration. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Questionnaire/interviews: SES, ethnicity, interview type (self or proxy), and lifestyle factors (such as smoking, alcohol consumption) | Histologically confirmed |

| **Dosemeci *et al.* 1999** | |
|---|---|
| **Related References** | **Geographic Location** |
| Chow *et al.* 1994 | Minnesota (USA) |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 438 (273 men, 165 women) | Referents: 687 (462 men, 225 women) |
| Case eligibility criteria: Newly diagnosed white cases RCC 1988 to 1990 from state cancer registry; deceased cases excluded. | Referent eligibility criteria: Randomly selected (random digit dialing) (ages 20 to 64) or systematic selection from health care financing agency (ages 65 to 85 yr old) white controls. |
| Participation rate: 87% cases, 86% controls; Occupational analysis with complete personal interviews: 64% cases; 97% controls | Matching criteria: Age and sex stratified |
| **Study Design and Analytical Methods** | |
| Population-based: Logistic regression controlling for age, smoking, hypertension status, use of diuretic or anti-hypertension drugs, BMI; Risk for ever-exposed reported separately for men and women. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| NR<br>Exposure prevalence to TCE among controls was 10%. | In-person interview with questionnaire for usual and most recent occupation, employment duration and duration for industries with specific exposure; Exposure assigned using JEM which linked occupation/industry code to exposure to chemicals (TCE and other chlorinated hydrocarbons). Interviewer blinded to case/control status and proxy interviews excluded from analysis. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Questionnaire/interview: demographic and ethnic variables, residential history, smoking habits, medical history, and drug use | Histologically confirmed |

**Table D-3. Study descriptions and methodologies: case-control studies of trichloroethylene exposure and NHL and related subtypes.**

| **Christensen *et al.* 2013** | |
|---|---|
| **Related References** | **Geographic Location** |
| Siemiatycki 1991 | Montreal, Canada |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 215 NHL | Referents: 2,341 cancer controls, 533 population controls |
| Case eligibility criteria: Male Canadian citizens, ages 35–70, incident cases 1979–1985 identified from 18 major hospitals | Referent eligibility criteria: Population controls randomly selected from electoral records; cancer controls - no more than 20% of one cancer, excluded lung and contiguous sites for the index cancer; Specific cancers not reported. |
| Participation rate: 82% total cancer cases (also used as cancer controls), 72% total population controls (used for analysis of 11 cancer sites) | Matching criteria: Age, sex |
| **Study Design and Analytical Methods** | |
| Hospital and population-based: Unconditional logistic regression using each type of control and pooled (weighted) controls controlling for age, ethnicity, SES, interview type (self or proxy); Risk calculated for any and substantial exposure. Exposures occurring 5 years before diagnosis were excluded. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| Levels NR<br>Exposure prevalence to TCE very rare; ≤ 2% of cancer controls or population controls had substantial exposure and 3% had any exposure.<br>Occupations considered to have the highest exposure were mechanics and repairmen, metal machining occupations, electrical and electronics and metal shaping and formulation. | In-person interviews (with subject or proxy) obtaining detailed information on lifetime occupational history and duration in 13 specific occupations/industries and seven jobs with specific exposures; Proxy interviews were done for 12% of population controls and 21.9% of cases.<br>Expert assessment (team) translated jobs into potential exposure for close to 300 substances and rated the confidence, frequency, and intensity for each exposure. Assessor blinded to case-control status. Substantial exposure based on duration, frequency, confidence, and concentration |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Questionnaire/interviews: SES, ethnicity, interview type (self or proxy), and lifestyle factors (such as smoking, alcohol consumption) | Histologically confirmed |

| **Cocco *et al.* 2013a** | |
|---|---|
| **Related References** | **Geographic Location** |
| Includes populations reported by Cocco *et al.* 2010, Miligi *et al.* 2006, Orsi *et al.* 2010, Purdue *et al.* 2011a | Multiple centers Europe, U.S. SEER regions |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 3,788 | Referents: 4,279 |
| Study eligibility criteria:<br>Study selected had (1) complete occupational history for all study participants, (2) expert exposure assessment to TCE, (3) incident NHL cases, and (4) histological information available for each case. | Matching criteria: Age and sex (frequency or individually) except MIS, selected to represent age and sex distribution in general population.<br>Participation rate: see individual studies. |
| **Study Design and Analytical Methods** | |
| Pooled analysis of four cased control studies (EPILYMPH, NCI-SEER, ENGELA, MIS): Risks calculated for ever, probability, intensity, frequency, and duration of exposure, and intensity, duration, and frequency among high probability subjects and all subjects using unexposed as reference group and calculating linear trend test. Unconditional logistic regression was used for NHL and NHL subtypes. Polytomous regression analysis was used for NHL adjusting for age, gender, and study. Fisher statistics using Bonferroni correction were conducted to test chance probability of trends for 4 exposure metrics. Sensitivity analysis also conducted; excluded subjects exposed to benzene. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| 9% of subjects ever exposed to TCE and 1% had high probability of exposure.<br>No assessment of exposure to other solvents but benzene not shown to be a confounder. | Expert assessment of questionnaire data, workplace inspection, industrial hygiene report and experience used to assign scores of intensity (4-point scale related to OSHA PEL), frequency (4-point scale on work time in contact with agent), duration, and probability of exposure (harmonized using *a priori* JEM). The objective was to harmonize the exposure assessment from the four studies. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| NR in pooled analysis | NHL incidence: Interlymph Consortium classification |

| **Cocco *et al.* 2010** | |
|---|---|
| **Related References** | **Geographic Location** |
| Besson *et al.* 2006 (Same EPILYMPH study population – association of alcohol and smoking on NHL risk)<br>Included in pooled InterLymph analysis: Cocco *et al.* 2013a | Multiple centers in Europe (Czech Republic, France, German, Ireland, Spain) |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 2,348 lymphoma (analysis for histologic subtypes of B-NHL including multiple myeloma) | Referents: 2,462 |
| Case eligibility criteria: Consecutive adult lymphoma at participating centers 1998–2004 | Referent eligibility criteria: Germany & Italy: Randomly selected from population; Others: Hospital controls (diagnoses other than cancer, infectious and immunodeficiency diseases) |
| Participation rate: Cases 88%; population controls - 52%; hospital controls 81% | Matching criteria: Age (5 yr), sex, residence |
| **Study Design and Analytical Methods** | |
| Multi-center population and hospital-based (EPILYMPH Study): Unconditional logistic regression adjusting for age, education and center using unexposed to any solvent as the reference group and calculated for ever exposed, combined confidence, intensity and frequency, and cumulative exposure (among subject with exposure assessed as having high degree of confidence) for histologic subtypes of NHL; Bonferroni correction for multiple comparisons. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| NR<br>TCE exposure prevalence is low: For B-cell lymphoma, 5% among controls with high confidence of exposure, 2% had high cumulative exposure<br>Approximately one third of chlorinated aliphatic solvent-exposed workers had concurrent exposure to benzene, toluene, or xylene. | In-person interviews with structured questionnaires: Detailed lifetime occupational history for jobs held more than one year; Detailed questionnaire on tasks, processes, and personal protective equipment for exposures of *a priori* concern<br>Expert review of questionnaire and assessment of 43 agents according to confidence, intensity and frequency; Cumulative exposure scores were calculated based on intensity, duration, and frequency. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Questionnaire/interview on social and demographic variables, lifestyle, health history | 2001 WHO Classification, 20% centrally reviewed by pathologist, B-NHL and major subtypes and Hodgkin lymphoma including multiple myeloma. |

| **Purdue *et al.* 2011a** | |
|---|---|
| **Related References** | **Geographic Location** |
| Chatterjee *et al.* 2004, Schenk *et al.* 2009; Included in InterLymph (Cocco *et al.* 2013a) | 4 SEER regions (Iowa, Los Angeles County, CA, Seattle, WA, Detroit, MI [USA]) |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 1,189 NHL | Referents: 1,057 |
| Case eligibility criteria: Ages 20–74, diagnosed 1988–2000; without known HIV infection | Referent eligibility criteria: Randomly selected from registry area by random digit dialing (< 65 yrs old) or in Medicare files (65–74); no previous diagnosis of NHL. |
| Participation rate: Cases 76%; controls 52% | Matching criteria: Age, sex, race and SEER area |
| **Study Design and Analytical Methods** | |
| Population-based: Unconditional logistic regression, adjusting for age, sex, race, and SEER region, used to calculate RR for each exposure category (probability, duration, average weekly, cumulative exposure, average intensity); Trend calculated as continuous variable. Analysis also for TCE exposure (probability, average weekly and cumulative exposure) and NHL histological subtypes; Sensitivity analysis for latency, interviewing variable, and unemployment | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| Not reported but estimated TCE exposure for the highest exposure category were > 234,000 ppm-hr cumulative exposure (0.7% prevalence in controls) cumulative exposure and > 99 ppm average intensity of exposure (2.3% prevalence among controls). | Interview on detailed and complete occupational history of jobs held for 12 months or greater since age 16; For selected occupation (solvent and TCE exposure) industry-specific interview module were given asking for detailed information on job, industry, tasks (including time and frequency), work practices, protection.<br>Expert and systematic assessment of probability, frequency and intensity of TCE for each job using questionnaire data, literature review of US TCE industry, occupational history, exposure metrics and decade-specific reported measurements for specific tasks. Job-specific estimates summed across all jobs used to develop metric of exposure (cumulative exposure average weekly, average exposure intensity) to TCE for each individual. Expert assessment was blinded to disease status. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| In general demographic characteristics were similar for cases and controls. | Histologically confirmed NHL subtypes according to the ICD for Oncology (1990) |

| **Miligi *et al.* 2006** | |
|---|---|
| **Related References** | **Geographic Location** |
| Include in InterLymph (Cocco *et al.* 2013a); same population base as Costantini *et al.* 2008 | Multi-center, Italy (analysis of 8 regions) |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 1,428 NHL (1,135 analyzed) | Referents: 1,528 (1,246 analyzed) |
| Case eligibility criteria: Newly diagnosed cases in 1991–1993, men and women 20–74 yr | Referent eligibility criteria: Random sample from population |
| Participation rate: Cases 83%, 73% controls | Matching criteria: age, sex, residence |
| **Study Design and Analytical Methods** | |
| Population-based: Multiple logistic regression controlling for sex, age, area, and education level; Analysis by intensity and duration of exposure and NHL subtype (among subjects with medium/high level of intensity) using individuals without exposure to any chemical as the referent.<br>Inclusions of relevant diseases and smoking in the models did not affect the magnitude of the risk level with the exception of the NHL subtype, follicular-cell cancer, which were adjusted for smoking (smoking was a risk factor for this subtype). | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| Study regions chosen because of large presence of manufacturing industries using solvents or agricultural areas.<br>TCE prevalence among controls was 2.8% for medium/high and 3.8% for low/very low exposure. | In person interviews (subject or proxy) using job/industry specific questionnaires; Expert assessment (ranked) by regional industrial hygienists of job information on the probability (3 levels) and intensity (4-point scale) of exposure to solvents; Experts blinded to case-control status. Subject interviews for 85% NHL and 97% of controls. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Education, relevant lifestyle factors (such as smoking), residential history, extra occupational history, medical history (including X-rays, medications, diseases, and reproductive history)<br>Characteristics (demographics and lifestyle, medical) were similar among cases and controls. | NCI classification, 20% and doubtful diagnosis reviewed by 3 pathologists; histological subtypes |

| **Deng *et al.* 2013/Wang *et al.* 2009a** | |
|---|---|
| **Related References** | **Geographic Location** |
| Morton *et al.* 2003, Zhang *et al.* 2004b | Connecticut (USA) |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 601 NHL (inc. DLBCL, FL, CLL/small lymphocytic-lymphoma); 518 for genotype analysis | Referents: 717; 597 for genotype analysis |
| Case eligibility criteria: Women 21–24 years old without history of other cancer (except non-melanoma skin cancer) and residents of Connecticut | Referent eligibility criteria: Selected via random digit dialing (RDD) (< 65) or Medicare/Medicaid service files (≥ 65) in Connecticut |
| Participation rate: Cases 72%; Controls - RDD 69%, Health care 47% | Matching criteria: Age (5 yr frequency) |
| **Study Design and Analytical Methods** | |
| Population-cancer registry-based: Unconditional logistic regression adjusting for age, family history of lymphohematopoietic cancers (LHC) (Wang only), alcohol consumption, race was used to calculate risks by ever, average (intensity and/or probability). Smoking, medical history, income, education levels and LHC history (Deng only) were not included in final models because they did not change the risk estimates. Polytomous logistic regression was used to evaluate using tertiles of cumulative exposure and histological subtype of NHL. Trends using continuous exposures; Deng reported risk estimates for ever vs. never stratified by immune gene polymorphisms. | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| NR<br>TCE exposure prevalence among controls was 11% for ever-exposed and 1.8% for medium/high exposure. | Interviews using structured questionnaire on detailed lifetime occupational history on job titles, companies and activities (jobs 1 yr or longer); Jobs were linked to a JEM, which assigned probability and intensity index of exposure to solvents for each occupation/industry. Individual assigned to exposure categories that combined duration with probability and intensity to estimate ever exposure, cumulative intensity, cumulative probability for each job, and the average intensity, average probability exposure across jobs. Exposure assessment was blinded to case/control status. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Age, family history of LHC, alcohol consumption, race (considered smoking, education, income, family history of immune disease) | Histologically confirmed by study pathologists using 2001 WHO (REAL) classification<br>ICD-O-2, M-9590-9642, 9690-9701, 9740-9750 |

| **Persson and Fredrikson *et al.* 1999** | |
|---|---|
| **Related References** | **Geographic Location** |
| Pooled analysis of two studies Persson *et al.* 1989, Persson *et al.* 1993 | Regional, Sweden |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 199 NHL [106 (1989) + 93 (1993) | Referents: 479 population controls |
| Case eligibility criteria: NHL in 2 hospital registries 1989 study: 1964–1986; 1993 study: 1975–1984. 20–80 years old, resident in hospital catchment area, Swedish-born | Referent eligibility criteria: population registry, 20-80 years old, resident in same catchment area as cases, Swedish-born; Unclear which years cases were recruited. |
| Participation rate: 1989: cases 96%; 1993: cases 90%, controls NR | Matching criteria: No matching specified; eligibility criteria required same age range, similar residence and citizenship. |
| **Study Design and Analytical Methods** | |
| Population-based: Mantel-Haenszel OR stratified by age and sex with 5-yr lag. Logistic regression if OR > 1.5 on separate analyses by exposures and occupations with at least 10 cases | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| NR<br><br>TCE exposure prevalence among referents ~7% | Mailed questionnaire on occupational and leisure exposures, medical data. Self-reported exposure by rank category; Minimum 1 yr of exposure and exposure window of 5 to 45 yr before disease diagnosis; Not clear if interviewers were blinded to case-control status. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Smoking, medication, X-rays, pets assessed by questionnaire and evaluated in separate analyses. Unclear whether case and controls varied on demographic variables. | Cancer registry; 1989 study– not histologically confirmed; 1993 study– 2 histologically confirmed with 4% misclassification rate cf. clinical diagnosis ICD code NR |

| **Nordström *et al.* 1998** | |
|---|---|
| **Related References** | **Geographic Location** |
| None | Sweden |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 111 HCL | Referents: 400 |
| Case eligibility criteria: Men identified from Swedish Cancer Registry 1987–1992 | Referent eligibility criteria: National Population Registry |
| Participation rate: cases 91%; controls 83% | Matching criteria: Age, sex, county |
| **Study Design and Analytical Methods** | |
| Population-based: TCE: Logistic regression controlling for age; matching dissolved in analysis. Total solvents: multivariate analysis, controlling for exposure to herbicides, fungicides, impregnating agents, all exhausts for ever-exposure and univariate exposure, controlling for age, for duration of exposure | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| Level: NR<br><br>TCE exposure prevalence among controls 7% | Mailed questionnaire on complete working history, information on leisure activity and protective equipment. Ever exposed – at least 1 working day and induction of at last one 1 yr.; Reviewer of questionnaire data blinded to case-control status. Proxy answers for 3 cases and 5 controls |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Smoking not a risk factor for HCL. No information on other lifestyle habits. | NCI classification, 20% and doubtful diagnosis reviewed by 3 pathologists; histological subtypes. |

| **Hardell *et al.* 1994** | |
|---|---|
| **Related References** | **Geographic Location** |
| Hardell *et al.* 1981 | Umea region, Sweden |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 105 NHL | Referents: 355 NHL |
| Case eligibility criteria: Men 25–85 yr old, diagnosed at hospital pathology dept. 1974–1978 | Referent eligibility criteria: National Population Registry, National Registry for Causes of Death |
| Participation rate: NR | Matching criteria: Age, sex, place of residence, vital status; deceased subjects also matched by year of death. |
| **Study Design and Analytical Methods** | |
| Population-based: TCE–specific analysis: Mantel-Haenszel stratified analysis by age and vital status.<br>Organic solvents class analysis: Multivariate logistic regression controlling for phenoxyacetic acids, chlorophenols, DDT, asbestos, for ever-exposed, and univariate analysis for subtype and stage of NHL | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| NR<br><br>Prevalence of TCE exposure among controls was 1% | Mailed questionnaire to subjects and next of kin: self-reported complete working history, information on leisure activity and protective equipment; Low grade exposure - less than 1 wk continuous or 1 mo; high-grade greater than that; Reviewer of questionnaire data (not clear that reviewer was an expert in exposure assessment) blinded to case-control status. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| NR | Histologically confirmed; reexamined Rappaport classification |

| **Costantini *et al.* 2008** | |
|---|---|
| **Related References** | **Geographic Location** |
| Costantini *et al.* 2001; same population base as Miligi *et al.* 2006 | 11 centers, Italy |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: Multiple myeloma (MM) (6 centers): 263 cases; chronic lymphatic leukemia (CLL): NR (7 centers), 2,737 total lymphohematopoietic (11 centers) | Referents: MM– 1,100 (6 centers); CLL– NR (7 centers); total– 1,799 (11 centers) |
| Case eligibility criteria: All LH cancers (M+F) in 11 centers, age 20–74 years of age 1991–1993 | Referent eligibility criteria: Random sample of population registers |
| Participation rate: 83% MM cases, 76% controls; CLL NR | Matching criteria: Age (5 yr), sex, region |
| **Study Design and Analytical Methods** | |
| Population-based: Multiple logistic regression models controlling for age, sex, education, region; Analyses for exposure intensity (very low/low and medium/high) and duration (< and > 15 years) using individual without exposure to any of the listed chemicals as the referent group | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| Study regions chosen because of large presence of manufacturing industries using solvents or they were agricultural areas.<br>TCE prevalence among controls was 2.5% for medium/high and 3.5% for low/very low exposure. | In-person interviews (subject or proxy) using job/industry specific questionnaires; Expert assessment (ranked) by regional industrial hygienists of job information on the probability (3 levels) and intensity (4-point scale) of exposure to solvents. Experts blinded to case-control status. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| Interviews: education, relevant lifestyle factors (such as smoking), residential history, extra occupational history, medical history (including X-rays, medications, diseases, and reproductive history)<br>Characteristics (demographics and ever smoking) were similar among cases and controls. | Hospitals<br>ICD-9 MM 203, CLL 204.1 |

| **Gold *et al.* 2011** | |
|---|---|
| **Related References** | **Geographic Location** |
| Chatterjee *et al.* 2004 | Seattle, WA and Detroit, MI SEER sites |
| **Population Characteristics** | |
| ***Cases: Selection and ascertainment*** | ***Controls: Selection and ascertainment*** |
| Cases: 181 MM | Referents: 481 (used for study of NHL; see Chatterjee *et al.* 2004) |
| Case eligibility criteria: M+F alive at time of study, 35–74 years old, resident in SEER area and diagnosed between 2000 and 2002 | Referent eligibility criteria: Randomly selected via random digit dialoging (< 65 yr) or Medicare files (> 65 yr) from two SEER regions, 35–74 yr old with no previous HIV infection, multiple myeloma or plasmacytoma |
| Participation rate: 60% eligible cases alive at study date; 71% of contacted cases, 52% eligible (living) controls | Matching criteria: Age, sex, residence |
| **Study Design and Analytical Methods** | |
| Population-based: Unconditional logistic regression, adjusted for age, sex, race, education, residence (SEER site) used to calculate risks for exposure categories – ever, exposure duration and cumulative exposure (unlagged and 10-yr lagged) for TCE and other chlorinated solvents. Sensitivity analysis considering low-exposed jobs as unexposed | |
| **Exposure Data and Information Assessment** | |
| ***Exposure: Levels and Co-exposures*** | ***Exposure assessment*** |
| Exposure prevalence of TCE among controls was 29% for ever-exposed and 14% in highest cumulative exposure category.<br>Highest cumulative exposure category > 7,794 ppm<br>Separate analyses for methylene chloride, tetrachloroethylene, 1,1,1-trichloroethane, chloroform and carbon tetrachloride (not clear if co-exposures) | In-person interview with subjects using questionnaires on work history (> 1 yr from 1941 cases, 1946 controls); Job-specific questionnaires (tasks and work environment) for 20 solvent-related occupations for jobs held for at least 2 years<br>Exposure metrics (probability, frequency, and intensity) were assigned by experts using questionnaire data and calendar-specific JEM for industries related to solvent exposure based on extensive literature review. Cumulative exposure was calculated as sum of the intensity, frequency and duration of all exposed jobs with a probability of exposure > 2 for each solvent.<br>Reviewer blind to case-control status. |
| ***Assessment of potential confounders*** | ***Disease Assessment*** |
| NR | SEER cancer registry (data from hospitals, physicians, laboratories, death certificates); ICD-O 2/3 |

**Table D-4a. Cohort and nested case-control studies of trichloroethylene exposure: Summary of study quality**

| Study and number of TCE-exposed subjects | Selection bias and completeness of follow-up | Quality of exposure assessment and misclassification of exposure | Quality of cancer assessment and misclassification of diagnosis |
|---|---|---|---|
| **Nordic Studies** | | | |
| **Hansen *et al.* 2013**<br>Pooled Nordic cohort incidence analysis; 5,553 workers (3,776 men, 1,777 women)<br>Axelson *et al.* 1994, Anttila *et al.*1995, Hansen *et al.* 2001 | *Unlikely*<br>Adequate methods to select cohort members. All workers with ≥ 1 urine TCA or air TCE measurement included in cohort. No evidence of HWE.<br>Loss to follow-up: *Minimal* (<1%). | *Adequate to good:* Biomonitoring at the individual level (urine-TCA); Few data on individual industries or jobs of workers, cumulative exposure and exposure duration; Diverse TCE-using industries included.<br>The U-TCA exposure assessment is expected to have high sensitivity but specificity may be a concern if workers were exposed to other chlorinated solvents that are metabolized to TCA. In addition, because few measurements (2 to 3) were available for most subjects and many subjects (55% of Swedish study) had only 1 measurement, individuals classified as unexposed could have been exposed to TCE and U-TCA and U-TCA exposure misclassification related to intensity level may occur. | *Case-ascertainment*: *Adequate*<br>Cases identified in cancer registries via ID linkage; only 0.1% of the cohort was lost to follow-up.<br>*Misclassification of diagnosis: Possible for NHL, unlikely for kidney and liver*<br>Histologically confirmed in Swedish study; Diagnosis of NHL based on broad ICD-7 classification which includes several diseases and does not differentiate subtypes. |
| **Raaschou-Nielsen *et al.* 2003**<br>Danish TCE blue-collar worker cohort; 40,049 workers approx. 70% men)<br>Record linkage incidence study | *Possible*<br>Cohort and comparison group differ with respect to socioeconomic status. Cohort included all "blue-collar" workers whereas reference population (Danish population) included both blue- and white-collar workers, which could lead to an under-or overestimate of expected cases for cancer sites that are associated with SES. Differences in SES may explain significant increase in all-cancer incidence (M and F) and of smoking-related cancers.<br>Loss to follow-up: *Minimal;* authors | *Limited:* Employment as a blue-collar worker in a TCE-using company used as a surrogate for potential TCE exposure and size of company used as surrogate for estimated percentage of workers exposed to TCE. Limited characterization of exposure: Urine TCA and air TCE data for some workers but not used in exposure assessment.<br>Exposure misclassification (non-differential): is a concern. Only 19%-81% (41% overall) with estimated exposure to TCE (working in the same room that TCE was used); Employment duration before 1964 was not considered, | *Case-ascertainment: Adequate*<br>Cases identified via ID linkage with cancer registry.<br>*Misclassification of diagnosis: Possible for NHL, unlikely for kidney and liver*<br>Diagnosis of NHL based on broad ICD-7 classification includes several diseases and does not differentiate subtypes. |

| Study and number of TCE-exposed subjects | Selection bias and completeness of follow-up | Quality of exposure assessment and misclassification of exposure | Quality of cancer assessment and misclassification of diagnosis |
|---|---|---|---|
| | report follow-up as being virtually complete. | which could attenuate exposure-duration relationships. | |
| **Vlaanderen *et al.* 2013**<br>Cancer registry-based (Nordic Occupational Cohort); Nested case-control analysis<br>76,130 kidney cancer cases (41% F); 380,650 controls (41% F); 23,896 liver cancer cases (38% F), 119,480 controls (38% F)<br>1960–90 to 2003–05<br>Mortality | *Unlikely*<br>Adequate methods (census, cancer registry, population registries) for identifying cohort; Controls matched to cases by age, sex, country.<br>Loss to follow-up: Not reported; assume complete because of linkage with registry data | *Limited:* Quantitative, calendar-year specific, country specific, generic JEM; Exposure was assigned based on limited occupation information on specific jobs from census data and assumed no changes in jobs between censuses. The JEM had poor sensitivity and did not account for jobs tasks, heterogeneity within jobs and changes over time.<br>Use of population-wide occupational exposure database may lack precision for individual participants.<br>Exposure misclassification (with respect to whether workers were ever exposed) is a concern because of the population-wide occupational exposure database, and limited occupational information for individual workers. The probability of exposure may be higher among subjects in the highest exposed groups. Misclassification of exposure intensity is also a concern. | *Case-ascertainment: Adequate*<br>Linkage via cancer registry<br>*Misclassification of diagnosis of cases:*<br>*Possible for NHL, unlikely for kidney and liver.*<br>RCC (histologically confirmed), liver and MM; Diagnosis of NHL based on broad ICD-7 classification which includes several diseases and does not differentiate subtypes. |
| **Rocket engine testing or aircraft manufacturing workers** | | | |
| **Zhao *et al.* 2005**<br>Los Angeles (USA) aerospace workers cohort<br>Mortality; 6,044 men<br>Incidence; 5,049 men | *Unlikely*<br>Adequate methods to select cohort; all workers with potential exposure to TCE included in cohort.<br>Loss to follow-up: *Minimal* (< 0.1 %) | *Adequate to good:* Semi-quantitative JEM (relative intensity), which was calendar-year specific, constructed using job titles and detailed description of job tasks. Each worker's exposure classified by cumulative relative intensity scores to TCE and co-exposures, by calendar period. No quantitative exposure measurements.<br>Exposure misclassification is not a concern, especially among individuals with the highest | *Case-ascertainment: Adequate*<br>NDI for cause of death (missing data NR) and multiple cancer registries used for diagnosis (missing data NR).<br>*Misclassification of diagnosis: Unlikely for incidence*<br>Incidence: ICD-O (extension of ICD-10). Deaths: ICD-9 and 10; Underlying and contributing causes of death |

| Study and number of TCE-exposed subjects | Selection bias and completeness of follow-up | Quality of exposure assessment and misclassification of exposure | Quality of cancer assessment and misclassification of diagnosis |
|---|---|---|---|
| | | cumulative exposure. Exposure misclassification between levels of cumulative exposure would most likely attenuate any exposure. | |
| **Boice *et al.* 2006**<br>Los Angeles (USA) rocket engine testing workers cohort; 1,111 men<br>Mortality study<br>Overlap with Zhao *et al.* 2005 cohort | *Possible for external analyses*<br>Adequate methods to select cohort; all workers with adequate employment data included in cohort. Evidence of HWE based on 13% (significant decrease in all-cause mortality among test stand mechanics with any exposure to TCE).<br>Loss to follow-up: *Minimal;* 3.1% missing vital status | *Limited to adequate*: Qualitative assessment of TCE exposure using test stand mechanics as a surrogate of exposure, exposure based duration of employment using TCE, walk-through surveys and dates that TCE was used and duration of exposure from engine flush. No assessment of exposure intensity.<br>The probability of being exposed to TCE is greatest in analyses by test engine flush; however, exposure misclassification is still possible. | *Case-ascertainment: Adequate*<br>Use of state vital records and NDI for vital status<br>*Misclassification of diagnosis: Possible (non-differential) for some tumor sites*<br>Death certificate using ICD at the time of diagnosis; possible concern for diagnosis of NHL<br>Potential for missing cases that do not result in death for cancers with long survival (kidney and NHL), which would decrease precision. |
| **Lipworth *et al.* 2011**<br>Burbank, CA (USA) aircraft manufacturing workers cohort; 5,443 (approx. 80% male)<br>Mortality Study | *Possible*<br>Adequate methods to select cohort: All workers with minimum of 1-yr employment. Some evidence for HWE based on 9% decrease in all-cause and all-cancer mortality than CA and U.S. population.<br>Loss to follow-up: *Minimal:* 1.7% total cohort | *Limited to adequate:* Qualitative JEM for occupational job groups based on plant data; Workers classified by ever exposure, type of exposure (routine or intermittent) and duration of potential exposure. No quantitative exposure assessment or ranking of relative intensity of exposure.<br>Exposure misclassification is a concern (non-differential) for all analyses. | *Case-ascertainment: Adequate*<br>Multiple sources used to determine vital status<br>*Misclassification of diagnosis: Possible (non-differential) for some tumor sites*<br>NDI using ICD at the time of diagnosis; possible concern for diagnosis of NHL<br>Potential for missing cases that do not result in death for cancers with long survival (kidney and NHL), which would decrease precision. |
| **Radican *et al.* 2008 (mortality update);** | *Unlikely*<br>Adequate methods to select cohort: All | *Adequate to good:* Semi-quantitative calendar year specific JEM constructed from detailed | *Case-ascertainment: Adequate*<br>Use of state vital records and NDI for |

| Study and number of TCE-exposed subjects | Selection bias and completeness of follow-up | Quality of exposure assessment and misclassification of exposure | Quality of cancer assessment and misclassification of diagnosis |
|---|---|---|---|
| **Blair *et al.* 1998 (incidence)**<br>Utah (USA) aircraft maintenance workers cohort; 7,204 (6,153 men, 1,051 women)<br>Mortality and incidence study | workers potentially exposed to TCE included in exposed cohort. Little evidence for HWE<br>Loss to follow-up: Not reported | occupational information used to develop exposure scores for each job based on intensity, frequency, and duration of exposure. Each worker classified by cumulative exposure score and pattern of exposure; however, exposure records that specific subjects were missing, and information was based on position descriptions. Some limited air monitoring by job/task but not used in exposure assessment.<br>Exposure misclassification (with respect to whether workers were ever exposed) is a concern (non-differential). Misclassification regarding intensity level would most likely attenuate any exposure-response relationships. | vital status (missing data NR).<br>*Misclassification of diagnosis:* Possible (non-differential) for some tumor sites in mortality study<br>NDI using ICDA-8 or 9, ICD-10. Underlying and contributing causes of death; possible concern for diagnosis of NHL; SEER (Utah) registry used for incident cases (1973–1999) so possible concern about earlier ICD classifications of NHL.<br>Potential for missing cases that do not result in death for cancers with long survival (kidney and NHL), which would decrease precision. |
| **Morgan *et al.* 1998**<br>Arizona USA aircraft manufacturing workers cohort; 4733 (2555 men, 2178 women)<br>Mortality study | *Possible for external analysis*<br>Adequate methods to select cohort (all workers employed for specific dates) but evidence of HWE based on 15% significant decrease in all-cause mortality for TCE- exposed subcohort.<br>Loss to follow up: *Minimal;* appears to be 0.1% (excluded due to "missing information" but not clear if applies to vital status or other data). | *Adequate:* Semi-quantitative expert assessment, using JEM by job title and based on location of jobs in proximity to degreaser area, used to estimate exposure category scores. Exposure assessment is limited with respect to calendar year, confidence, frequency, or probability of exposure and information on tasks. Limited quantitative exposure measurements available during most of period TCE used (not reported or used in exposure assessment).<br>The probability of being exposed to TCE is greatest among workers in the "high" and "peak" exposure categories. Exposure misclassification (with respect to whether workers were ever exposed) is more of a concern (non-differential) in the med/low exposure categories. | *Case-ascertainment: Adequate*<br>Use of SSA, NDI, or state vital records.<br>Potential for missing cases that do not result in death for cancers with long survival (kidney and NHL), which would decrease precision.<br>*Misclassification of diagnosis: Possible (non-differential) for some tumor sites*<br>Death certificate using ICD at the time of diagnosis (7 to 9); possible concern for diagnosis of NHL. |
| **Other *industries: Cohort and Nested case-control studies*** | | | |

| Study and number of TCE-exposed subjects | Selection bias and completeness of follow-up | Quality of exposure assessment and misclassification of exposure | Quality of cancer assessment and misclassification of diagnosis |
|---|---|---|---|
| **Bahr *et al.* 2011**<br>Kentucky (USA) uranium enrichment workers cohort; 5,535 men<br>Mortality study | *Probable*<br>Difficult to evaluate because of limited information. Selection of workers based on complete work histories; however, information about other eligibility criteria (e.g., age of workers, enrollment, number of subjects excluded due to missing data) were not provided. Evidence of HWE, based on ~20% to 30% decrease in all-cause mortality in TCE-exposed groups. Evidence of healthy worker survival effect<br>Loss to follow-up: Not reported | *Limited:* Generic qualitative JEM based on work history but little data provided on ranking of probability of TCE exposure. No quantitative exposure measurements<br>Exposure misclassification (non-differential) is a concern and likely to be substantial. | *Case-ascertainment: Unknown*<br>Source and completeness of vital status and cause of death data NR<br>*Misclassification of diagnosis:* Possible (non-differential) for some tumor sites<br>Death certificate using ICD code at time of death used; possible concern for diagnosis of NHL<br>Potential for missing cases of cancers with long survival (kidney and NHL), which would decrease precision. |
| **Yiin *et al.* 2009**<br>Tennessee (USA)<br>Uranium enrichment workers<br>Nested case-control mortality study; 47,941 men and women<br>114 cases of multiple myeloma (ICD 203) | Unlikely<br>Cohort selection based on employee roster for all workers prior to 1985 and employed >30 days; cases and controls selected based on availability of uranium dose data (appears complete).<br>Loss to follow-up: NR | Limited to adequate: Individual cumulative exposure score for TCE assigned based on modified JEM that estimated levels for exposure activities by decade. Inadequate information to link monitoring data to workers and work history data missing information on building/work location. Limited information available on assessment.<br>Exposure misclassification (non-differential) is a concern. | *Misclassification of diagnosis of cases: Possible (non-differential):* Cases of multiple myeloma (underlying and contributory causes of death, ICD 203) identified from death certificates (no other details reported) |
| **Ritz 1999**<br>Ohio (USA) uranium processing workers cohort; 2972 men<br>Mortality study | *Possible*<br>Selection of workers based on all workers with data on chemical exposure and monitored for radiation exposure included in cohort but 35% total cohort excluded due to absence of radiation records. Some evidence of HWE based on ~15% statistically significant decrease in all-cause mortality. Also, a possible bias if radiation exposure associated with TCE | *Limited to adequate:* Semi-quantitative JEM for individual workers based on verified job title and department using company industrial hygienists and workers but does not appear to be calendar-period specific. Exposure categorized by 2 levels (light and moderate) and 2 categories of duration. No quantitative exposure measurements.<br>Exposure misclassification (with respect to whether workers were ever exposed) is a concern (non-differential). Most of the workers | *Case-ascertainment: Adequate*<br>Use of appropriate methods (Social Security Administration Records (SSA) or National Death Index (NDI)) to ascertain vital status<br>*Misclassification of diagnosis:* Possible (non-differential) for some tumor sites<br>Death certificate (NDI) using ICDA-8 (external analysis) and ICD-9 |

| Study and number of TCE-exposed subjects | Selection bias and completeness of follow-up | Quality of exposure assessment and misclassification of exposure | Quality of cancer assessment and misclassification of diagnosis |
|---|---|---|---|
| | exposure:<br>Loss to follow up: Not reported. | in this study had low levels of exposure. | (internal analysis); possible concern for diagnosis of NHL<br>Potential for missing cases that do not result in death for cancers with long survival (kidney and NHL) which would decrease precision. |
| **Silver *et al.* 2014**<br>New York State (USA) electronics manufacturing workers cohort; 24, 037 men, 10,457 women (total cohort)<br>Mortality study | *Unknown for internal analysis used for TCE-exposed subcohort*<br>Strong evidence for healthy worker effect in total cohort; not clear if there is a healthy worker survival effect. | *Limited:* Exposure assessment based on work history and dept.-year JEM, Cumulative exposure assigned based on potential exposure to TCE (based on dept. use and board categories of position) and duration of TCE. No information on job tasks or exposure condition or levels of use. Exposure intensity could vary within a dept and over time. Position title could not be used to compare exposure across dept. (except for to classify admin. staff as unexposed). Company record and work history incomplete, especially for time periods before 1974. Incomplete and contradictory work history records.<br>Exposure misclassification *(*with respect to whether workers were ever exposed) is a concern (non-differential). | *Case ascertainment: Adequate*<br>Use of appropriate methods (State vital records or National Death Index (NDI)) to ascertain vital status.<br>*Misclassification of diagnosis:*<br>Possible (non-differential) for some tumor sites<br>Death certificate using ICD code at time of death used; possible concern for diagnosis of NHL.<br>Young cohort (17% deaths) and potential for missing cases of cancers with long survival (especially kidney and NHL), which would decrease precision. |
| **Henschler *et al.* 1995**<br>German cardboard manufacturing cohort; 169 men<br>Incidence & mortality study of kidney cancer | *Probable*<br>Selection of cohort may be based on cluster of renal cancers, which would bias towards an overestimate of the risk estimate. Comparison group from different countries from exposed cohort (if a bias, the direction would most likely be towards underestimating the risk estimate from using possibly inflated expected rates); Evidence for a HWE based on statistically significant 30% decrease in all | *Limited:* Exposure assigned based on job location in the plant and descriptions of plant conditions (walk-through and interview) for ever exposure only. Level and duration of exposure not characterized.<br>Although the exposure assessment was of limited quality (based on workspace), exposure to TCE occurred in an open system. Thus exposure misclassification is not a concern for most workers although exposure duration and intensity is likely to vary among workers. It is | *Case-ascertainment: Limited*<br>Multiple methods used to identify deaths and cases such as hospital/medical records, rather than central death records or cancer registry. Different methods may have been used to assign cause of death or cases for exposed cohort (physicians and records and abdominal sonogram) than the general population in external analysis, which |

| Study and number of TCE-exposed subjects | Selection bias and completeness of follow-up | Quality of exposure assessment and misclassification of exposure | Quality of cancer assessment and misclassification of diagnosis |
|---|---|---|---|
| | cancer mortality.<br><br>Loss to follow-up: *Minimal;* 8% (refusal, ill-health, or untraced) suggesting most cases and deaths were identified. | not clear if the unexposed workers included in the internal analysis could have had some exposure to TCE (no details are provided.). | could potentially bias external (but not internal) analyses towards an overestimate of the risk estimate.<br><br>*Misclassification of diagnosis: Unlikely for incidence, possible for deaths (but only 2 deaths reported).*<br><br>Deaths classified from medical records or physicians using ICD-9; different sources may vary in reliability. Histological confirmation of renal-cell cancer from incident cases (the only tumors that were reported.) |
| **Greenland *et al.* 1994**<br><br>Massachusetts (USA) electrical manufacturing workers nested case-control study<br><br>15 deaths NHL, 12 kidney cancer, 9 liver cancers (men) | *Probable*<br><br>Selection is not adequate because the case control study only included analysis of deaths for pensioned workers with job history for 7 selected chemicals and death benefit claims for specific time period. Cases were cancer deaths for specific sites. Controls (not matched to the cases) included any deaths "unrelated" to these exposures. No information on the size of the underlying cohort (males 21–90 years old employed < 1984.<br><br>Loss to follow-up: Cohort selection based on deceased employees (known to pension fund) and appears that death certificate data were available for all cohort members. | *Limited:* Qualitative JEM constructed based on job title and interviews and combined with work history used to classify workers as ever/never exposure. Doesn't appear to be calendar-specific; No quantitative exposure measurements<br><br>Exposure misclassification (non-differential) is a concern and likely to be substantial. Exposure duration and intensity are likely to vary among workers classified as ever exposed. | *Misclassification of diagnosis: Unlikely for kidney and liver, possible for NHL.*<br><br>Death certificate diagnoses verified using hospital records for subset of deaths.<br><br>Potential for missing cases that do not result in death for cancers with long survival (kidney and NHL) which would decrease precision. |
| **Wilcosky *et al.* 1984**<br><br>Ohio (USA) rubber manufacturing workers | *Unlikely*<br><br>Original cohort deaths (1,793) ascertained among life insurance benefit recipients | *Inadequate:* Qualitative assessment for ever work in area of authorized use of 1 or more of 25 chemicals based on solvent products that were authorized for use and is not known | *Misclassification of diagnosis of cases: Possible (non-differential) for some cancer sites*<br><br>Death certificate using ICD-8; |

| Study and number of TCE-exposed subjects | Selection bias and completeness of follow-up | Quality of exposure assessment and misclassification of exposure | Quality of cancer assessment and misclassification of diagnosis |
|---|---|---|---|
| nested case-control study; 6,678 (men)<br><br>9 cases of NHL (lymphosarcoma, ICD 200) | (McMichael *et al.* 1974) so workers leaving early were excluded from analysis; however, only 2 deaths occurred in this latter group.<br><br>Loss to follow-up*:* Complete work histories available in 1964 (start of follow-up) | whether they were actually used. Individual work histories (department, dates, and job title) used to assign exposure.<br><br>Exposure misclassification (non-differential) is a serious concern and likely to be substantial. | possible concern for NHL.<br><br>Potential for missing cases of cancers with long survival (kidney and NHL), which would decrease precision |
| **Drinking Water Studies** | | | |
| **Bove *et al.* 2014**<br><br>Cohort study (drinking water contamination)<br><br>Camp Lejeune, NC and Camp Pendleton, CA (USA)<br><br>154,932 (C Lejeune)<br>154,969 (C Pendleton)<br><br>Mortality Study | *Unlikely*<br>Adequate methods for selecting cohort cohort: All active service personnel eligible<br><br>Loss to follow-up: *Minimal;* <2% | *Limited:* Reconstruction of exposure is based on historical sampling of two water supply systems in defined regions. Estimate of cumulative exposure based on duration at residence and modeled TCE concentration levels from the water supply system associated with the residence. No data on individual consumption; May have had errors in assignment of residential location.<br><br>Exposure misclassification (with respect to whether residents were ever exposed) is a concern) although to a lesser degree among individuals with higher estimated cumulative exposure. Exposure misclassification regarding cumulative exposure would most likely attenuate any exposure-response relationship. | *Case-ascertainment: adequate*<br>Multiple sources used to determine vital status including the NDI<br><br>Potential for missing cases of cancers with long survival (kidney and NHL), which would decrease precision.<br><br>*Misclassification of diagnosis: possible for some tumor sites.*<br>Death certificate; underlying and contributing causes; ICD NR; possible concern for NHL |

## Table D-4b. Cohort studies: Study sensitivity and exposure-response analyses

| Study<br>Summary (study sensitivity) | Study size/length of Follow-up | Reported or estimated exposure levels or duration | Exposure-response analyses: dose metrics/range |
|---|---|---|---|
| **Nordic studies** | | | |
| **Hansen *et al.* 2013**<br>Pooled Nordic cohort incidence analysis<br>*Limited for high exposure effects*<br>*Large numbers of exposed cases that were ever exposed to TCE but few deaths with high exposure (especially liver or NHL); Most of the cohort was exposed to low levels for short time periods.* | Median size cohort: 5,553 workers; ~ 1000 cancer cases<br>Number of exposed cases: 32 kidney 36 liver, 38 NHL ever exposed; 9 kidney, 3 liver, 4 NHL in highest exposure group<br>49% total workers with > 30 years of follow-up | Low exposure levels and short exposure duration<br>Estimated TCE ambient levels: 4 ppm (median, Finland), 12 ppm (median, Denmark); > 80% of Swedish study with < 20 ppm<br>Only ~20% of subjects had U-TCA levels > 50 mg/L (~ 20 ppm)<br>Mean duration of employment (yr): 5.5 (Sweden) and 6.3 (Denmark), NR for Finland<br>Estimated exposure group [a] for highest U-TCA exposure group (20 ppm): moderate. | Average U-TCA (4 levels).<br>Denmark study: Cumulative, duration of exposure, and calendar period)<br>Range: Appears adequate based on U-TCA in exposure groups |
| **Raaschou-Nielsen *et al.* 2003**<br>Danish TCE blue-collar worker cohort<br>Record linkage incidence study<br>*Adequate in subcohort of higher exposed subjects*<br>*Large number of exposed cases for NHL and kidney cancer in both cohort and subcohort analysis; fewer deaths from liver cancer* | Large cohort: > 40,000 workers, ~14,000 subcohort considered to have higher exposure; > 3,000 cancer cases; 76 RCC, 25 liver, 96 NHL<br>Follow-up to approx. 30 years but cohort is relatively young; 56% were 38 to 57 years old at end of follow-up, and 29% of subjects were older than 57 years of age. | Low exposure levels after 1980<br>Median exposures to TCE (ppm) (NAS 2006)<br>1960-1969: 49<br>1970–1979: 20<br>1980–1989: ~ 4<br>Only 21% of workers began employment before 1970 (highest levels). Only 42% of the cohort were considered to be exposed to TCE.<br>Estimated exposure group [a] for high exposure group (since 1970): moderate. | Exposure duration, year of first employment (surrogate for level), company size (surrogate for level), lag time; Sensitivity analysis on presumed higher exposed workers<br>Range: Appears to be wide based on exposure changes over time. |
| **Vlaanderen *et al.* 2013**<br>Cancer registry-based, Nordic countries nested case-control study.<br>*Limited* | Large cohort: number of exposed cases: 4145 kidney, 1610 liver, 3607 NHL, 1583 multiple myeloma<br>Follow-up: up to 45 years | Levels not reported. Estimated median exposure (unit-yr)[b] for the cumulative exposure categories:<br>1st tertile: 0.04 (for liver, kidney, NHL, MM) | Cumulative exposure (categorical and continuous models)<br>Range not reported; tertiles of estimated cumulative exposure only used to evaluate for exposure- |

| Study Summary (study sensitivity) | Study size/length of Follow-up | Reported or estimated exposure levels or duration | Exposure-response analyses: dose metrics/range |
|---|---|---|---|
| *Large number of exposed cases and controls; however, exposure levels very low and the potential for misclassification of exposure is likely.* | | 2nd tertile: 0.25 (liver), 0.13 (kidney), 0.12 (NHL), 0.13 (MM)<br>3rd tertile: 0.77 (liver), 0.72 (kidney), 0.72 (NHL), 0.74 (MM)<br>Estimated cumulative levels of exposure based on occupational group (not individual job data).<br>High exposure was assigned to shoe and leather industry workers, mechanics, laundry workers. Laundry workers may not be a good population to evaluate exposure to TCE.<br>Estimated exposure group[a] for highest cumulative exposure: assumed low (uncertain because calculation includes prevalence). | response relationship. |
| **Rocket engine or aircraft manufacturing workers** | | | |
| **Zhao *et al.* 2005**<br>Los Angeles (USA) aerospace workers cohort<br>Mortality and incidence study<br>*Limited*<br>*Small numbers of cases for subgroup analysis for kidney; however, strengths are analysis of risks for high exposed workers and exposure-response relationships.* | Median size cohort: 6,107; Exposed cases/deaths: Kidney- 17 deaths, 16 cases; NHL- 60 deaths, 45 cases<br>Follow-up*:* Average 29 yr | Workers with job titles indicating technical or mechanical work on rocket engines were presumed to have high hydrazine rocket fuel exposure and high TCE exposure, which was used in cleaning rocket engines and parts.<br>80% of workers employed before 1970 when exposure levels were high. Intensity estimated to be > 200 for 1970 and 400 to 600 for intensity. Cumulative exposure estimated to range up to 38 ppm-yr[b].<br>Estimated exposure group[a] for cumulative exposure: moderate. | Cumulative exposure category lagged and unlagged.<br>Range: Adequate |
| **Boice *et al.* 2006**<br>Los Angeles (USA) rocket engine testing workers cohort | Small cohort: 1,111 workers; 121 cancer deaths; Exposed deaths: 7 kidney<br>Follow-up: 88% of test mechanics | Approx. 58% exposed to TCE during engine flushing/cleaning (high exposure); approx. 42% exposed to TCE during utility cleaning (lower exposure) | Exposure duration<br>Range: Unknown, only two exposure duration categories |

| Study Summary (study sensitivity) | Study size/length of Follow-up | Reported or estimated exposure levels or duration | Exposure-response analyses: dose metrics/range |
|---|---|---|---|
| Mortality study<br>*Limited*<br>*Few exposed deaths but presumably high exposure.* | followed for over 20 years | | |
| **Lipworth *et al.* 2011**<br>Burbank, CA (USA) aircraft manufacturing workers cohort<br>Mortality study<br>*Limited*<br>*Adequate numbers exposed cases but exposure duration may be relatively short; few exposed cases worked longer than 5 years. No information or analysis by exposure intensity.* | Median size cohort: 5,443; ~1000 cancer deaths; Exposed deaths: 16 kidney, 24 liver, over 50 NHL<br>*Follow-up* Average 32 years | No information on reported levels<br>Exposure duration mostly likely short for unknown portion of the workers; Cohort includes workers employed since 1960, but TCE exposure ceased in 1966. Enrollment of cohort started in 1960, so maximum possible exposure duration was 6 years.<br>12% of the cohort with potential exposure to TCE<br>Estimated exposure group[a] for longest duration: low (includes workers with high and low exposure). | Duration of exposure<br>Range: limited for duration, highest category 5 years |
| **Radican *et al.* 2008 (mortality update); Blair *et al.* 1998 (incidence)**<br>Utah (USA) aircraft maintenance workers cohort<br>Mortality and incidence study<br>*Limited for subgroup analysis*<br>*Adequate number of exposed deaths but few deaths or cases among highest exposed group (especially for kidney and liver cancer)* | Median size cohort: 7,204; 729 cancer deaths; 528 cancer cases. Exposed cases deaths (men): 16 deaths, 13 cases kidney; 37 deaths, 21 cases NHL; 28 deaths, 12 cases liver). Few cases or deaths (≥ 5) for kidney & liver in highest exposure category<br>Follow-up: Average length of follow-up not reported, but extended follow-up approx. 44 years after latest date of first employment (1956–2000) | Cherrie *et al.* (2001) estimated long-term exposure as 50 ppm and short term up to 600 ppm TCE. The NAS (2006) concluded the cohort had a modest number of highly exposed (~ 100 ppm) but most were exposed to low TCE concentrations (~10 ppm).<br>Other estimates for cumulative exposure are up to 38 ppm-yr from degreasing and up to 15 ppm-yr from benchwork. Intensity would be high[c]<br>Estimated exposure group[a] for highest cumulative exposure; moderate. | Cumulative exposure and exposure pattern (peak and intermittent exposure)<br>Range. Appears adequate (categories of exposure ranged up to 25 units-year) |
| **Morgan *et al.* 1998**<br>Arizona (USA) aircraft manufacturing workers cohort<br>Mortality study | Median size cohort: 4,733; 270 cancer deaths. Exposed deaths: 8 kidney, 6 liver, 3 NHL<br>*Follow-up: not reported* | High exposure jobs were considered to be > 50 ppm TCE. Unclear on the number of workers in high exposed jobs<br>Estimated exposure group[a] for highest | Cumulative exposure peak exposure<br>Range: Not known, but only analyzed low vs. high |

| Study Summary (study sensitivity) | Study size/length of Follow-up | Reported or estimated exposure levels or duration | Exposure-response analyses: dose metrics/range |
|---|---|---|---|
| *Limited statistical power in overall and subgroup analysis; Some workers with potential for exposure to high levels but number not known* | | exposure group (peak/cumulative): moderate. | |
| **Other cohorts** | | | |
| **Bahr *et al.* 2011**<br>Kentucky (USA) uranium enrichment workers cohort<br>Mortality study<br>*Unclear*<br>*Inadequate information to evaluate* | Median size cohort: 5,335 men; 32 NHL deaths<br>Follow-up*:* Information not reported; up to 50 years for some workers, but may be more limited for others. | No information on exposure levels or nature of work. Exposure scores and categories not clear. | Exposure score and category<br>Range: not known |
| **Yiin *et al.* 2009**<br>Tennessee (USA) uranium enrichment workers nested case-control study<br>*Limited*<br>*Number of exposed deaths and exposure levels unknown.* | Number exposed to TCE unknown<br>*Follow-up*: NR, minimum of 13 years, analysis lagged 15 years. | Exposure levels or duration not reported. Mean cumulative exposure in cases 183.8 ± 668.2 for cases and 113.4 ± 558.3 for controls. Units not reported | Cumulative exposure score based on estimated exposure level for activity, duration and fraction spent in activity.<br>Range: Wide range of estimated cumulative exposure, No analyses by exposure category. |
| **Ritz 1999**<br>Ohio (USA) uranium processing workers cohort<br>Mortality study<br>*Limited*<br>*Few exposed deaths* | Median size cohort: 2,971; 328 deaths; Exposed deaths: 6 deaths TC light, and 2 deaths TCE moderate; Analysis not specific for kidney or NHL.<br>*Adequate:* Average 31 years | 94% workers have low exposure, only 6% of cohort had moderate exposure and no workers had heavy exposure.<br>54% were employed for > 5 years | Exposure level (2 categories)<br>Range: limited, most exposed to light work |
| **Silver *et al.* 2014**<br>New York State (USA) electronics manufacturing workers cohort<br>Mortality study<br>*Limited* | Medium size exposed cohort: 3113 ever exposed to TCE.<br>Follow-up: Average 26 years, but young cohort with only 17% deaths in total cohort at end of follow-up. | Level of exposure NR. Only 13.9% of male hourly workers exposed to TCE. | Cumulative exposure score only based on potential of exposure and duration of exposure.<br>Range: Not known |

| Study Summary (study sensitivity) | Study size/length of Follow-up | Reported or estimated exposure levels or duration | Exposure-response analyses: dose metrics/range |
|---|---|---|---|
| *Exposure prevalence in total cohort low, # exposed deaths and exposure levels NR Analysis by 1 cumulative exposure score* | | | |
| **Henschler *et al.* 1995**<br>German cardboard manufacturing cohort<br>Renal cancer incidence and mortality study<br>*Adequate for very high exposure effects*<br>*Few numbers of exposed cases but very high exposure levels* | Small cohort: 169; 7 RCC deaths<br>Follow-up: greater than 30 years for both exposed and unexposed | Estimated to be very high from inhalation and dermal due to degreasing under open conditions<br>Estimated peak exposures (during machine cleaning were > 2,000 ppm) and sustained long-term exposure exceeding 100 ppm (Cherrie *et al.* 2001)<br>Long exposure periods (17.8 months) Estimated exposure group[a] for ever exposure: high to very high (although highest exposure group is not reported, data suggest all workers are highly exposed. | Ever exposure<br>Range not reported |
| **Greenland *et al.* 1994**<br>Massachusetts (USA) electrical manufacturing workers nested case-control study<br>*Limited*<br>*Inadequate to evaluate effects from moderate or high exposure* | Small studies: 15 deaths NHL, 12 kidney cancer, 9 liver cancers (men)<br>Follow-up time for cohort: Short 1969–1984 | Fewer than 10% of jobs had potential for TCE exposure, most of which were from indirect exposure. | Ever vs. never exposed<br>Range: not applicable |
| **Wilcosky *et al.* 1984**<br>Ohio (USA) rubber manufacturing workers nested case-control study<br>*Limited*<br>*Unclear if workers were exposed to TCE* | Small studies: 14 deaths from lymphosarcoma + reticulosarcoma<br>9 observed cases of lymphosarcoma + reticulosarcoma in case-control study<br>Follow-up: 10 years | No quantitative exposure assessment or industrial hygiene measurements available; Exposure based on authorized use | Ever vs. never exposed<br>Range: not applicable |
| **Drinking water study** | | | |
| **Bove *et al.* 2014** | Large cohort: 154,932 (Camp | Estimated mean levels (μg/L): TCE: 358.7 | *TCE drinking water levels* |

| **Study Summary (study sensitivity)** | **Study size/length of Follow-up** | **Reported or estimated exposure levels or duration** | **Exposure-response analyses: dose metrics/range** |
|---|---|---|---|
| Cohort studies using an ecological exposure (drinking water contamination)<br>Mortality<br>*Unclear*<br>*Adequate number of cases in cohort, number in subgroups not reported; unclear how to compare with occupational studies due to differences in exposure route.* | Lejeune); 1,008 cancer deaths. 42 kidney, 58 liver, 51 NHL; 11–15 for 3 cancers in high exposure groups<br>Follow-up ranged from 23 to 30 years; however, probably insufficient because it was a young cohort. | Overall cumulative exposure (µg/L months) for TCE, mean 6,369.3, median 5,289, 20% were exposed to levels between 7,700 and 39,745.<br>Potential daily exposure from TCE-contaminated water system up to 3.6 mg/day (showering and drinking water), which could be equivalent to 0.07 ppm/day and 20 ppm-yr.<br>Estimated exposure group[a:] for cumulative exposuere: low (could be moderate, but because of uncertainity about different route, is rated as low. | *Range: adequate* |

[a] Estimated exposure groups across studies for Forest plot of kidney cancer and highest exposure group reported in the study (Figure 4-2). This information is only provided for studies reporting a risk estimate for highest exposure and kidney cancer

[b]NOCCA-JEM estimates exposure as ppm-yr but author reported as units per year because of uncertainty in the estimates (personal communication with authors).

[c]Personal communication from technical advisor

## Table D-5a. Case-control studies of trichloroethylene and kidney or liver cancer: Study quality

| Study | Selection bias<br>Participation Rates | TCE exposure assessment: Quality and misclassification | Cancer assessment:<br>Misclassification of disease |
|---|---|---|---|
| **Studies in specific areas with knowledge of local industries.** | | | |
| Brüning *et al.* 2003<br>Hospital-based, Germany<br>134 cases RCC, 401 controls<br>1992–2000 | *Possible*<br>Prevalent cases from different hospital departments (presumably most from the same hospital) than residual controls. Cases and control matched by age and gender.<br>Participation rate high among cases but not reported for controls. | *Limited:* Exposure assessed via 3 methods: Self-reported exposure, including narcotic symptoms using subjects (cases and controls) and/or proxies (cases only); CAREX database (expert assessment of occupation groups using TCE) and agent specific (solvents as a group); British JEM; British JEM and CAREX are broad and not country or calendar-year specific. No information was provided on whether the interviewers were blinded to disease status but may not have been blinded.<br>The potential for recall bias (differential, over- or under-estimate of the risk estimate) is usually a concern for self-reported exposure. Self-reported exposure can also be associated with non-differential misclassification; however, it is less likely in this study because exposure to TCE was probably high among at least some (symptomatic) workers, and common knowledge. It seems reasonable that most of the workers with self-reported exposure had high exposure. Exposure misclassification (non-differential) is a concern for subjects classified by the CAREX and JEM assessment. Exposure prevalence varied greatly depending on the methods (80% for CAREX versus 18% for self-reported). | *Unlikely*<br>RCC cases histologically confirmed |
| Vamvakas *et al.* 1998<br>Hospital-based, Germany<br>58 cases RCC, 84 controls<br>1987–2002 | *Probable (differential)*<br>Differences in case and control selection. Cases were selected from a hospital in a highly industrial area with small industries from 1987 to 1993. Unmatched controls selected from different hospitals in adjacent geographical region and at a later time period (time of case-interview) than prevalent cases. If potential bias | *Adequate:* Self-reported TCE exposure (duration, use of TCE) and self-reported narcotic symptoms (frequency, severity); Physician interview with subject (case and controls) or proxy (cases only) not blinded to case status; Expert assignment to exposure categories based on integration of exposure duration and symptoms. The study population was located in a geographical area with similar industries with widespread exposure to TCE with details on the exposure conditions.<br>Potential for recall and interviewer bias (differential, overestimate of risk estimate), especially for reporting | *Unlikely*<br>RCC cases histologically confirmed |

| Study | Selection bias<br>Participation Rates | TCE exposure assessment: Quality and misclassification | Cancer assessment:<br>Misclassification of disease |
|---|---|---|---|
| | (differential, overestimate of the risk estimate) could occur if TCE exposure prevalence was lower in these areas and time periods. Cases were older than controls. Study done during period in which legal proceedings were in progress.<br><br>Participation rate: 87% cases and 75% controls | symptoms due to a legal investigation; However, exposure levels were very high in this study, which may mitigate this concern. | |
| Pesch *et al.* 2000a<br><br>Population-based, Germany<br><br>935 cases RCC, 4,298 controls<br><br>1991–1995 | *Unlikely*<br><br>Cases and controls selected from same population using the same inclusion criteria<br><br>Participation rates high for cases and controls (88% cases, 71% controls) | *Adequate:* Questionnaire and expert assessment using JEM and JTEM which ranked probability and intensity to a given agent but few details on job tasks; Self-reported exposure also used; The JTEM is considered to be a better assessment than JEM. The British JEM may not reflect differences in occupational exposures across studies.<br><br>Exposure misclassification (non-differential) is a concern because of the lower probability of exposure and limited JEM. The level of concern is greater for subjects classified by JEM than individuals classified by JTEM. Exposure misclassification is probably highest among individuals in the lower exposure categories for both matrices. Exposure misclassification regarding exposure group (e.g., low, medium, high) would most likely attenuate any exposure-response relationships. | *Unlikely*<br><br>Most RCC cases histologically confirmed; some sonographically confirmed |
| Charbotel *et al.* 2006, Charbotel *et al.* 2009<br><br>Population-based, France<br><br>86 cases RCC, 326 controls<br><br>1993–2003 | *Unlikely*<br><br>Cases and controls (matched on area of residence, sex, and age) were randomly selected from same practitioners (excluding patients with kidney or bladder cancer, or chronic kidney disease)<br><br>Participation rate similar among cases and controls | *Good:* Semi-quantitative estimates of TCE exposure based on detailed questionnaire, JTEM, and exposure monitoring data (air and urine) of industries in the area; Temporal trends were considered.<br><br>Exposure misclassification (with respect to whether workers were ever exposed) is not a concern especially among individuals in the highest exposure categories (e.g., cumulative, cumulative + peaks). Study was conducted in a localized area with screw-cutting industry. Exposure prevalence and intensity was high, which increases the | *Unlikely*<br><br>RCC cases histologically confirmed |

| Study | Selection bias<br>Participation Rates | TCE exposure assessment: Quality and misclassification | Cancer assessment:<br>Misclassification of disease |
|---|---|---|---|
| | | probability of exposure among the exposed group. | |
| Moore *et al.* 2010<br>Hospital-based, Central and E. Europe<br>1,097 cases RCC, 1,476 controls<br>1999–2003 | *Possible (direction unclear)*<br>Hospital controls excluded smoking-related diseases<br>*Participation bias:* Unknown: NR | *Good:* Structured, special job-specific questionnaire (job titles, tasks, working conditions) and expert assessment (with knowledge of plants in area) of intensity, frequency, and confidence; Assessment re-evaluated at a later time period with 83% agreement for TCE in 1 country and 100% in 2 countries<br>Exposure misclassification with respect to whether workers were ever exposed to TCE is not a concern among workers (~50%) with high confidence assessment (especially among workers with higher or longer exposure) but is more a concern for analysis of all workers. | *Unlikely*<br>RCC cases histologically confirmed |
| **Other studies** | | | |
| Christensen *et al.* 2013<br>Hospital and population-based, Canada<br>177 cases RCC, 48 liver cancer cases; 533 population controls, 2299 cancer controls<br>1975–1985 | *Unlikely* for population controls<br>Cases and cancer controls selected from same hospital and controls randomly from same underlying population using similar inclusion criteria<br>Insufficient data regarding the tissue sites of cancer controls, but < 20% of any given cancer site used.<br>Participation rates were 82% for cancer cases (both cancer cases and controls) and 72% for population controls. | *Adequate to good:* Detailed interview and expert assessment; duration, frequency, intensity and confidence assessed; Proxy interviews conducted with 12% to 14% of subjects.<br>The use of a population-wide occupational database may decrease the probability of exposure and the precision of exposure estimates for individuals. Although expert assessment is detailed and systematic, exposure misclassification (non-differential) is still possible. | *Unlikely*<br>RCC, liver cases histologically confirmed |
| Pesch *et al.* 2000a<br>Population-based, Germany<br>935 cases RCC, 4,298 controls | *Unlikely*<br>Cases and controls selected from same population using the same inclusion criteria.<br>Participation rates high for cases and | *Adequate:* Questionnaire and expert assessment using JEM and JTEM which ranked probability and intensity to a given agent but few details on job tasks; Self-reported exposure also used; The JTEM is considered to be a better assessment than JEM. The British JEM may not reflect differences in occupational exposures across studies. | *Unlikely*<br>Most RCC cases histologically confirmed; some sonographically confirmed |

| Study | Selection bias Participation Rates | TCE exposure assessment: Quality and misclassification | Cancer assessment: Misclassification of disease |
|---|---|---|---|
| 1991–1995 | controls (88% cases, 71 controls) | Exposure misclassification (non-differential) is a concern because of the lower probability of exposure and limited JEM. The level of concern is greater for subjects classified by JEM then individuals classified by JTME. Exposure misclassification is probably the highest among individual in the lower exposure categories for both matrices. Exposure misclassification regarding exposure group (e.g., low, medium, high) would most likely attenuate any exposure-response relationships. | |
| Dosemeci *et al.* 1999<br>Population-based, Minnesota US<br>438 cases RCC, 687 controls<br>1988–1999 | *Unlikely*<br>Cases identified via state cancer registry and controls randomly selected from the same underlying population using similar inclusion criteria.<br>Participation rate was lower among cases (64%) than controls (97%) but no information to suspect that participation was related to exposure and thus the lower participation rate would most likely reduce precision. | *Limited:* JEM assigned by expert but based on broad occupational and industry codes; Only considered current and usual jobs and duration of employment only assessed; Duration by calendar period not considered.<br>Exposure misclassification (non-differential) for ever-exposure to TCE is a concern because of the limited JEM and lower probability of exposure. | *Unlikely*<br>RCC cases histologically confirmed. |

BMI = body mass index; JEM = job exposure matrix; JTEM = job-task exposure matrix; RCC = renal cell carcinoma; TCE = trichloroethylene.

## Table D-5b. Kidney case-control studies: Study sensitivity and exposure response analyses

| Study Summary | Study size/Exposure prevalence | Reported or estimated exposure levels or duration | Exposure response analyses: Dose metrics /range |
|---|---|---|---|
| **Studies in specific areas with knowledge of local industries** | | | |
| Brüning *et al.* 2003<br>Hospital-based, Germany<br>1992–2000<br>*Adequate to good*<br>*Adequate number of subjects exposed to high levels of TCE with confidence in exposure classification* | Small/medium study: 134 RCC cases/401 controls<br>Exposure prevalence: 18.7% (N = 25) cases, 9.5% (N = 38) using self assessment<br>87% cases, 79% controls using CAREX (less confidence) | Very high exposure and long exposures<br>Estimated to be 400–600 ppm during peak (hot dipping) and > 100 ppm overall (Cherrie *et al.* 2001)<br>Approx. 50% cases > 10 years' exposure<br>Estimated exposure group[a] for workers with daily narcotic symptoms: very high. | Jobs using TCE (CAREX), exposure to solvent (JEM)<br>Self-assessed: ever exposed, duration and time since first and last exposure<br>Range: not known, but may be shallow due to exposure from open conditions. |
| Vamvakas *et al.* 1998<br>Hospital-based, Germany<br>1987–2002<br>*Adequate*<br>*Limited number of subjects but exposed to high levels of TCE with high confidence in the exposure classification* | Small study: 58 RCC cases/84 controls<br>Exposure prevalence: 33% (N = 19) cases; 6% (N = 5) controls | Very high exposure and long exposures<br>Estimated to be 400 to 600 ppm during peak (hot dipping) and > 100 ppm overall (Cherrie *et al.* 2001)<br>Mean duration of exposure among cases was 16 years and 7 years among controls<br>Estimated exposure group[a] for highest rank exposure category: very high. | Ever/never and ranked exposure category (integration of exposure time and symptoms)<br>Range: not known, but may be shallow due to exposure from open conditions |
| Charbotel *et al.* 2006, Charbotel *et al.* 2009<br>Population-based, France<br>1993-2003<br>*Adequate to good*<br>*Adequate number of subjects exposed to high levels of TCE with confidence in the exposure classification. May not have adequate statistical* | Small study: 86 RCC cases; 326 referents<br>Exposure prevalence: 43% (N = 37) cases, 35% (N = 110) controls for ever exposed, and 19% (N = 16) cases, and 11.7% (N = 37) among highest exposure group | High intensity of exposure (duration NR); Among controls the median exposure for low, medium and high categories = 60,252 and 630 ppm, respectively; Among cases median exposure = 30, 300 and 885 ppm respectively<br>Estimated TCE intensities (ppm) for specific jobs<br>15–18 for open cold degreasing<br>120 for jobs near open hot degreasing machines | Ever exposed, cumulative exposure, and combined cumulative and peak exposure, trend analysis<br>Range: good (see previous column) |

| Study Summary | Study size/Exposure prevalence | Reported or estimated exposure levels or duration | Exposure response analyses: Dose metrics /range |
|---|---|---|---|
| *power in subgroup analysis but good range in exposure intensity.* | | up to 300 ppm for work directly above tank<br>300–600 for emptying, cleaning and refilling degreasers.<br>Cumulative exposure categories: low 5–150 ppm-yr, medium 155–335 ppm-yr and > 35 ppm-yr<br>Estimated exposure group[a] for highest cumulative exposure: very high | |
| Moore *et al.* 2010<br>Hospital-based, Central and Eastern Europe<br>1999–2003<br>*Adequate*<br>*Adequate cases and controls with high confidence of exposure; Ability to evaluate effects of high exposure is increased by stratifying on probability and exposure intensity or duration.* | Large study: 1097 RCC cases/1476 controls<br>Exposure prevalence: 5.8% (N = 48) cases and 3.4 (N = 40) controls for any exposure and ~ 2%–4% (N = 17–31) cases and 1%–2% controls (N = 10–21) for high exposure categories | No information on actual exposure<br>Estimated TCE intensity in JEM were coded into 3 categories: 0 to < 5 ppm, 5 to 50 ppm, and > 50 ppm (2.5, 25, and 75 ppm midpoints)<br>Duration (years): 1.35 (6.3–26.3 for controls) 19.5 (5.8–31) for cases<br>Estimated exposure group for individuals with highest average exposure: moderate to high. | Ever, cumulative, average-intensity, hours, and years; Separate analyses conducted for all and high confidence exposure assessments (> 40% workers probably or definitely exposed jobs).<br>Range: Appears to be adequate based on estimated interquartile range and differences in exposure intensity among jobs; however, only two exposure groups for each metric. |
| **Other studies** | | | |
| Christensen *et al.* 2013<br>Hospital and population-based, Canada<br>1975–1985<br>*Limited*<br>*Few exposed cases and controls with substantial exposure* | Moderate size: 177 RCC cases/ 1999 cancer controls, 533 population controls<br>Small size: 48 liver cases, 1834 liver cancer controls and 533 population controls<br>Exposure prevalence: < 3% (N = 15 population controls; 63 cancer cases, and 5 RCC cases, 1 liver cancer) for any exposure and controls and < 2 (N = 9 population controls, N = 2 | Levels and duration not reported.<br>Occupations considered to have the highest exposure were mechanics and repairmen, metal machining occupations, electrical and electronics and metal shaping and formulation.<br>Estimated exposure group for individuals with substantial exposure: assumed low (unclear because category includes confidence of exposure). | Two categories of exposure: Any and substantial (integration of probability, frequency, concentration and duration)<br>Range: not applicable |

| Study Summary | Study size/Exposure prevalence | Reported or estimated exposure levels or duration | Exposure response analyses: Dose metrics /range |
|---|---|---|---|
| | RCC, 1 liver cancer) for substantial exposure | | |
| Pesch *et al.* 2000a<br>Population-based, 5 German regions<br>1991–1995<br>*Limited*<br>*Few exposed cases and controls, most of which were likely exposed to low levels of TCE.* | Large study size: 935 (570 men & 375 women) cases/4,298 controls<br>Prevalence of substantial TCE exposure was low among male cases and varied by type of JEM: 10% (N = 55) males German JEM 3.9 (N = 15) (JTEM). Prevalence was less than 2% (N < 5) in females. Exposed controls NR | No information on the types of job that were considered to be exposed to TCE or on estimated exposure levels.<br>Includes the Arnsberg and other regions; NAS (2006) estimated that most subjects had minimal contact with TCE averaging concentration of 10 ppm or less.<br>Estimated exposure group for individuals with substantial exposure: assumed low (unclear because category includes probability of exposure). | Rank category of exposure index (integration of probability, duration and intensity) for two JEM and JTEM; Reported separately for men and women<br>Range: Not applicable |
| Dosemeci *et al.* 1999<br>Population-based, Minnesota, (USA)<br>1988–1999<br>*Limited to adequate*<br>*Adequate numbers of exposed cases and controls to evaluate ever versus never exposure; No evaluation of exposure level.* | Moderate size: 438 (273 men 165 women) cases; 687 (462 men, 225 women) controls<br>Exposure prevalence: 13% cases (N = 55); 10% controls (N ~69) | No information on level duration or jobs considered to have TCE exposure. | Ever-exposed reported separately for men and women.<br>Range: not applicable |

JEM = job exposure matrix; JTEM = job-task exposure matrix; RCC = renal cell carcinoma; TCE = trichloroethylene

[a] Estimated exposure groups across studies for forest plot of kidney cancer and highest exposure group reported in the study (Figure 4-2). This information is only provided for studies reporting a risk estimate for highest exposure and kidney cancer

**Table D-6a. Case-control studies of trichloroethylene and NHL and related subtypes: Summary of study quality.**

| Study and number of TCE-exposed cases/controls | Selection/participation bias | Quality of TCE exposure assessment and exposure misclassification | Cancer assessment: Misclassification of cases |
|---|---|---|---|
| **NHL** | | | |
| Christensen *et al.* 2013<br>Hospital and population-based, Canada<br>215 cases NHL, 533 controls | *Unlikely*<br>Cases and cancer controls selected from same hospital and controls randomly from same underlying population using similar inclusion criteria<br>Participation rates were 82% for cancer cases (both cancer cases and controls) and 72% for population controls. | *Adequate to good:* Detailed occupational information, expert assessment by team of experts; semi-quantitative rating of duration, frequency, intensity and confidence assessed; Not clear if calendar-year specific<br>The probability of exposure is less certain in population-based studies. Although expert assessment is detailed and systematic, exposure misclassification (non-differential) is still possible. | *Possible*<br>Histologically confirmed but older classification<br>(ICD-9) |
| Cocco *et al.* 2013 and studies included in the analysis:<br>ENGELA (Orsi *et al.* 2010)<br>MIS (Miligi *et al.* 2006)<br>EPILYMPH Cocco *et al.* 2010)<br>NCI-SEER (Purdue *et al.* 2011)<br>3,788 cases NHL+ subtypes (DLBCL, FL, CLL), 4279 controls<br>MM evaluated in Cocco *et al.* 2011 | *Unlikely*<br>Adequate methods to select cases and controls in all studies; consecutive incident cases and matched controls in 3 studies or selected to represent age and gender in the MIS study.<br>Population controls: EPILYMPH, NCI-SEER, MIS<br>Hospital controls: EPILYMPH and ENGELA<br>Participation rates in the individual studies ranged from 76% to > 90% among cases, 81% to 73% among hospital controls, and 52% to 73% in population controls. There are no concerns of differential bias in the pooled analysis although lower rates may decrease precision. | *Good*: Detailed questionnaire and occupational data; expert assessment by team of experts, semi-quantitative rating of exposure using multiple scales (intensity, frequency, duration, probability); Calendar-year specific; Exposure assessment from the four studies was harmonized.<br>NCI-SEER analysis also assessed average exposure, average weekly, and average exposure intensity for each subject.<br>Exposure misclassification (with respect to whether workers were ever exposed) is not a concern among individuals classified as having high probability of exposure or with the higher level of exposure (frequency, duration, or intensity) but is possible (non-differential) among individuals in the lower exposure categories. Exposure misclassification regarding intensity level (e.g., low, medium, high) may be more of a concern and would most likely attenuate any exposure-response relationships. | *Unlikely*<br>Histologically confirmed; a subset re-reviewed in some studies; Classification harmonized using the WHO Interlymph consortium classification |
| Deng *et al.* 2013, Wang *et al.* 2009 | *Unlikely*<br>Cases and matched controls selected | *Limited to adequate*: Occupational data on job titles and companies, genetic JEM based on | *Unlikely*<br>Cases reviewed by pathologists; |

| Study and number of TCE-exposed cases/controls | Selection/participation bias | Quality of TCE exposure assessment and exposure misclassification | Cancer assessment: Misclassification of cases |
|---|---|---|---|
| Population-based Connecticut (USA)<br>601 NHL+subtypes cases, 7171 controls | from the same underlying population using similar inclusion criteria; Cases selected from cancer registry.<br>Participation rates: cases 72%; Controls - RDD 69%, Health care 47%. Low rates may decrease precision. | semi-quantitative rating of occupations (rather than tasks); Not calendar year specific.<br>Overall, exposure misclassification (non-differential) is a concern among individuals classified as ever exposed. The likelihood of exposure is increased among workers in the higher probability or higher intensity categories. | 2001 WHO (REAL) classification |
| Persson and Fredrikson 1999<br>Population-based (pooled study)<br>Sweden<br>199 cases NHL, 479 controls | *Unlikely*<br>Cases and matched controls selected from the same underlying population using similar inclusion criteria.<br>Controls drawn for other studies and unclear which years controls were recruited.<br>Participation rate*:* 90% among cases but NR for controls | *Limited:* Self-reported ranked exposures (~ 19 occupational exposures); Not clear if interviewers were blinded to case-control status.<br>Exposure misclassification is a concern and likely to be substantial. Direction of potential of bias is unknown since self-reported exposures can vary between cases and control; however, considerable non-differential misclassification for cases and controls is likely. | *Possible*<br>2nd study histologically confirmed but not 1st study (not histologically confirmed); ICD coding NR |
| Nordstrom *et al.* 1998<br>Population-based<br>Sweden<br>121 cases HCL, 484 controls | *Unlikely*<br>Cases and matched controls selected from the same underlying population using similar inclusion criteria; Cancer selected from cancer registry.<br>Participation rates: cases 91%; controls 83% | *Limited:* Complete occupational history and self-reported exposure (primarily job titles, not tasks or working conditions); Exposure assigned based on occupation, qualitative; Minimal requirements for ever exposure based on very low exposure.<br>Exposure misclassification (most likely non-differential) is a concern and likely to be substantial. | *Possible*<br>Subset of cases re-reviewed: NCI classification |
| Hardell *et al.* 1994<br>Population-based<br>Sweden<br>105 cases NHL, 355 controls | *Unlikely*<br>Cases and matched controls selected from the same underlying population using similar inclusion criteria; Cases selected from hospital dept.<br>Participation rates: unknown | *Limited:* Complete occupational history and self-reported exposure (primarily job titles, not tasks or working conditions); Exposure assigned based on occupation, qualitative; Minimal requirements for ever exposure based on very low exposure.<br>Exposure misclassification (most likely non-differential) is a concern and likely to be substantial. | *Possible*<br>Cases histologically confirmed by subtype, stage, and site but older Rappaport classification. |

| Study and number of TCE-exposed cases/controls | Selection/participation bias | Quality of TCE exposure assessment and exposure misclassification | Cancer assessment: Misclassification of cases |
|---|---|---|---|
| **Multiple Myeloma** | | | |
| Gold *et al.* 2011<br>Seattle, WA and Detroit, MI (USA) SEER registry<br>181 cases MM, 481 controls | *Unlikely*<br>Cases and matched controls selected from the same underlying population using similar inclusion criteria; Cases selected from cancer registry.<br>Participation rates*:* cases (71%) and controls (52%) | *Good:* Detailed occupational information, JTEM specific for 6 solvents assigned by experts; quantitative rating of exposure intensity and assignment of cumulative exposure (based on exposure measurement reported in the literature); (Same exposure assessment as Purdue *et al.* 2011 for NH.).<br>Exposure misclassification is not a concern, especially among individuals with the highest cumulative exposure. Exposure misclassification between levels of cumulative exposure would most likely attenuate any exposure-response | *Unlikely*<br>Most SEER registry cases histologically confirmed; ICD – O-2 or 3) |
| Costantini *et al.* 2008<br>Population-based, Italy (MIS)<br>263 cases MM, 1100 controls; cases CLL NR; (total LH cases 2,737, 1799 controls) | *Unlikely*<br>Cases and matched controls selected from the same underlying population using similar inclusion criteria .<br>Participation rates were moderately high: 83% cases, 76% controls | *Adequate:* Job/industry specific questionnaire, regional experts, semi-quantitative rating of exposure using two exposure scales; calendar-year specific; Individuals classified by 2 exposure levels and 2 duration levels; Intensity was primarily based on control measures used to limit exposure.<br>Although individuals with low probability of exposure were excluded from the study, exposure misclassification (with respect to whether individuals were ever exposed) is possible (random, non-differential), especially among individuals in the low exposure group. | *Possible*<br>Cancer diagnosis from local hospital reclassified using the NCI classification; Pathologists verified subset of cases; NHL and CLL classified based on biological properties. |

CLL = chronic lymphocytic lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin lymphoma; JEM = job exposure matrix; JTEM = job-task exposure matrix; MIS = Multicentre Italian Study; NHL = non-Hodgkin lymphoma; NR = not reported; OR = odds ratio; SEER = Surveillance, Epidemiology and End Results Program (US National Cancer Institute); SLL = small cell lymphocytic lymphoma; TCE = trichloroethylene; VOC = volatile organic compounds.

## Table D-6b. NHL case-control studies: Study sensitivity and exposure response analysis

| Study<br>Summary (study sensitivity) | Study size/exposure prevalence | Reported or estimated exposure levels or duration | Exposure response analyses: dose metrics/range |
|---|---|---|---|
| **NHL** | | | |
| Christensen *et al.* 2013<br>Hospital and population-based, Canada<br>*Limited*<br>*Small numbers of exposed cases and controls* | Moderate size: 215 NHL cases/23,141 cancer controls, 533 population controls<br>Exposure prevalence: < 3% (N = 15 population controls; 65 cancer cases, and 7 NHL) for any exposure and controls and < 2 (N = 9 population controls, N = 30 cancer controls, N = 2 NHL) for substantial exposure | Levels and duration not reported.<br>Occupations considered to have the highest exposure were mechanics and repairmen, metal machining occupations, electrical and electronics and metal shaping and formulation. | Any and substantial<br>Range: NA |
| Cocco *et al.* 2013 and studies included in the pooled analysis:<br>ENGELA (Orsi *et al.* 2010)<br>MIS (Miligi *et al.* 2006<br>EPILYMPH Cocco *et al.* 2010)<br>NCI-SEER (Purdue *et al.* 2011)<br>*Adequate*<br>*Adequate number of cases and controls all NHL but not all NHL subtypes; Estimated levels suggest levels relatively high for the highest exposed workers, relatively good confidence in exposure classification.* | Very large study: 3788 cases/4279 controls<br>Exposure prevalence in total population: 9% (N = 711) ever exposed, 1% (N = 88) definite exposed<br>Exposure prevalence among highest exposure intensity category: < 1.5 % (N = 57 controls, 48 cases) for total population; < 10 cases or controls among those with high probability of exposure | Levels not reported: levels estimated for analysis: Highest exposure intensity category > 75 ppm<br>Estimated levels<br>NCI-SEER: levels not reported; levels estimated for analysis<br>Highest cumulative exposure category: > 234,000 ppm-hr (prevalence: 0.7% controls, 2.5% cases)<br>Highest average intensity exposure category: > 99 ppm (prevalence: 2.3% controls, 3.4% cases)<br>MIS<br>Study regions chosen because of large presence of manufacturing industries using solvents or they were agricultural areas. | Probability, intensity, frequency, duration among all subjects and high probability subjects<br>*Additional metrics in individual studies*<br>Cumulative exposure: EPILYMPH, NCI-SEER<br>Average weekly: NCI-SEER<br>Sensitivity by latency, interviewing variable, & unemployment – NCI-SEER<br>Range: Adequate range based on estimates of intensity, duration and frequency of exposure. |
| Deng *et al.* 2013, Wang *et al.* 2009<br>Population-based Connecticut, | Large study: 601 NHL/ 717 controls<br>Exposure prevalence: 11% controls (N = 79) and 13% (N = 77) for | No information on reported or estimated level. | Low or medium/high exposure and high or low probability of exposure<br>Range: No information |

| **Study Summary (study sensitivity)** | **Study size/exposure prevalence** | **Reported or estimated exposure levels or duration** | **Exposure response analyses: dose metrics/range** |
|---|---|---|---|
| (USA) (Women)<br>*Limited*<br>*Few numbers of exposed cases and controls; Limited ability to detect an effect because there are no workers with high exposure and high probability of exposure.* | ever exposed; < 2% (N = 8 controls and 13 cases) for medium high exposure; and (N = 31) controls and 5.7% (N = 34) cases for median high probability; 0 cases and controls with high probability and median and high intensity | | |
| Nordstrom *et al.* 1998<br>Population-based<br>Sweden<br>*Limited*<br>*Relatively few exposed cases and controls with possibly low levels of exposure and low confidence in exposure classification* | Small study: 121 cases NHL, 484 controls<br>TCE exposure prevalence among referents ~7% (9 cases and 26 controls) | No information on reported or estimated levels or duration of exposure; Minimum requirement for being classified as exposed was 1 day | Ever/never only.<br>Range: Not applicable |
| Persson and Fredrikson 1999<br>Population-based (pooled study)<br>Sweden<br>*Limited*<br>*Relatively small number of exposed cases with possibly low levels of exposure and low confidence in exposure classification* | Medium size study: 199 cases NHL, 479 controls<br>TCE exposure prevalence among referents ~7% (16 cases/32 controls) | No information on reported or estimated levels or duration of exposure reported; Authors state quantitative information available but merged intensity categories.<br>Minimum of 1 year exposure duration | Ever/never exposure only.<br>Range: Not applicable |
| Nordstrom *et al.* 1998<br>Population-based<br>Sweden<br>*Limited*<br>*Relatively few exposed cases and controls with possibly low levels of exposure and low confidence* | Small study: 121 cases NHL, 484 controls<br>TCE exposure prevalence among referents ~7% (9 cases and 26 controls) | No information on reported or estimated levels or duration of exposure; Minimum requirement for being classified as exposed was 1 day | Ever/never only.<br>Range: Not applicable |

| **Study Summary (study sensitivity)** | **Study size/exposure prevalence** | **Reported or estimated exposure levels or duration** | **Exposure response analyses: dose metrics/range** |
|---|---|---|---|
| *in exposure classification* | | | |
| Hardell *et al.* 1994<br>Population-based<br>Sweden<br>*Limited*<br>*Few cases and controls with possibly low levels of exposure and low confidence in exposure classification* | Small study: 105 cases and 355 controls<br>Prevalence of TCE exposure among controls was 1% (4 cases/4 controls) | No information on exposure levels or duration; Minimal criteria for being considered exposed is low: less than 1 week continuous exposure or less than 1 month total exposure was considered low grade, and more than that was considered high grade. | Ever/never only<br>Range: Not applicable |
| Gold *et al.* 2011<br>Seattle, WA and Detroit, MI (USA) SEER registry<br>181 cases MM, 481 controls<br>*Adequate*<br>*Adequate number of cases in control in subgroup analysis, including the highest exposure group and relatively good confidence in the exposure classification* | Medium size study: 181 MM cases, 481 controls<br>Exposure prevalence: 29% (N = 138) controls and 37% (N = 66) cases for ever-exposed and 7.1 (N = 34) controls and 13% (N = 24) in highest cumulative exposure category | Exposure levels not reported. Levels estimated for analysis: Highest cumulative exposure category > 7,794-57,000 ppm. | Exposure duration and cumulative exposure<br>Range: adequate (estimated) range of exposures |
| Costantini *et al.* 2008<br>Population-based, Italy<br>*Limited statistical power*<br>*Few exposed cases and controls* | Median size study: 263 cases MM, 1100 controls; cases CLL NR<br>TCE prevalence among controls was ~2.5% (N = 5 cases and 27 controls for medium/high and 3.5% (N = 9 cases and 28 controls) for low/very low exposure | Study regions chosen because of large presence of manufacturing industries using solvents or they were agricultural areas. | Intensity and duration of exposure.<br>Range: No information |

CLL = chronic lymphocytic lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin lymphoma; JEM = job exposure matrix; JTEM = job-task exposure matrix; NHL = non-Hodgkin lymphoma; NR = not reported; OR = odds ratio; SEER = Surveillance, Epidemiology and End Results Program (US National Cancer Institute); SLL = small cell lymphocytic lymphoma; TCE = trichloroethylene; VOC = volatile organic compounds.

**Table D-7. Studies included in three meta-analyses by cancer site**

| Studies included | Kidney | | | Liver | | NHL | |
|---|---|---|---|---|---|---|---|
| | S-J 2011[a] | Karami 2012[b] | Kelsh 2010[c] | S-J 2011[a] | Alexander 2007[d] | S-J 2011[a] | Karami 2013[b] |
| ***Cohort and nested case-control studies*** | | | | | | | |
| Anttilla 1995 | X | X | X | X | X | X | X |
| Axelson 1994 | X | X | X | X | X | X | X |
| Bahr 2011 | | | | | | | X |
| Blair 1998 | | | X | | X | | |
| Boice 1999 | X | | X | X | X | X | |
| Boice 2006 | | X | X | X | X | X | X |
| Greenland 1994 | X | X | | X | X | X | |
| Hansen 2001 | X | X | X | X | X | X | X |
| Lipworth 2011 | | X | | | | | X |
| Morgan 1998 | X | X | X | X | X | X | X |
| Raaschou-Nielson 2003 | X | X | X | X | X | X | X |
| Radican 2008 | X | X | X | X | | X | X |
| Ritz 1999 | | X | | | X | | X |
| Zhao 2005 | X | | | X | | X | |
| ***Case-control studies*** | | | | | | | |
| Asal 1988 | | X | | | | | |
| Brüning 2003 | X | X | X | | | | |
| Charbotel 2006 | X | X | X | | | | |
| Cocco 2010 | | | | | | X | X |
| Dosemeci 1999 | X | X | X | | | | |
| Hardell 1994 | | | | | | X | X |
| Harrington 1989 | | X | | | | | |
| Henschler 1995 | | X | X | | | | |
| Kato 2005 | | | | | | | X |
| Moore 2010 | X | X | | | | | |
| Miligi 2006 | | | | | | X | X |
| Nordstrom 1998 | | | | | | X | X |
| Persson-Frederickson 1999 | | | | | | X | X |
| Pesch 2000 | X | X | X | | | | |
| Purdue 2011 | | | | | | X | X |
| Siemiatycki | X | X | X | | | X | X |

| Studies included | Kidney | | | Liver | | NHL | |
|---|---|---|---|---|---|---|---|
| | S-J 2011[a] | Karami 2012[b] | Kelsh 2010[c] | S-J 2011[a] | Alexander 2007[d] | S-J 2011[a] | Karami 2013[b] |
| 1991 | | | | | | | |
| Vamvakas 1998 | | X | X | | | | |
| Wang 2009 | | | | | | X | X |

S-J = Scott and Jinot 2011 (see also EPA 2011).
[b]Karami *et al.* 2012, 2013: Studies classified as TCE-exposed only; chlorinated solvent studies not included.
[c]Kelsh *et al.* (2010): Group I studies (classified as having adequate exposure data to identify workers with TCE exposure) only; Group II studies (limited exposure data) excluded.
[d]Alexander *et al.* 2007a: Group 1 studies, TCE-exposed subgroup (classified as having adequate exposure data to identify subgroup of workers with TCE exposure) only; Group II studies (limited exposure data) excluded.

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# Appendix E: Immune Effects (Animals)

This section has the tables summarizing the findings of immune effects in experimental animals. It also has tables related to methods, including study design and endpoints measured.

To return to text citing Appendix E in Section 5, click here

To return to text citing Appendix E in Section 6, click here

**Table E-1. Designs of studies evaluated for trichloroethylene or metabolite induced immunomodulation relevant to lymphoma and liver cancer**

| Species | Strain | Route | Chemical | Number of studies |
|---|---|---|---|---|
| Mouse | MRL+/+ | Drinking Water | TCE | 12* |
| | | | TCA | 1 |
| | | | TCAH | 2 |
| | | IP | TCE | 5** |
| | | | DCAA | 1 |
| | | | DCAC | 3 |
| | | SC | Formyl-albumin adduct | 1 |
| | | | Dichloroacetyl-albumin adduct | 1 |
| | | | Trichloroethene oxide-albumin adduct | 1 |
| | | Inhalation | TCE | 1 |
| | NOD/Born | Drinking water | TCE | 1 |
| | NZBWF1 | Drinking water | TCE | 1 |
| | SV/129 (PPAR-null) | Inhalation | TCE | 1 |
| | C3H/HeJ | Drinking water | TCAH | 1 |
| | $B6C3F_1$ | Drinking water | TCE | 2 |
| | | IP | TCE | 1 |
| | CD-1 | Drinking water | TCE | 1 |
| | | | CH | 1 |
| | | Gavage | CH | 1 |
| | | Inhalation | TCE + bacteria | 4 |
| Rat | Sprague-Dawley | IP | TCE | 2 |
| | | Intradermal | TCE | 1 |
| Guinea pig | FMMU | Dermal | TCE | 1 |
| | | Intradermal | TCE | 2 |
| Dog | Cross-bred | Intratracheal intubation | TCE | 2 |
| | | IV | TCE | 1 |

TCE = trichloroethylene, TCA = trichloroacetic acid, TCAH = trichloroacetyl hydrate, DCAA = dichloroacetyl chloride, DCAC = dichloroacetyl anhydride, CH = chloral hydrate, SC = subcutaneous injection, IP = intraparitoneal injection, IV = intravenous injection.

*One study had a group co-exposed to diallyl sulfide, a CYP2E1 inhibitor.

**One study had a group co-exposed to *N*-acetylcysteine, an enhancer of the antioxidant activity of glutathione.

To return to text citing Table E-1, click here.

## Table E-2. Immunomodulatory endpoints relevant to cancer

| Endpoint | + | - | = | +/- |
|---|---|---|---|---|
| ***Serum*** | | | | |
| dichloroacetyl-protein adduct | 1 | | | |
| dichloroacetyl-albumin adduct | 1 | | | |
| dichloroacetyl-CYP2E1 adduct | 1 | | | |
| hydroxynonenal-protein adduct | 2 | | | |
| malondialdehyde-protein adduct | 2 | | | |
| IgG | 6 | 1 | 2 | |
| anti-dichloroacetyl-protein adduct antibody | 2 | | 1 | |
| anti-dichloroacetyl-albumin adduct antibody | 4[e] | | 1 | |
| anti-formyl-albumin adduct antibody | 3[e] | | | |
| anti-trichloroethene oxide-albumin adduct antibody | 3[e] | | | |
| anti-albumin antibody | 3[e] | | 2 | |
| anti-hydroxynonenal-protein adduct antibody | 4[a] | | | |
| anti-malondialdehyde-protein adduct antibody | 5[a] | | 1 | |
| anti-liver antibody | 1 | | 1 | |
| anti-nuclear antibody | 9 | | 3 | |
| anti-DNA antibody | 1[a] | | 2 | |
| anti-ssDNA antibody | 6[a] | | 7[d] | |
| anti-dsDNA antibody | 3[a] | | 4[d] | |
| anti-sheep RBC IgM response | | | 1 | 1 |
| ***Peripheral blood*** | | | | |
| leukocyte number | | 4 | 1 | |
| neutrophil number | | 3 | | |
| lymphocyte number | | 1 | 3 | |
| CD4 T-cell numbers | | 2 | | |
| CD8 T-cell numbers | | 1 | 1 | |
| B-cell number | | 1 | | |
| ***Spleen*** | | | | |
| lymphocyte number | 2 | | | |
| lymphocyte proliferation | 1 | | | |
| T-cell proliferation | | | 4[d] | |
| CD4 T-cell numbers | | 2[d] | 1 | 1[d] |
| CD4 T-cell proliferation | 2[b] | | 1[d] | |
| CD8 T-cell numbers | | 1[d] | 6[d] | |
| CD8 T-cell proliferation | | | 2[ad] | |
| B-cell number | | 2[d] | 5 | |
| B-cell proliferation | | | 6[d] | |
| B-cell activation | | | 4[d] | |
| anti-sheep RBC IgM response | 1 | 2[d] | | |
| NK cell proliferation | | | 2[d] | |
| NK cell cytolytic activity | | | 3 | |
| Splenocytes stimulated with hydroxynonenal-albumin adduct - IFN-gamma | 2 | | | |
| Splenocytes stimulated with malondialdehyde-albumin adduct - IFN-gamma | 2 | | | |
| Splenocytes stimulated with hydroxynonenal-albumin adduct - IL-2 | 2 | | 1 | |
| Splenocytes stimulated with malondialdehyde-albumin adduct - IL-2 | 2 | | 1 | |
| ***Lymph node*** | | | | |
| CD4 T-cell numbers | | | 5 | |
| CD8 T-cell numbers | | | 4 | |

| Endpoint | + | - | = | +/- |
|---|---|---|---|---|
| B-cell number | | | 2 | |
| B-cell activation NOS | | | 2 | |
| ***Liver*** | | | | |
| TCE-protein adduct | 1 | | | |
| dichloroacetyl-protein adduct | 2[b] | | | |
| dichloroacetyl-CYP2E1 adduct | 1 | | | |
| hydroxynonenal-protein adduct | 2[a] | | | |
| malondialdehyde-protein adduct | 2[a] | | | |
| Inflammation | 7[c] | | 5 | |
| T-cell infiltration | 2 | | | |
| NK cell cytolytic activity | | 2 | | |
| hepatocyte proliferation | 2[c] | | | |
| ***Kidney*** | | | | |
| glomerular antibody deposits | 1 | | | |
| hydroxynonenal-protein adduct | 1[a] | | | |
| Malondialdehyde-protein adduct | 1[a] | | | |
| Inflammation | 1 | | 1 | |
| ***Bacterial infection*** | | | | |
| Death from bacterial infection | 2 | | | |
| Lung - bacterial infection/bacteria clearance | 1 | | | 1 |
| Lung - macrophage phagocytosis of bacteria | | 1 | | |

"+" = increased effect, "-" = decreased effect, "=" = no change in effect, +/- = both increases and decreases in effect were seen depending on dose or time point.
[a]Prevented by *N*-acetylcysteine.
[b]Prevented by diallyl sulfide.
[c]PPAR$^{-/-}$ had no effect.
[d]Exposure started before conception.
[e]Exposed to TCE albumin adducts (formyl-, trichlorethene oxide-, diacetyl-).

To return to text citing Table E-2, click here.

The tables below provide study-by-study information on the immune effects of trichloroethylene in experimental animals (see Section 5.2.1 and 6.2.1.5). The designs of 51 studies are reported along with the results of 62 endpoints. The five tables are divided by the endpoints studied (F-3: Blood – Adducts and Leukocytes; F-4: Blood – Antibodies; F-5: Spleen; F-6: Liver and Kidney; F-7: Splenic ex vivo cytokines, Lymph nodes, and Anti-bacterial response).

**Table E-3. Blood – Adducts and leukocytes**

| Reference | Design | Dichloroacetyl-protein adduct | Dichloroacetyl-albumin adduct | Dichloroacetyl-CYP2E1 adduct | Hydroxynonenal-protein adduct | Malondialdehyde-protein adduct | Leukocyte number | Neutrophil number | Lymphocyte number | CD4 T-cell number | CD8 T-cell number | B-cell number |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Trichloroethylene; Mouse (MRL+/+); Drinking water** | | | | | | | | | | | | |
| Wang 2007b | 48 wk | | | | + | + | | | | | | |
| Wang 2012 | 12, 24, 36 wk | | | | + | + | | | | | | |
| **Trichloroethylene; Mice (NOD/Born); Drinking water** | | | | | | | | | | | | |
| Ravel 2004 | 4, 8, 12 wk | | | | | | - | | - | - | - | - |
| **Chloral hydrate; Mice (CD-1); Drinking water** | | | | | | | | | | | | |
| Kauffmann 1982 | 90 d | | | | | | = | | | | | |
| **Trichloroethylene; Rat (Sprague-Dawley); IP** | | | | | | | | | | | | |
| Halmes 1997 | 4 hr | + | + | + | | | | | | | | |
| Chen 2006 | 5, 7 wk | | | | | | | | | - | = | |
| **Trichloroethylene; Dog (cross-bred); Intratracheal intubation** | | | | | | | | | | | | |
| Hobara 1984 | 1 hr | | | | | | - | - | = | | | |
| Hobara 1984 | 1, 4 hr | | | | | | - | - | = | | | |
| **Trichloroethylene; Dog (cross-bred); IV** | | | | | | | | | | | | |
| Hobara 1984 | Single dose | | | | | | - | - | = | | | |

**Table E-4. Blood – Antibodies**

| Reference | Design | IgG | Anti-dichloroacetyl-protein adduct antibody | Anti-dichloroacetyl-albumin adduct antibody | Anti-formyl-albumin adduct antibody | Anti-trichloroethene oxide-albumin adduct antibody | Anti-albumin antibody | Anti-hydroxynonenal-protein adduct antibody | Anti-malondialdehyde-protein adduct antibody | Anti-liver antibody | Anti-nuclear antibody | Anti-DNA antibody | Anti-ssDNA antibody | Anti-dsDNA antibody | Anti-sheep red blood cell IgM response |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Trichloroethylene; Mice (MRL+/+); Drinking water** | | | | | | | | | | | | | | | |
| Blossom 2007b | Preconception to 4, 6, 8 wk old | | | | | | | | | | | | = | | |
| Cai 2008 | 36, 48 wk | | | | | | | | | | = | | | | |
| Gilbert 2009 | 10, 18, 26 wk | | | | | | | | | + | | | | | |
| Gilbert 2011 | 8 wk | | | | | | | | | = | = | | | | |
| Griffin 2000a | 4, 6, 8, 22 wk | + | + | | | | | | | | + | | | | |
| Griffin 2000b | 4, 32 wk | | | | | | | | | | + | | | | |
| Wang 2007b | 48wk | | | | | | | | | | + | | = | | |
| Wang 2012 | 12, 24, 36 wk | | | | | | | + | + | | + | | + | | |
| **Trichloroacetic acid; Mice (MRL+/+); Drinking water** | | | | | | | | | | | | | | | |
| Blossom 2004 | 4 wk | | | | | | | | | | | | = | | |
| **Trichloroacetaldehyde hydrate** | | | | | | | | | | | | | | | |
| Blossom 2004 | 4 wk | | | | | | | | | | | | = | | |
| Blossom 2007a | 4, 40 wk | | | | | | | | | | | | = | = | |
| **Trichloroethylene; Mice (MRL+/+); IP** | | | | | | | | | | | | | | | |
| Khan 1995 | 6 wk | + | = | | | | | | | | + | = | + | | |
| Khan 2001 | 6 wk | | | | | | | | = | | | | | | |
| Wang 2007a | 6, 12 wk | | | | | | | + | + | | + | | + | + | |

| Reference | Design | IgG | Anti-dichloroacetyl-protein adduct antibody | Anti-dichloroacetyl-albumin adduct antibody | Anti-formyl-albumin adduct antibody | Anti-trichloroethene oxide-albumin adduct antibody | Anti-albumin antibody | Anti-hydroxynonenal-protein adduct antibody | Anti-malondialdehyde-protein adduct antibody | Anti-liver antibody | Anti-nuclear antibody | Anti-DNA antibody | Anti-ssDNA antibody | Anti-dsDNA antibody | Anti-sheep red blood cell IgM response |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Wang 2008 | 4 wk | + | | | | | | + | + | | + | | | | |
| Wang 2013* | 6 wk | | | | | | | + | + | | | + | + | + | |
| **Dichloroacetyl anhydride; Mice (MRL+/+); IP** | | | | | | | | | | | | | | | |
| Cai 2006 | 6 wk | = | | = | | | = | | | | + | | | | |
| **Dichloroacetyl chloride; Mice (MRL+/+); IP** | | | | | | | | | | | | | | | |
| Cai 2006 | 6 wk | + | | + | | | = | | | | + | | | | |
| Khan 1995 | 6 wk | + | + | | | | | | | | = | = | + | | |
| Khan 2001 | 2, 4, 6, 8 wk | | | | | | | | + | | | | | | |
| **Trichloroethylene; Mice (MRL+/+); Inhalation** | | | | | | | | | | | | | | | |
| Kaneko 2000 | 4, 6, 8 wk | - | | | | | | | | | | | | | |
| **Formyl-albumin adduct; Mice (MRL+/+); SC** | | | | | | | | | | | | | | | |
| Cai 2007 | 4 wk | | | + | + | + | + | | | | | | | | |
| **Dichloroacetyl-albumin adduct; Mice (MRL+/+); SC** | | | | | | | | | | | | | | | |
| Cai 2007 | 4 wk | | | + | + | + | + | | | | | | | | |
| **Trichloroethene oxide-albumin adduct; Mice (MRL+/+); SC** | | | | | | | | | | | | | | | |
| Cai 2007 | 4 wk | | | + | + | + | + | | | | | | | | |
| **Trichloroethylene; Mice (NZBWF1); Drinking water** | | | | | | | | | | | | | | | |
| Keil 2009 | 2, 9, 10, 13, 19, 22, 24, 27 wk | = | | | | | | | | | | | = | = | |
| **Trichloroacetaldehyde hydrate; Mice (C3H/HeJ); Drinking water** | | | | | | | | | | | | | | | |

| Reference | Design | IgG | Anti-dichloroacetyl-protein adduct antibody | Anti-dichloroacetyl-albumin adduct antibody | Anti-formyl-albumin adduct antibody | Anti-trichloroethene oxide-albumin adduct antibody | Anti-albumin antibody | Anti-hydroxynonenal-protein adduct antibody | Anti-malondialdehyde-protein adduct antibody | Anti-liver antibody | Anti-nuclear antibody | Anti-DNA antibody | Anti-ssDNA antibody | Anti-dsDNA antibody | Anti-sheep red blood cell IgM response |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Blossom 2006b | 4, 40 wk | | | | | | | | | | | | = | = | |
| **Trichloroethylene; Mice ($B6C3F_1$); Drinking water** | | | | | | | | | | | | | | | |
| Keil 2009 | 30 wk | + | | | | | | | | | | | + | + | |
| Peden-Adams 2006 | Preconception to 3, 8, wk | | | | | | | | | | | | | = | |
| **Trichloroethylene; Mice (CD-1); Drinking water** | | | | | | | | | | | | | | | |
| Sander 1982 | 4, 6 mo | | | | | | | | | | | | | | +/- |
| **Chloral hydrate; Mice (CD-1); Drinking water** | | | | | | | | | | | | | | | |
| Kauffmann 1982 | 90 d | | | | | | | | | | | | | | = |

[*] Included a group co-exposed to N-acetylcystine, an enhancer of the antioxidant activity of glutathione, which prevented the results

## Table E-5. Spleen

| Reference | Design | Lymphocyte numbers | Lymphocyte proliferation | T-cell proliferation | CD4 T-cell numbers | CD4 T-cell proliferation | CD8 T-cell numbers | CD8 T-cell proliferation | B-cell numbers | B-cell proliferation | B-cell activation | Anti-sheep red blood cell IgM response | NK-cell proliferation | NK-cell cytolytic activity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Trichloroethylene; Mice (MRL+/+); Drinking water** | | | | | | | | | | | | | | |
| Blossom 2007b | Preconception to 4, 6, 8 wk old | | | | - | | - | | - | | = | | | |
| Gilbert 2011 | 8 wk | | | | = | | = | | = | | | | | |
| Griffin 2000a | 4, 6, 8, 22 wk | | | | = | | | | | | = | | | |
| Griffin 2000c* | | | | | | + | | | | | | | | |
| Peden-Adams 2008 | Preconception to 12 mo | | | | | = | | = | | = | | | | |
| **Trichloroacetic acid; Mice (MRL+/+); Drinking water** | | | | | | | | | | | | | | |
| Blossom 2004 | 4 wk | | | | = | | = | | = | | = | | | |
| **Trichloroacetaldehyde hydrate; Mice (MRL+/+); Drinking water** | | | | | | | | | | | | | | |
| Blossom 2004 | 4 wk | | | | = | | = | | = | | = | | | |
| Blossom 2007a | 4, 40 wk | | | | - | | = | | = | | | | | |
| **Trichloroethylene; Mice (MRL+/+); IP** | | | | | | | | | | | | | | |
| Wang 2008 | 4 wk | | | | | + | | = | | = | | | | |
| **Dichloroacetyl anhydride; Mice (MRL+/+); IP** | | | | | | | | | | | | | | |
| Cai 2006 | 6 wk | + | | | | | | | | | | | | |
| **Dichloroacetyl chloride; Mice (MRL+/+); IP** | | | | | | | | | | | | | | |
| Cai 2006 | 6 wk | + | | | | | | | | | | | | |
| **Trichloroethylene; Mice (NZBWF1); Drinking water** | | | | | | | | | | | | | | |
| Keil 2009 | 2, 9, 10, 13, 19, | | | = | | | | | | = | | | | = |

| Reference | Design | Lymphocyte numbers | Lymphocyte proliferation | T-cell proliferation | CD4 T-cell numbers | CD4 T-cell proliferation | CD8 T-cell numbers | CD8 T-cell proliferation | B-cell numbers | B-cell proliferation | B-cell activation | Anti-sheep red blood cell IgM response | NK-cell proliferation | NK-cell cytolytic activity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 22, 24, 27 wk | | | | | | | | | | | | | |
| **Trichloroacetaldehyde hydrate; Mice (C3H/HeJ); Drinking water** | | | | | | | | | | | | | | |
| Blossom 2006b | 4, 40 wk | | | | = | | = | | | | | | | |
| **Trichloroethylene; Mice (B6C3F$_1$); Drinking water** | | | | | | | | | | | | | | |
| Peden-Adams 2006 | Preconception to 3, 8 wk | | | = | +/- | | = | | - | = | | - | = | |
| Keil 2009 | 30 wk | | | = | | | | | | = | | | = | |
| Wright 1991 | 3 d | | | | | | | | | | | | | = |
| **Trichloroethylene; Mice (CD-1); Drinking water** | | | | | | | | | | | | | | |
| Sander 1982 | 4, 6 mo | | + | | | | | | | | | + | | |
| **Chloral hydrate; Mice (CD-1); Drinking water** | | | | | | | | | | | | | | |
| Kauffmann 1982 | 90 d | | | = | | | | | | = | | - | | |
| **Chloral hydrate; Mice (CD-1); Gavage** | | | | | | | | | | | | | | |
| Kauffmann 1982 | 15 d | | | | | | | | = | | | | | |
| **Trichloroethylene; Rat (Sprague-Dawley); IP** | | | | | | | | | | | | | | |
| Wright 1991 | 3 d | | | | | | | | | | | | | = |

[*]Included a group co-exposed to diallyl sulfide, a CYP2E1 inhibitor, which prevented the results

**Table E-6. Liver and Kidney**

| Reference | Design | Trichloroethylene-protein adduct | Dichloroacetyl-protein adduct | Dichloroacetyl-CYP2E1 adduct | Hydroxynonenal-protein adduct | Malondialdehyde-protein adduct | Inflammation | T-cell infiltration | NK-cell cytolytic activity | Hepatocyte proliferation | Glomerular antibody deposits | Hydroxynonenal-protein adduct | Malondialdehyde-protein adduct | Inflammation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | **Liver** | | | | | | | | **Kid-ney** | | |
| **Trichloroethylene; Mice (MRL+/+); Drinking water** | | | | | | | | | | | | | | |
| Cai 2008 | 36, 48 wk | | | | | | + | | | + | + | | | + |
| Gilbert 2009 | 10, 18, 26 wk | | | | | | + | | | | | | | |
| Griffin 2000a | 4, 6, 8, 22 wk | + | | | | | | | | | | | | |
| Griffin 2000b | 4, 32 wk | | + | | | | | + | | | | | | = |
| Griffin 2000c** | 4, 32 wk | | + | | | | | | | | | | | |
| Kondraganti 2012 | 24, 36, 48 wk | | | | | | + | + | | | | | | |
| **Trichloroethylene; Mice (MRL+/+); IP** | | | | | | | | | | | | | | |
| Wang 2007a | 6, 12 wk | | | | + | + | | | | | | | | |
| Wang 2013* | 6 wk | | | | + | + | | | | | | + | + | |
| **Formyl-albumin adduct; Mice (MRL+/+); SC** | | | | | | | | | | | | | | |
| Cai 2007 | 4 wk | | | | | | + | | | | | | | |
| **Dichloroacetyl-albumin adduct; Mice (MRL+/+); SC** | | | | | | | | | | | | | | |
| Cai 2007 | 4 wk | | | | | | = | | | | | | | |
| **Trichloroethene oxide-albumin adduct; Mice (MRL+/+); SC** | | | | | | | | | | | | | | |

| Reference | Design | Trichloroethylene-protein adduct | Dichloroacetyl-protein adduct | Dichloroacetyl-CYP2E1 adduct | Hydroxynonenal-protein adduct | Malondialdehyde-protein adduct | Inflammation | T-cell infiltration | NK-cell cytolytic activity | Hepatocyte proliferation | Glomerular antibody deposits | Hydroxynonenal-protein adduct | Malondialdehyde-protein adduct | Inflammation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cai 2007 | 4 wk | | | | | | = | | | | | | | |
| **Trichloroethylene; Mice (MRL+/+); Inhalation** | | | | | | | | | | | | | | |
| Kaneko 2000 | 4, 6, 8 wk | | | | | | + | | | | | | | |
| **Trichloroethylene; Mice (NOD/Born); Drinking water** | | | | | | | | | | | | | | |
| Ravel 2004 | 4,8, 12 wk | | | | | | = | | | | | | | |
| **Trichloroethylene; Mice (SV/129) [wt/PPAR-null/PPAR-tet-off]; Inhalation** | | | | | | | | | | | | | | |
| Ramdhan 2010 | 7 d | | | | | | + | | | + | | | | |
| **Trichloroethylene; Mice ($B6C3F_1$); IP** | | | | | | | | | | | | | | |
| Wright 1991 | 3 d | | | | | | | | - | | | | | |
| **Trichloroethylene; Rat (Sprague-Dawley); IP** | | | | | | | | | | | | | | |
| Halmes 1997 | 4 hr | | | + | | | | | | | | | | |
| Wright 1991 | 3 d | | | | | | | | - | | | | | |
| **Trichloroethylene; Guinea pig (FMMU); Dermal** | | | | | | | | | | | | | | |
| Tang 2008 | 48 hr | | | | | | = | | | | | | | |
| **Trichloroethylene; Guinea pig (FMMU); Intradermal/Dermal** | | | | | | | | | | | | | | |
| Tang 2008 | 23 d | | | | | | = | | | | | | | |
| **Trichloroethylene; Guinea pig (FMMU); Intradermal** | | | | | | | | | | | | | | |
| Tang 2008 | 48 hr | | | | | | + | | | | | | | |

[*] Included a group co-exposed to N-acetylcystine, an enhancer of the antioxidant activity of glutathione, which prevented the results.
[**] Included a group co-exposed to diallyl sulfide, a CYP2E1 inhibitor, which prevented the results.

**Table E-7. Splenic *ex vivo* cytokines, lymph node, and anti-bacterial response**

| Reference | Design | Splenocytes stimulated with hydroxynonenal-albumin adduct – IFN-gamma | Splenocytes stimulated with malondialdehyde-albumin adduct – IFN-gamma | Splenocytes stimulated with hydroxynonenal-albumin adduct – IL-2 | Splenocytes stimulated with malondialdehyde -albumin adduct – IL-2 | CD4 T-cell numbers | CD8 T-cell numbers | B-cell Numbers | B-cell activation | Death from bacterial infection | Lung- bacterial infection | Lung – macrophage phagocytosis of bacteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Trichloroethylene; Mice (MRL+/+); Drinking water** | | | | | | | | | | | | |
| Gilbert 2011 | 8 wk | | | | | = | = | | | | | |
| Gilbert 2012 | 12, 17 wk | | | | | = | | | | | | |
| Wang 2012 | 12, 24, 36 wk | + | + | | | | | | | | | |
| **Trichloroacetic acid; Mice (MRL+/+); Drinking water** | | | | | | | | | | | | |
| Blossom 2004 | 4 wk | | | | | = | = | = | = | | | |
| **Trichloroacetaldehyde hydrate; Mice (MRL+/+); Drinking water** | | | | | | | | | | | | |
| Blossom 2004 | 4 wk | | | | | = | = | = | = | | | |
| **Trichloroethylene; Mice (MRL+/+); IP** | | | | | | | | | | | | |
| Wang 2008 | 4 wk | + | + | + | + | | | | | | | |
| **Dichloroacetyl anhydride; Mice (MRL+/+); IP** | | | | | | | | | | | | |
| Cai 2006 | 6 wk | | | = | = | | | | | | | |
| **Dichloroacetyl chloride; Mice (MRL+/+); IP** | | | | | | | | | | | | |
| Cai 2006 | 6 wk | | | + | + | | | | | | | |
| **Trichloroethylene; Mice (C3H/HeJ); Drinking water** | | | | | | | | | | | | |
| Blossom 2006b | 4, 40 wk | | | | | = | = | | | | | |

| Reference | Design | Splenocytes stimulated with hydroxynonenal-albumin adduct – IFN-gamma | Splenocytes stimulated with malondialdehyde-albumin adduct – IFN-gamma | Splenocytes stimulated with hydroxynonenal-albumin adduct – IL-2 | Splenocytes stimulated with malondialdehyde -albumin adduct – IL-2 | CD4 T-cell numbers | CD8 T-cell numbers | B-cell Numbers | B-cell activation | Death from bacterial infection | Lung- bacterial infection | Lung – macrophage phagocytosis of bacteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Trichloroethylene + Streptococcus zooepidermicus; Mice (CD-1); Inhalation** | | | | | | | | | | | | |
| Aranyi 1986 | 3 hr; 5 d | | | | | | | | | + | | |
| Selgrade 2010 | 24, 72 hr; 20 d | | | | | | | | | + | + | |
| **Trichloroethylene + Streptococcus zooepidermicus; Mice (CD-1); Inhalation + intratracheal instillation** | | | | | | | | | | | | |
| Selgrade 2010 | 3.5 hr | | | | | | | | | | | - |
| **Trichloroethylene + kiebsiella pneumonia; Mice (CD-1); Inhalation** | | | | | | | | | | | | |
| Aranyi 1986 | 3 hr; 5 d | | | | | | | | | | +/- | |

# Appendix F: Mechanism of Action Tables

To return to text citing the Appendix F tables in Section 5, click here.

To return to text citing the Appendix F tables in Section 6, click here.

**Table F-1. Superoxide anion production in male B6C3F$_1$ mice administered acute, subacute, and subchronic doses of dichloroacetic acid or trichloroacetic acid**

| Compound | Dose (mg/kg/day) | Time | PLCs[a] | Liver[a] | Reference |
|---|---|---|---|---|---|
| Dichloroacetic acid | 300 (single dose) | 6 hr<br>12 hr | 1.5*<br>1.4* | 1.4*<br>INS | Hassoun and Dey 2008 |
| Dichloroacetic acid | 7.7<br>77<br>154<br>410 | 4 wk | INS<br>1.8*<br>2.5*<br>3.7* | 1.2*<br>2.5*<br>4.0*<br>4.3* | Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b, Hassoun *et al.* 2010a |
| Dichloroacetic acid | 7.7<br>77<br>154<br>410 | 13 wk | 1.8*<br>2.4*<br>2.1*<br>INS | 1.4*<br>3.2*<br>4.3*<br>2.2* | Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b, Hassoun *et al.* 2010a |
| Dichloroacetic acid | 7.5<br>15<br>30 | 13 wk | 1.8*<br>2.0*<br>2.2* | 1.4*<br>1.9*<br>2.3* | Hassoun *et al.* 2013<br>Hassoun *et al.* 2014 |
| Trichloroacetic acid | 300 (single dose) | 6 hr<br>12 hr | INS<br>1.5* | INS<br>1.2* | Hassoun and Dey 2008 |
| Trichloroacetic acid | 7.7<br>77<br>154<br>410 | 4 wk | INS<br>1.4*<br>1.9*<br>2.5* | INS<br>INS<br>1.3*<br>2.8* | Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b, Hassoun *et al.* 2010a |
| Trichloroacetic acid | 7.7<br>77<br>154<br>410 | 13 wk | INS<br>2.0*<br>INS<br>INS | 1.2*<br>1.8*<br>2.5*<br>2.8* | Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b, Hassoun *et al.* 2010a |
| Trichloroacetic acid | 12.5<br>25<br>50 | 13 wk | 1.5*<br>1.6*<br>1.8* | 1.3*<br>1.5*<br>1.7* | Hassoun *et al.* 2013<br>Hassoun *et al.* 2014 |
| Mixtures | 7.5/12.5[b]<br>15/25<br>30/50 | 13 wk | 2.1*<br>2.7*<br>2.6* | 1.7*<br>2.6*<br>3.2* | Hassoun *et al.* 2013<br>Hassoun *et al.* 2014 |

– = Not measured; INS = insignificant change compared to controls; PLCs = peritoneal lavage cells.
* $P < 0.05$.
[a] Superoxide anion production measured as cytochrome c reduced/min/mg protein and expressed as the approximate fold increase over control values (some values estimated from figures).
[b] Concentration of dichloroacetic acid/trichloroacetic acid in the mixture.

**Table F-2. Lipid peroxidation and DNA single strand breaks in the liver of male B6C3F$_1$ mice administered acute, subacute, and subchronic doses of dichloroacetic acid or trichloroacetic acid**

| Compound | Dose (mg/kg/day) | Time | LP[a] | SSBs[a] | Reference |
|---|---|---|---|---|---|
| Dichloroacetic acid | 300 (single dose) | 6 hr<br>12 hr | 1.3*<br>1.4* | 2.6*<br>3.9* | Hassoun and Dey 2008 |
| Dichloroacetic acid | 7.7<br>77<br>154<br>410 | 4 wk | 2.5*<br>5.0*<br>7.5*<br>14.0* | INS<br>3.5*<br>7.2*<br>7.2* | Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b |
| Dichloroacetic acid | 7.7<br>77<br>154<br>410 | 13 wk | 3.5*<br>12.5*<br>15.0*<br>4.0* | 1.6*<br>5.6*<br>5.6*<br>4.0* | Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b |
| Dichloroacetic acid | 7.5<br>15<br>30 | 13 wk | 2.8*<br>4.0*<br>7.2* | 1.6*<br>2.8*<br>4.0* | Hassoun *et al.* 2014 |
| Trichloroacetic acid | 300 (single dose) | 6 hr<br>12 hr | INS<br>1.3* | INS<br>2.8* | Hassoun and Dey 2008 |
| Trichloroacetic acid | 7.7<br>77<br>154<br>410 | 4 wk | INS<br>2.0*<br>2.5*<br>11.0* | INS<br>1.8*<br>2.3*<br>4.3* | Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b |
| Trichloroacetic acid | 7.7<br>77<br>154<br>410 | 13 wk | 1.5*<br>7.0*<br>8.5*<br>13.5* | INS<br>2.3*<br>3.3*<br>4.3* | Hassoun and Cearfoss 2011, Hassoun *et al.* 2010b |
| Trichloroacetic acid | 12.5<br>25<br>50 | 13 wk | 1.6*<br>2.6*<br>4.0* | INS<br>1.6*<br>2.0* | Hassoun *et al.* 2014 |
| Mixture | 7.5/12.5[b]<br>15/25<br>30/50 | 13 wk | 3.2*<br>6.2*<br>13* | 1.7*<br>3.6*<br>6.2* | Hassoun *et al.* 2014 |

INS = insignificant change compared to controls; LP = lipid peroxidation (measured a nmole TBARS/mg protein and expressed as the approximate fold increase over control values); SSBs = single strand breaks (alkaline elution technique, data reported as fold increase over control values).
* $P < 0.05$.
[a] Data are the ratio of treated/controls (some values estimated from figures).
[b] Concentration of dichloroacetic acid/trichloroacetic acid in the mixture

**Table F-3. Phagocytic activation and antioxidant enzyme activity in peritoneal lavage cells from male B6C3F$_1$ mice administered subacute and subchronic doses of dichloroacetic acid or trichloroacetic acid**

| Compound | Dose (mg/kg/day) | Time | SOD[a] | MPO[a] | TNF-α[a] | Reference |
|---|---|---|---|---|---|---|
| Dichloroacetic acid | 7.7<br>77<br>154<br>410 | 4 wk | INS<br>2.5*<br>4.1*<br>6.5* | 5.0*<br>4.3*<br>12.3*<br>12.3* | INS<br>2.0*<br>3.0*<br>6.8* | Hassoun *et al.* 2010a |
| Dichloroacetic acid | 7.7<br>77<br>154<br>410 | 13 wk | 1.7*<br>3.7*<br>4.5*<br>5.2* | 6.3*<br>10.8*<br>9.0*<br>INS | 2.4*<br>6.2*<br>5.2*<br>INS | Hassoun *et al.* 2010a |
| Dichloroacetic acid | 7.5<br>15<br>30 | 13 wk | –<br>–<br>– | 5.3*<br>7.8*<br>9.3* | 2.1*<br>2.7*<br>3.3* | Hassoun *et al.* 2013 |
| Trichloroacetic acid | 7.7<br>77<br>154<br>410 | 4 wk | INS<br>2.1*<br>4.0*<br>5.0* | 36*[b]<br>52*[b]<br>66*[b]<br>18*[b] | INS<br>2.6*<br>4.3*<br>11.8* | Hassoun *et al.* 2010a |
| Trichloroacetic acid | 7.7<br>77<br>154<br>410 | 13 wk | 1.7*<br>2.6*<br>4.2*<br>5.2* | 6*[b]<br>16*[b]<br>4*[b]<br>INS | INS<br>3.0*<br>INS<br>INS | Hassoun *et al.* 2010a |
| Trichloroacetic acid | 12.5<br>25<br>50 | 13 wk | –<br>–<br>– | 5.7*<br>7.0*<br>9.5* | 1.9*<br>2.2*<br>2.6* | Hassoun *et al.* 2013 |
| Mixtures | 7.5/12.5[b]<br>15/25<br>30/50 | 13 wk | –<br>–<br>– | 9.5*<br>13.2*<br>12.5* | 3.1*<br>4.1*<br>4.1* | Hassoun *et al.* 2013 |

– Not measured; INS = insignificant change compared to controls; MPO = myeloperoxidase (units/mg); SOD = superoxide dismutase (units/mg); TNF-α = tumor necrosis factor-alpha (pg/mg).
* $P < 0.05$.
[a] Data are the ratio of treated/controls (all values estimated from figures).
[b] Ratios are highly uncertain because the control levels were very small.

**Table F-4. Antioxidant enzyme activity in liver from male B6C3F$_1$ mice administered subacute and subchronic doses of dichloroacetic acid or trichloroacetic acid**

| Compound | Dose (mg/kg/day) | Time | SOD[a] | CAT[a] | GPO[a] | GSH[a] |
|---|---|---|---|---|---|---|
| Dichloroacetic acid | 7.7 | 4 wk | 0.05* | INS | INS | INS |
| | 77 | | 0.05* | INS | INS | INS |
| | 154 | | 0.1* | INS | INS | INS |
| | 410 | | 0.5* | INS | INS | INS |
| Dichloroacetic acid | 7.7 | 13 wk | 0.4* | INS | 0.29* | INS |
| | 77 | | 0.4* | INS | 0.29* | 0.73* |
| | 154 | | 2.1* | 1.9* | 1.8* | 0.66* |
| | 410 | | 3.6* | 2.2* | 2.5* | INS |
| Trichloroacetic acid | 7.7 | 4 wk | 1.3* | INS | 0.34* | INS |
| | 77 | | 1.8* | 1.5* | 0.39* | INS |
| | 154 | | 3.0* | 1.7* | 0.37* | INS |
| | 410 | | 4.9* | 1.9* | 0.42* | INS |
| Trichloroacetic acid | 7.7 | 13 wk | 2.4* | 1.7* | 0.62* | INS |
| | 77 | | 3.6* | 1.9* | 0.30* | INS |
| | 154 | | 6.4* | 2.3* | 0.20* | INS |
| | 410 | | 8.1* | 2.7* | 0.24* | INS |

Source: Hassoun and Cearfoss 2011.
* $P < 0.05$.
[a] Data are the ratio of treated/controls (all values estimated from figures).
CAT = catalase (units × 10/mg protein).
GPO = glutathione peroxidase (nmoles NADPH oxidized/min/mg protein).
GSH = total glutathione (nmoles/g tissue).
INS = insignificant change compared to controls.
SOD = superoxide dismutase (units/mg).

# Part 2

# Draft RoC Profile for Trichloroethylene

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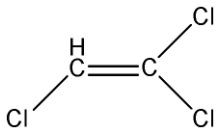
# Trichloroethylene

## CAS No. 79-01-6

Known to be a human carcinogen[1]

First listed in the *Ninth Report on Carcinogens* (2000) *as reasonably anticipated to be a human carcinogen*

Also known as 1,1,2-trichloroethene or TCE




## Carcinogenicity

Trichloroethylene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans. This conclusion is based on evidence from human epidemiological studies together with toxicokinetic, toxicological, and mechanistic studies showing that it causes kidney cancer in humans. There is limited evidence for the carcinogenicity of trichloroethylene from studies of non-Hodgkin lymphoma (NHL) in humans. Supporting evidence is provided by studies in experimental animals demonstrating that trichloroethylene causes cancer at several tissue sites, including some of the same sites as seen in humans.

### *Cancer Studies in Humans*

#### *Kidney Cancer*

Epidemiological studies have demonstrated a credible association between exposure to trichloroethylene and kidney cancer based on consistent evidence across studies with different study designs, in different geographical areas, and in different occupational settings; evidence of increasing cancer risk with increasing level or duration of exposure; and meta-analyses showing statistically significantly increased cancer risk across studies.

The body of literature reporting kidney cancer risk estimates specific for trichloroethylene exposure consisted of twelve cohort and nested case-control studies and seven case-control studies. The cohort studies included three studies of Nordic workers identified from broad occupational or population-based databases (Hansen *et al.* 2013, Raaschou-Nielsen *et al.* 2003, Vlaanderen *et al.* 2013); several studies of workers from specific industries, including five studies in aerospace or aircraft manufacturing (Boice *et al.* 2006, Lipworth *et al.* 2011, Morgan *et al.* 1998, Radican *et al.* 2008, Zhao *et al.* 2005) and one study each in the manufacture of cardboard (Henschler *et al.* 1995), microelectronics (Silver *et al.* 2014), and electrical components (Greenland *et al.* 1994); and a study of subjects exposed to trichloroethylene in contaminated drinking water (Bove *et al.* 2014). The case-control studies included four studies conducted in areas with presumably elevated levels and prevalence of trichloroethylene exposure, using experts with knowledge of the local industry to assess exposure (Brüning *et al.* 2003, Charbotel *et al.* 2006, 2009, Moore *et al.* 2010, Vamvakas *et al.* 1998), and three studies of more widespread populations with varying exposure potential to trichloroethylene and overall

[1] NTP preliminary listing recommendation proposed for the RoC.

lower average trichloroethylene (Christensen *et al.* 2013, Dosemeci *et al.* 1999, Pesch *et al.* 2000). The three most informative studies were a cohort study of aerospace workers (Zhao *et al.* 2005), a French case-control study of screw-cutting workers (Charbotel *et al.* 2006, 2009), and a case-control study in central and eastern Europe (Moore *et al.* 2010), which were considered to be high-quality studies because of good exposure assessment, detailed analysis of exposure-response relationships, or presumed high levels of exposure. Most other studies had lower sensitivity to detect an association, because of the rarity of kidney cancer in the cohort studies and the low prevalence of trichloroethylene exposure in some case-control studies, but otherwise raised no major methodological concerns and were considered informative. Meta-analysis (quantitative analysis that combines the results of several independent studies) is an approach that can partially overcome these limitations.

The most convincing evidence for an association between kidney cancer and exposure to trichloroethylene comes from the three most informative studies (Charbotel *et al.* 2006, 2009, Moore *et al.* 2010, Zhao *et al.* 2005), a Nordic cohort of blue-collar workers in companies using trichloroethylene (Raaschou-Nielsen *et al.* 2003), and a case-control study from an area in Germany with known trichloroethylene exposure (Brüning *et al.* 2003), all of which found statistically significant elevated risks of kidney cancer among workers with the highest exposure to trichloroethylene. These findings are supported by weaker associations found in several other cohort studies (Boice *et al.* 2006, Bove *et al.* 2014, Hansen *et al.* 2013, Morgan *et al.* 1998, Silver *et al.* 2014) and case-control studies (Dosemeci *et al.* 1999, Pesch *et al.* 2000). Although very high risks of kidney cancer were found among German workers exposed to high levels of trichloroethylene (Henschler *et al.* 1995, Vamvakas *et al.* 1998), these studies should be viewed with some caution because of potential biases that would most likely result in overestimation of the risk, though they would probably not nullify the positive association.

Two recent meta-analyses found statistically significant elevated risks of kidney cancer among subjects ever exposed to trichloroethylene (meta–relative risk [mRR] = 1.27, 95% CI = 1.13 to 1.43, Scott and Jinot 2011; mRR = 1.32, 95% CI = 1.17 to 1.50, Karami *et al.* 2012). Importantly, in the analysis by Scott and Jinot, the mRR was robust and not sensitive to removal of individual studies or use of alternative risk estimates. Increased risks were found in separate meta-analyses of cohort and case-control studies and there was no evidence of publication bias in either meta-analysis.

The risks of kidney cancer increased with increasing level or duration of exposure as measured by several metrics of exposure (duration, intensity, and cumulative exposure) in both cohort (Raaschou-Nielsen *et al.* 2003, Zhao *et al.* 2005) and case-control studies (Charbotel *et al.* 2006, 2009, Moore *et al.* 2010). Furthermore, a higher mRR was found for the highest exposure group across studies (mRR = 1.58, 95% CI = 1.28 to 1.96, Scott and Jinot 2011) than for those ever exposed, which provides support for an exposure-response relationship.

Although several studies (Dosemeci *et al.* 1999, Greenland *et al.* 1994, Lipworth *et al.* 2011, Radican *et al.* 2008, Vlaanderen *et al.* 2013), including some large studies, did not find an association between kidney cancer and trichloroethylene exposure or evidence of an exposure-response relationship, their sensitivity to detect an association may have been low because of low exposure levels, small numbers of subjects with higher levels of exposure, or non-differential exposure misclassification.

Biases or confounding from known or suspected co-exposures, smoking, or other lifestyle factors are unlikely to explain the positive findings across studies. Most of the case-control studies found positive associations after controlling for smoking, and there was little evidence for

an association between trichloroethylene and lung cancer, which strongly suggests that smoking is unlikely to be a confounding factor. Studies of specific industries found positive associations after considering known occupational co-exposures in their analyses (Charbotel *et al.* 2006, 2009, Zhao *et al.* 2005). Although co-exposures are not known for several other cohort and case-control studies, the studies include workers in diverse occupations with varying levels and patterns of co-exposures, and the prevalence of any one specific co-exposure across studies was probably low. Furthermore, increased risks were found across studies with different study designs and in different occupational settings and geographical regions.

*Non-Hodgkin Lymphoma*

Epidemiological studies provided limited evidence for an association between exposure to trichloroethylene and NHL, based on positive associations in several studies and combined evidence of increased risk for NHL across studies reported in two meta-analyses. The evidence across studies was less consistent than for kidney cancer, and alternative explanations such as chance or confounding could not reasonably be ruled out.

Studies reporting risk estimates specific for NHL (histological subtypes and related B-cell lymphomas) included ten cohort or nested case-control studies, four case-control studies, a pooled analysis of four case-control studies by the International Lymphoma Epidemiology Consortium (InterLymph), and two recent meta-analyses. The cohort and nested case-control studies included nine of the twelve studies discussed above that reported on kidney cancer (Boice *et al.* 2006, Bove *et al.* 2014, Hansen *et al.* 2013, Lipworth *et al.* 2011, Morgan *et al.* 1998, Raaschou-Nielsen *et al.* 2003, Radican *et al.* 2008, Silver *et al.* 2014, Vlaanderen *et al.* 2013) and an additional study of uranium processing workers (Bahr *et al.* 2011). (One aerospace manufacturing study [Zhao *et al.* 2005], the cardboard manufacturing study [Henschler *et al.* 1995], and the nested case-control study of electrical component manufacturing workers [Greenland *et al.* 1994] did not report risk estimates specific for NHL.) The case-control studies included two Swedish studies (Hardell *et al.* 1994, Persson and Fredrikson 1999). a large study in Connecticut (Deng *et al.* 2013, Wang *et al.* 2009), a study in Montreal, Canada (Christensen *et al.* 2013), and the InterLymph pooled analysis (Cocco *et al.* 2013). The pooled analysis was considered to be the most informative because of its high-quality exposure assessment, large size, and analyses of exposure-response relationships and NHL histological subtypes.

The strongest evidence of an association between exposure to trichloroethylene and NHL comes from the InterLymph pooled analysis (*P* for Fisher combined probability = 0.004) and the two meta-analyses (mRR = 1.23, 95% CI = 1.07–1.42, Scott and Jinot 2011; mRR = 1.23, 95% CI = 1.07–1.42, Karami *et al.* 2013). In the meta-analysis by Scott and Jinot, the mRR was robust and not sensitive to removal of individual studies or use of alternative risk estimates. There was little evidence of publication bias or of heterogeneity across studies in the most recent analysis (Karami *et al.* 2013); however, there was low to moderate heterogeneity and some evidence of publication bias in the somewhat earlier analysis (Scott and Jinot 2011). The risk of NHL increased with level or duration of exposure in the pooled InterLymph study (Cocco *et al.* 2013), one of its component studies (Purdue *et al.* 2011), and another case-control study (Wang *et al.* 2009).

Support for an association between NHL and exposure to trichloroethylene comes from relatively small increases in risks of NHL found in several case-control studies (Hardell *et al.* 1994, Wang *et al.* 2009) and cohort studies (Hansen *et al.* 2013, Lipworth *et al.* 2011, Morgan *et al.* 1998, Raaschou-Nielsen *et al.* 2003, Radican *et al.* 2008). Except in the study by Wang *et al.*

(2009), the evidence for an association was not considered to be strong, because exposure-response relationships were not observed, and risk estimates were relatively small or not statistically significant. Nonetheless, these studies collectively contributed to the statistically significant risks observed in the meta-analyses. There was little evidence (Persson and Fredrikson 1999, Christensen *et al.* 2013, Bove *et al.* 2014) or no evidence (Vlaanderen *et al.* 2013, Bahr *et al.* 2011) of an association between trichloroethylene exposure and NHL in the other studies, most of which had limited sensitivity to detect an effect for an uncommon cancer such as NHL or concerns about exposure misclassification. Only one exposed case was observed in the study of aerospace workers (Boice *et al.* 2006).

Few specific histological subtypes of NHL or related B-cell lymphomas have been studied with respect to trichloroethylene exposure. The strongest evidence for an association with exposure to trichloroethylene is for chronic lymphocytic leukemia and follicular-cell lymphoma (Cocco *et al.* 2013, Purdue *et al.* 2011).

#### *Liver Cancer*

The available database for liver cancer included twelve cohort or nested-case-control studies (Bahr *et al.* 2011, Boice *et al.* 2006, Bove *et al.* 2014, Greenland *et al.* 1994, Hansen *et al.* 2013, Lipworth *et al.* 2011, Morgan *et al.* 1998, Raaschou-Nielsen *et al.* 2003, Radican *et al.* 2008, Ritz 1999, Silver *et al.* 2014, Vlaanderen *et al.* 2013) and two meta-analyses (Alexander *et al.* 2007, Scott and Jinot 2011); the only available case-control study (Christensen *et al.* 2013) had too few cases of trichloroethylene-exposed subjects to be informative. The epidemiological data suggest that trichloroethylene may be associated with a modest increase in the risk of liver cancer, based primarily on the two meta-analyses. However, findings were inconsistent across studies, and there was little evidence of exposure-response relationships in the individual studies or the meta-analyses. In addition, the role of chance or confounding by one or more common co-exposures or lifestyle factors could not be completely ruled out.

### *Cancer Studies in Experimental Animals*

Trichloroethylene caused tumors in mice and rats at several different tissue sites by two different routes of exposure. In mice, exposure to trichloroethylene by inhalation or stomach tube caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in both sexes (IARC 1995, Maltoni *et al.* 1988, NCI 1976, NTP 1990); inhalation exposure also caused lung tumors in both sexes and lymphoma in females (Henschler *et al.* 1980, IARC 1995). In rats, exposure to trichloroethylene by inhalation or stomach tube caused kidney cancer (tubular adenocarcinoma) and testicular tumors (interstitial-cell tumors) in males (Maltoni *et al.* 1988, NTP 1988, 1990), and leukemia also was observed in males whose survival was reduced after exposure by stomach tube (Maltoni *et al.* 1988).

### *Studies on Mechanisms of Carcinogenesis*

The available evidence indicates that trichloroethylene causes genotoxicity, toxicity, and cancer via metabolic activation to reactive metabolites (EPA 2011, Lash *et al.* 2014). Two distinct metabolic pathways for trichloroethylene have been identified that are common to all mammalian species studied: cytochrome P450 (CYP) oxidation and glutathione (GSH) conjugation. Kidney cancer is most likely mediated through the GSH-conjugation pathway, whereas liver cancer (and toxicity) is thought to be mediated through the CYP-oxidation pathway (EPA 2011, Rusyn *et al.* 2014). Although these pathways operate in parallel, the

oxidative pathway, primarily through CYP2E1, predominates in all species studied (Lash *et al.* 2014). Genetic polymorphisms or exposure to CYP inducers or inhibitors can alter the balance between oxidation and GSH conjugation of trichloroethylene, and their impacts may be more substantial at higher substrate concentrations; this is consistent with the findings of increased risk of kidney cancer primarily among workers with high exposure to trichloroethylene. Differences across the study populations in co-exposures or genetic susceptibility factors, both of which could affect the flux of the two metabolic pathways, may explain some of the heterogeneity across studies and cancer end points.

*Kidney Cancer*

Toxicokinetic and mechanistic data in both humans and animals provide evidence for biologically plausible mechanisms of trichloroethylene's carcinogenicity in humans. Both human epidemiological studies and animal bioassays identified the kidney as a site of trichloroethylene carcinogenicity, and a common mechanism of action has been proposed. The key events most likely contributing to tumorigenicity include (1) GSH-conjugation-derived metabolites produced *in situ* or delivered systemically to the kidneys and (2) mutagenic, genotoxic, and nephrotoxic effects induced by metabolites in the kidneys (EPA 2011). Humans and experimental animals metabolize trichloroethylene similarly and have similar mixtures of trichloroethylene and metabolites in their tissues. *In vitro* studies in kidney and liver cells from humans and animals demonstrate the formation of several GSH-reactive metabolites. *N*-Acetyl-*S*-dichlorovinyl-L-cysteine (NAcDCVC) and *S*-(2,2-dichlorovinyl)glutathione (DCVG) have been detected in the urine of trichloroethylene-exposed humans and experimental animals.
The available mechanistic data strongly support a mutagenic mode of action mediated by GSH-conjugated metabolites (EPA 2011). These metabolites have been shown to be genotoxic both *in vitro* and *in vivo,* most notably causing damage to both human and animal kidney cells *in vitro*, transformation of rat kidney cells *in vitro*, and DNA damage and micronucleus formation in kidney cells from rats exposed *in vivo.* Finally, the importance of the GSH-conjugation pathway in humans is supported by the finding of significant risk of renal-cell cancer among trichloroethylene-exposed individuals with a functionally active glutathione S-transferase theta 1 (GSTT1) genotype but not among subjects with a GST-null genotype (Moore *et al.* 2010). A mechanism that may potentially contribute to trichloroethylene carcinogenicity is cytotoxicity and associated regenerative proliferation (EPA 2011). Studies in humans also provide evidence that trichloroethylene causes nephrotoxicity (Bolt *et al.* 2004, Brüning *et al.* 1999a, Brüning *et al.* 1999b, Vermeulen *et al.* 2012), supporting the relevance of this mechanism in humans. Thus, the mode of action for kidney carcinogenicity may involve a combination of mutagenicity and cytotoxicity.

*NHL and Liver Cancer*

The mechanisms by which trichloroethylene may potentially cause lymphoma are largely unknown. There is evidence that trichloroethylene causes immunomodulation in both humans and animals, with some support for both immunosuppression and autoimmunity (EPA 2011). Immunomodulation and immunosuppression are strongly linked to NHL (Baecklund *et al.* 2014, Hardell *et al.* 1998, Ponce *et al.* 2014), suggesting a biologically plausible role in induction of NHL by trichloroethylene. It has been proposed that lymphomas can develop from errors arising during the hypermutable stages of B-cell activation, arising from either chronic antigenic stimulation (autoimmunity) or impaired pathogen control (immunosuppression). However, the

results of some studies in humans and animals that measured immune biomarkers (such as those for B-cell activation) were not entirely consistent with this model (Bassig *et al.* 2013, Hosgood *et al.* 2012, Keil *et al.* 2009, Lan *et al.* 2010, Peden-Adams *et al.* 2006, Peden-Adams *et al.* 2008). Deng *et al.* (2013) found an elevated risk of NHL among individuals with polymorphisms associated with higher interleukin-10 production, which provides some support for a link between immunosuppression and NHL. Neither the proposed model nor the potential association between trichloroethylene-induced immune effects and lymphoma has been directly tested in either humans or animals.

The mode of action for trichloroethylene-induced liver cancer is unknown but likely is complex, involving key events from several pathways (EPA 2011). These may include genotoxicity, oxidative damage, peroxisome proliferation, epigenetic events, and autoimmunity (hepatitis), resulting primarily from oxidative stress (EPA 2011, Wang *et al.* 2013). Oxidative metabolites are considered to be more important in liver carcinogenicity, because trichloroethylene and its metabolites trichloroacetic acid, dichloroacetic acid, and chloral hydrate have similar toxic and carcinogenic effects on liver. These metabolites are found in humans, and chloral or chloral hydrate is genotoxic in several *in vitro* and *in vivo* test systems. Although species differences in sensitivity to the proposed modes of action are likely, no data suggest that trichloroethylene causes liver tumors in mice by mechanisms that are not relevant to humans.

### *Properties*

Trichloroethylene is a halogenated alkene that exists at room temperature as a clear, colorless, or blue mobile liquid with an ethereal odor. It is slightly soluble in water, soluble in ethanol, acetone, diethyl ether, and chloroform, and miscible in oil. It is relatively stable, but oxidizes slowly when exposed to sunlight in air (HSDB 2012). Upon combustion, trichloroethylene produces irritants and toxic gases, which may include hydrogen chloride. In the presence of moisture and light, it breaks down into hydrochloric acid. Physical and chemical properties of trichloroethylene are listed in the following table.

| Property | Information |
|---|---|
| Molecular weight | 131.4 |
| Specific gravity | 1.4642 at 20°C/4°C |
| Melting point | –84.7°C |
| Boiling point | 87.2°C |
| Log $K_{ow}$ | 2.61 |
| Water solubility | 1.28 g/L at 25°C |
| Vapor pressure | 69 mm Hg at 25°C |
| Vapor density relative to air | 4.53 |

Source: HSDB 2012.

### *Use*

Trichloroethylene is used as an intermediate for hydrofluorocarbon production (67%) and as a degreaser for metal parts (30%) (CMR 2002). The remaining 3% is used primarily as a modifier for polyvinyl chloride polymerization. Past use of trichloroethylene was primarily as a degreaser, although that use in the United States declined beginning in the 1970s (Bakke *et al.* 2007). Five

main industrial groups use trichloroethylene in vapor or cold degreasing operations: furniture and fixtures production, fabricated metal products, electrical and electronic equipment, transport equipment, and miscellaneous manufacturing industries. Trichloroethylene is used as a solvent in the rubber industry, adhesive formulations, dyeing and finishing operations, printing inks, paints, lacquers, varnishes, adhesives, and paint strippers (IARC 1995). Use of trichloroethylene in the production of agricultural chemicals such as fungicides and insecticides has also been reported (Bakke *et al.* 2007). Other uses of trichloroethylene have included as an extraction solvent for natural fats and oils, as a solvent in extracting spices, hops, and decaffeinated coffee, and as an anesthetic and analgesic in obstetrics and for minor surgical procedures. However, uses of trichloroethylene as an extraction solvent for foods or in cosmetics or drug products essentially ceased in the United States as a result of 1977 U.S. Food and Drug Administration (FDA) regulations (IARC 1995). Tetrachloroethylene replaced trichloroethylene as a drycleaning agent in the mid 1950s.

### *Production*

Trichloroethylene is a high-production-volume chemical commercially produced by 21 companies worldwide, including two in the United States (SRI 2011). The two U.S. producers of trichloroethylene were reported to have a total capacity of 330 million pounds in 2009 (CMR 2002). In 2014, trichloroethylene was available from 101 suppliers worldwide, including 37 U.S. suppliers (ChemSources 2014). Recent volumes of U.S. trichloroethylene production, imports, and exports are listed in the following table.

| Category | Year | Quantity (million lb) |
|---|---|---|
| Production + imports[a] | 2012 | > 100 to 500 |
| U.S. imports[b] | 2013 | 58 |
| U.S. exports[b] | 2013 | 3.2 |

Sources: [a]EPA 2014. [b]USITC 2014.

U.S. imports of trichloroethylene generally increased from 1989 to 2007, reaching an all-time high of 27.2 million kilograms (60 million pounds) in 2007, but imports for 2010 to 2013 were less than 5% of that level (USITC 2014). From 1989 to 2013, U.S. exports of trichloroethylene ranged from a low of 16.6 million kilograms (36.7 million pounds) in 2005 to a high of 48.7 million kilograms (107.4 million pounds) in 1992, showing no consistent trends over that period.

Stabilizers, in the form of antioxidants or acid receptors (such as phenolic, olefinic, pyrrolic, or oxiranic derivatives and aliphatic amines), are usually added to commercial trichloroethylene in concentrations that normally range from 20 to 600 mg/kg but may be as high as 5,000 mg/kg. Which stabilizers are used depends on patent ownership and technical specifications (WHO 1985).

Trichloroethylene is reported to occur naturally in some algae in temperate to tropical climates and in one red macroalga (IARC 1995).

### *Exposure*

A significant number of people living in the United States are or have been exposed to trichloroethylene because of its widespread presence from past and present use. Occupational exposure occurs primarily by inhalation of vapors and dermal contact with vapors or liquid. The

general public can be exposed to trichloroethylene in drinking-water supplies, ambient air, certain consumer products, and contaminated foods (ATSDR 1997, 2013). Exposure has been documented by direct measurement of trichloroethylene in ambient air in workplace and non-workplace environments. The presence of trichloroethylene in groundwater and drinking-water supplies near sites of past trichloroethylene use has also been confirmed.

Workplace exposure to trichloroethylene has been documented by its measurement in over 4,000 air samples reported by U.S. government agencies, at levels ranging from 0.0002 to 16,000 ppm (reported as 1.6%) for the period from 1940 to 2011. The highest values reported were from the Occupational Safety and Health Administration (OSHA) Chemical Exposure Health Database for 1984 to 2011, which included over 300 samples (from about 100 facilities) containing trichloroethylene at concentrations above the OSHA permissible exposure limit (PEL) of 100 ppm, including 6 samples with concentrations above the National Institute for Occupational Safety and Health "immediately dangerous to life or health" level of 1,000 ppm. From 2000 to as recently as May 2010, 92 samples had concentrations above the PEL (OSHA 2011).

According to the U.S. Environmental Protection Agency's (EPA's) Toxics Release Inventory (TRI) database, environmental releases of trichloroethylene from 211 U.S. facilities in 2011 totaled 2.3 million pounds (TRI 2014). Based on historical TRI data, environmental releases of trichloroethylene have declined by more than 95% since 1988, when over 57 million pounds were released.

For the general public, the levels of exposure appear to have also decreased over time. Results from the third National Health and Nutrition Examination Survey (NHANES), conducted from 1988 to 1994 (in which 677 whole-blood samples were tested for trichloroethylene) suggested that approximately 10% of the U.S. population had detectable levels of trichloroethylene in their blood (limit of detection = 0.01 ng/mL). However, the NHANES survey data for 2001 to 2002 (922 samples), 2003 to 2004 (1,228 samples), and 2005 to 2006 (3,178 samples) reported blood trichloroethylene levels below the limit of detection for the 50th, 75th, 90th, and 95th percentiles of all age groups, genders, and races or ethnicities studied in the surveys.

Exposure to the general public is primarily by inhalation of ambient air and ingestion of contaminated drinking water (ATSDR 1997, 2013). Trichloroethylene volatilizes readily from contaminated tap water, and inhalation exposure of volatilized trichloroethylene may equal or exceed the exposure from ingestion of contaminated drinking water. One study estimated that inhalation exposure from a 10-minute shower in trichloroethylene-contaminated water would equal the exposure expected from drinking the contaminated water (McKone and Knezovich 1991). Based on a trichloroethylene concentration of 3.0 μg/L (the median concentration in a large California water survey) and daily water consumption of 2 L, average daily trichloroethylene exposure through ingestion of drinking water was estimated as 6 μg (Wu and Schaum 2000), which is consistent with the Agency for Toxic Substances and Disease Registry's estimate of 2 to 20 μg for daily exposure of the general population (ATSDR 1997).

Trichloroethylene concentrations in ambient air were measured during EPA's large-scale Total Exposure Assessment Methodology studies conducted in Maryland, New Jersey, and California from 1981 through 1987 (Wallace *et al.* 1996). Median personal trichloroethylene exposure concentrations measured with personal air monitors carried by 750 individuals for 24 hours ranged from 0.3 to 3.0 $\mu g/m^3$ (0.00006 to 0.0006 ppm). As part of the Minnesota Children's Pesticide Exposure Study, personal, indoor-air, and outdoor-air trichloroethylene

concentrations were measured in 284 households with children. The median values for indoor, outdoor, and personal sampling all were between 0.5 and 1 μg/m$^3$ (0.00009 to 0.0002 ppm) (Adgate *et al.* 2004). Vapor intrusion (migration of volatile chemicals from the subsurface into overlying buildings) can likely be an important contributor to indoor air levels where residences are located near soil or groundwater with high contamination levels (EPA 2011).

Trichloroethylene is a common groundwater and drinking-water contaminant (ATSDR 1997, 2013, Gist and Burg 1995, Heneghan 2000, IARC 1995, Wu and Schaum 2000). Industrial wastewater is a source of trichloroethylene released into surface-water systems. Trichloroethylene background levels in 1995 were 0.001 ppb (μg/L) in the Gulf of Mexico, 0.007 ppb in the northeastern Atlantic Ocean, and 0.0008 to 0.039 ppb in rainwater and snow (Gist and Burg 1995). In EPA's Contract Laboratory Program Statistical Database, trichloroethylene occurred in about 3% of surface-water samples and 19% of groundwater samples (IARC 1995). Based on its past widespread use for industrial and maintenance processes (e.g., as a metal degreasing agent) at U.S. military installations, trichloroethylene is also a common groundwater contaminant at many military sites (NRC 2006, 2009).

Trichloroethylene is a major ingredient in numerous consumer products. For example, it is listed as a major ingredient of twelve household aerosol products, constituting 80% to 100% of three products and 90% to 99% of two other products used as cleaners or degreasers and intended for use primarily in hobbies, crafts, and home maintenance (HPD 2013). Trichloroethylene has also been present in typewriter correction fluids, paint removers and strippers, adhesives, spot removers, and rug-cleaning fluids (Gist and Burg 1995).

The U.S. FDA Total Diet Study identified 72 food items containing trichloroethylene, including fruits, beverages, and many foods prepared with oils and fats. The highest mean concentration (0.012 ppm) was found in samples of raw avocado (FDA 2006). Other studies also have found trichloroethylene in a variety of foods, with the highest levels in meats and margarine. Although trichloroethylene has not been used as a solvent for extraction of natural fats and oils, spices, hops, and caffeine (from coffee) since the FDA imposed limitations on these uses in 1977, trichloroethylene contamination of foods can still occur from the use of contaminated water in food processing or from food-processing equipment cleaned with trichloroethylene (ATSDR 1997).

## Regulations

### *Coast Guard, Department of Homeland Security*

Minimum requirements have been established for safe transport of trichloroethylene on ships and barges.

### *Department of Transportation (DOT)*

Trichloroethylene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

### *Environmental Protection Agency (EPA)*

#### *Clean Air Act*

*National Emission Standards for Hazardous Air Pollutants:* Listed as a hazardous air pollutant.

*New Source Performance Standards:* Manufacture of trichloroethylene is subject to certain provisions for the control of volatile organic compound emissions.

*Urban Air Toxics Strategy:* Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

*Clean Water Act*

Designated a hazardous substance.

*Effluent Guidelines:* Listed as a toxic pollutant.

*Water Quality Criteria:* Based on fish or shellfish and water consumption = 2.5 µg/L; based on fish or shellfish consumption only = 30 µg/L.

*Comprehensive Environmental Response, Compensation, and Liability Act*

Reportable quantity (RQ) = 100 lb.

*Emergency Planning and Community Right-To-Know Act*

*Toxics Release Inventory:* Listed substance subject to reporting requirements.

*Resource Conservation and Recovery Act*

*Characteristic Hazardous Waste:* Toxicity characteristic leaching procedure (TCLP) threshold = 0.5 mg/L.

*Listed Hazardous Waste:* Waste codes for which the listing is based wholly or partly on the presence of trichloroethylene = U228, F001, F002, F024, F025, K018, K019, K020.

Listed as a hazardous constituent of waste.

*Safe Drinking Water Act*

Maximum contaminant level (MCL) = 0.005 mg/L.

***Food and Drug Administration (FDA)***

Maximum permissible level in bottled water = 0.005 mg/L.

Trichloroethylene may be used as a solvent in the manufacture of modified hop extract provided the residue does not exceed 150 ppm.

Trichloroethylene may be used as a solvent in the manufacture of specified foods with maximum residue levels ranging from 10 to 30 ppm.

***Occupational Safety and Health Administration (OSHA)***

Permissible exposure limit (PEL) = 100 ppm.
This legally enforceable PEL was adopted from the United States of America Standards Institute (USAI) (later the American National Standards Institute, ANSI) shortly after OSHA was established. The PEL may not reflect the most recent scientific evidence and may not adequately protect worker health.

Ceiling concentration = 200 ppm.

Acceptable peak exposure = 300 ppm (5 min in any 2 h).

## Guidelines

### *American Conference of Governmental Industrial Hygienists (ACGIH)*

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

Threshold limit value – short-term exposure limit (TLV-STEL) = 25 ppm.

### *Environmental Protection Agency (EPA)*

Integrated Risk Information System (IRIS) oral reference dose (RfD) = 0.0005 mg/kg b.w. per day.

IRIS inhalation reference concentration (RfC) = 0.0004 ppm [0.4 ppb, or 2 $\mu g/m^3$].

IRIS oral cancer slope factor = $5 \times 10^{-2}$ per mg/kg b.w. per day.

IRIS inhalation unit risk = $2 \times 10^{-2}$ per ppm [$4 \times 10^{-6}$ per $\mu g/m^3$].

Regional Screening Levels (formerly called Preliminary Remediation Goals): residential soil = 0.44 mg/kg; industrial soil = 2.0 mg/kg; residential air = 0.21 $\mu g/m^3$; industrial air = 0.88 $\mu g/m^3$; tap water = 0.26 µg/L; maximum contaminant level (MCL) = 5.0 µg/L.

### *National Institute for Occupational Safety and Health (NIOSH)*

Recommended exposure limit (REL) = 25 ppm (10-h TWA).

Ceiling recommended exposure limit = 2 ppm (60-min ceiling) during use as an anesthetic agent.

Immediately dangerous to life and health (IDLH) limit = 1,000 ppm.

Listed as a potential occupational carcinogen.

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